# Current Pharmacotherapy for Alzheimer's Disease

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ABSTRACT

This article describes current pharmacological approaches to Alzheimer's disease. The author delineates the two families of drug treatments currently available and the aspects of Alzheimer's pathophysiology which these drugs assess. The cholinesterase inhibitors are described along with their history of development. The newly approved NMDA inhibitor memantine is described along with how it will be used in practice given the prevalence of the cholinesterase inhibitors.

LEARNING OBJECTIVES

1. Understand the current concept of Alzheimer's disease pathogenesis and pathophysiology.
2. Gain knowledge of cholinergic therapies for Alzheimer's disease currently approved.
3. Learn the contribution of a new glutamatergic therapy for Alzheimer's disease, memantine.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative condition which results in loss of neurons in the cortex and other grey matter regions of the brain. While it typically is associated with later years, patients can be as young as 40 for the common late-onset sporadic type. The upper limit for age of onset is 90 in the NINCDS-ADRDA criteria for the disease[1]. Patients with the autosomal dominant early-onset familial type can be in their 20s potentially, but this type accounts for less than five percent of individuals with the condition.[2] Current evidence supports the notion that Alzheimer's disease is an *amyloidosis*, or protein accumulating illness, in which an *amyloid* called amyloid-beta-42 accumulates in the form of *plaques*.[3] Plaques occupy the space between brain cells, surrounded by mobile inflammatory cells (*microglia*) and degenerating cell projections called *neurites*. The immobile brain cells which are affected by the condition contain tangles, paired helical filaments, which are composed of abnormal tau protein. Tau protein is involved in stabilizing microtubules necessary for axon transport. If the tau protein has been hyperphosphorylated it will begin to stick to other copies of itself, and this leads to tangle formation. It is surmised that cells containing tangles will overproduce amyloid, and also that amyloid tends to induce tangle formation by hyperphosphorylating tau, an NMDA-receptor mediated interaction. The NMDA receptor, so-called because it binds N-methyl-D-aspartate, is a glutamate receptor which is involved in learning and memory as well as being a site that can mediate cell death via excitotoxicity. This is what permits the disease to spread

throughout the brain, amyloid begetting tangles and tangles helping to beget amyloid. Experiments involving placing amyloid on neurons in culture demonstrate that amyloid itself is sufficient to produce Alzheimer's pathology, and so is likely to be the final common pathway for producing AD.[4]  Other work by Schenk et al. has shown that immunizing against amyloid in animal models of cerebral amyloidosis abolishes existing amyloid stores and prevents new ones from forming, which also supports the notion that amyloid itself is central to the disease process.[5]  While intuitive, the notion that 'amyloid causes amyloidosis' (i.e., the *amyloid cascade hypothesis*) has had its detractors and took nearly a century from 1907 (the first description of Alzheimer's disease) to the present to become accepted as a cause of the disease. [6]

AD is very gradual and nearly imperceptible initially.  It may begin with short-term memory loss which slowly worsens from minor annoyance to a major source of disability.  AD typically has no abrupt onset, and patients and family members are hard-pressed to say exactly when it started. It can proceed relentlessly in some patients, and in others enter plateau phases where no progression occurs for months to years.  AD can be thought of as having three major stages— mild, moderate, and severe—and a precursor state ('stage 0') which is often called *mild cognitive impairment* (MCI).  Each major stage lasts roughly 3-5 years in the untreated patient, and can be broken into early, middle, and late substages which are useful clinically. A number of scales are used to measure cognition in the elderly.  The MMSE, or mini-mental state examination, is a rapid and simple general cognitive measure introduced by Folstein in 1975.[7]  It ranges from 0-30, where 30 is normal, and roughly corresponds to the stages of AD: mild, 20-26; moderate, 10-19; severe, 0-9.  The ADAS-Cog is a more extensive battery used in clinical trials, ranging from 0-70, where 0 is normal and 70 is severely impaired.[8]

Mild stage AD is typically limited to loss of short-term memory and the decreased ability to do mental arithmetic (*dyscalculia*).  Some patients have anomia (i.e., loss of the ability to retrieve names for objects), which can eventually cause them to have few substantives (nouns) in their speech.  Loss of navigating ability also begins in this stage, making it harder to get somewhere in the car or just walking.  A common presentation is when an individual is still not home hours after he is expected and the police had to be called, or when someone keeps losing her car in parking lots.  Eventually, it becomes clear to caregivers that driving is no longer safe for patients even in this relatively early stage of AD.  The problem is that it is possible for short-term memory loss to interfere with keeping track of other vehicles around one's own, which leads promptly to accidents.  For both societal and medico-legal reasons, many practice parameters recommend that clinicians inform an AD patient that he can no longer drive safely, and in some states physicians and other healthcare workers may be required to inform the state motor vehicle department which typically revokes the individual's license.

As the AD moderate stage is entered, patients will begin to have more psychiatric manifestations, including anxiety and paranoia.  These can be seen as arising from the mismatch of past and present, in that long-term memory tends to be preserved for a long time and short-term memory becomes profoundly impaired or absent.  This leads to the patient literally 'living in the past'. He or she may experience *reduplicative paramnesia*, in which their family members often are accepted as bona fide, but the patient is convinced that duplicates of them exist somewhere else. These duplicate family members are their past versions, which do not match their present

versions in the patient's accessible memory any more.  While recognizing her spouse in a wedding photo, one patient was nevertheless unable to say who the man sitting next to her was; while quite strong and fit in his early 80s, he no longer resembled the young man she had married.  Patients in this stage may also have *wandering*, which seems to be initiated by looking for a familiar place like the house as it used to look, or *pacing*, a prominent form of organic anxiety disorder in which patients are driven to move and cannot be still.   It is instructive to consider the world of a patient with Alzheimer's disease:  nothing stays where you leave it, inanimate objects seem to move around of their own accord, and there is always the sense that the place and people around you are unfamiliar, even as they tell you that you are at home and among family and friends.

The AD moderate stage is also where prominent sleep disturbances may occur.  Sleep is tied to the *circadian rhythm*, which is a clock driven by the suprachiasmatic nucleus, a group of neurons in the hypothalamus.  The clock itself is set by the sun's bright light, but with AD there is a loss of entrainment, which is the process by which the clock is set to a particular period.  Patients can now have a free-running clock with a period of 40 or so hours.  This is out of synchronization with the quotidian 24 hours the world operates on, and creates a lot of difficulty for the patient's family or caregivers.  It is typical for an AD patient to awake at 1 am and demand breakfast, or wish to go to sleep at 3 pm in the afternoon.  If awakened an hour later, as if from a nap, she might well ask for breakfast again.   Phototherapy, designed to re-entrain the circadian rhythm for jet lagged travelers or night shift workers, does not work for sleep disturbances in AD,[9] although there is reason to think that bright light exposure can have good effects on cognitive testing.[10]

As AD progresses into the severe stage, patients lose both short-term and long-term memory and often lose the power of speech as well.  Gait disturbance and incontinence predominate and often lead to frequent falls and difficulty in care at home, leading to nursing home placement.  The incontinence is typically bladder before bowel, and is related initially to not knowing where the bathroom is or how to get there.  Later incontinence is due to not knowing that a bathroom is necessary, and later still the awareness of a full bladder is lost, so that when incontinence occurs it is typically due to overflow.  Patients typically become less interested in eating and drinking, and may become dangerously dehydrated and malnourished.  This leads to reduced resistance to common pathogens, and so urinary tract infections, urosepsis, bronchitis, and pneumonia becomes frequent.  Gait disturbance can lead to injuries with high morbidity, like hip fractures and head injuries with subdural hematoma, and mortality typically follows within a matter of weeks.   Hospice assistance is very appropriate in the latter part of the severe stage.  Clearly a fatal condition, AD is one of the top ten leading causes of death in American adults.[11]

It should be unsurprising that the theories of the day shaped the development of drugs for Alzheimer's disease.   Before the 1990s the prevailing theory of Alzheimer's pathogenesis was termed the *cholinergic hypothesis.*[12]  This was based on the seminal finding that acetylcholine (ACh) and choline-acetyltransferase (ChAT) levels were low in the brains of Alzheimer's patients.[13]  The basal nucleus of Meynert, which lies beneath the forebrain, is the brain's major source of acetylcholine (ACh).  ACh is synthesized in large cholinergic neurons, some as large as 1 mm across.  Low acetylcholine levels or cholinergic blockade can produce cognitive impairment and this was accepted as the explanation for the loss of function seen in Alzheimer's.

Until quite recently, the only drugs available for treating AD have been based on the cholinergic hypothesis and are all *cholinesterase inhibitors*, drugs which inhibit the breakdown of acetylcholine.   It is ironic to note that while they do in fact have beneficial effects, their development was based on what is known now to be false:  Alzheimer's disease is not due to loss of acetylcholine but is in fact due to loss of cholinergic and other neurons.   The cholinergic deficit is an effect of the illness, not a cause.  A new line of drug development has emerged from a more amyloid-based consideration of the pathogenesis of Alzheimer's disease.  These are the *selective NMDA receptor inhibitors*, typified by the first commercially available agent in the USA, memantine.   The rest of this paper will discuss cholinesterase inhibitors and will also discuss pharmacological treatments for psychiatric manifestations and sleep disturbance associated with AD.

OVERVIEW OF THE CHOLINESTERASE INHIBITORS

The cholinesterase inhibitors are a heterogenous group.[14]   The drugs in current use for Alzheimer's disease include donepezil, rivastigmine, and galantamine.  An earlier drug, tacrine, introduced the class but has fallen into disuse.   These drugs are not related to the classical irreversible non-selective inhibitors of acetylcholinesterase, the organophosphates. Nor are they nerve toxins like sarin, as their molecular heritage affords selectivity for the central acetylcholinesterase and reversibility.   This cuts down on typical cholinergic side effects including nausea, vomiting, diarrhea, bradycardia, and muscle cramps.  With the drugs approved for AD there are clear ceilings to dosing, above which side effects predominate due to loss of central selectivity and peripheral spillover.   Many of the side effects attributed to these drugs are in fact more akin to toxicity, typical of the narrow therapeutic windows of anticonvulsants like phenytoin.    Of interest, one of the first centrally selective cholinesterase inhibitors is a natural product found in Chinese club moss, huperzine A.[15]   Several cholinesterase inhibitors have been under commercial development including ganstigmine, phenserine, velnacrine, and metrifonate.

TACRINE

Tacrine was the first drug ever approved for Alzheimer's disease in 1993 as the brand Cognex. Remarkably, it was the efforts of a single individual, Dr. William Summers, a psychiatrist now in solo practice in Albuquerque, New Mexico, that brought tacrine to market.[16, 17]    It is plausible that further development in this area would not have occurred if tacrine had not been approved.  An aminoacridine, tacrine has a very short half-life which requires four times daily (qid) dosing and can be unpredictably hepatotoxic in some patients, necessitating periodic liver monitoring.  It can be given with or without food, but is probably better tolerated with food. More than a third of patients cannot tolerate it due to gastro-intestinal side effects including nausea, vomiting, and diarrhea.  Also, four times daily dosing makes compliance difficult to maintain.  Tacrine is no longer in general use.  However, if the maximum dose of 40 mg qid is reached, patients do experience sometimes dramatic improvement in memory and cognition (see Fig. 1), and one study showed delayed entry into the nursing home for patients on drug.[18] Subsequent to the acquisition of Warner-Lambert by Pfizer Pharmaceuticals, tacrine was sold to First Horizon Pharmaceuticals, where it has been rumored to be in development for a once daily

sustained release preparation.  Hence, tacrine may make a comeback; it is still distributed in its original form today.[19]

Tacrine inhibits both the central acetylcholinesterase and the butyrylcholinesterase enzymes, what used to be called the pseudocholinesterase enzyme.  Butyrylcholinesterase inhibition may be associated with enhanced effect for cognition or more peripheral side effects, especially gastro-intestinal.[20]
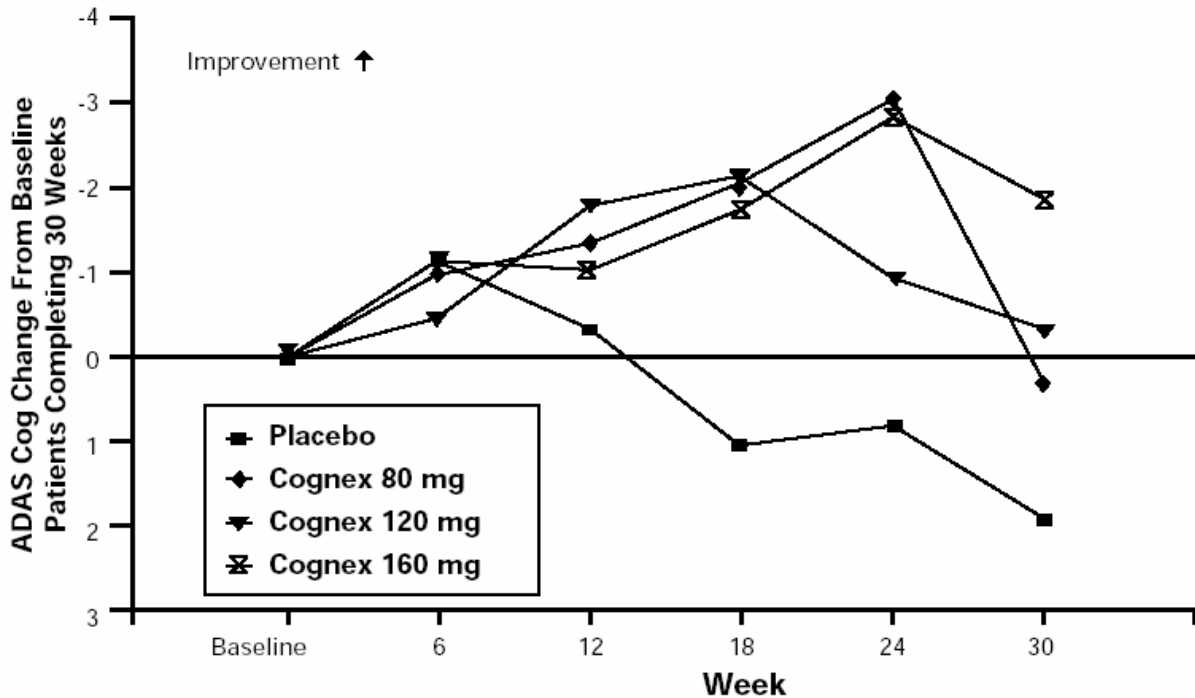


*Fig 1.  Cognitive effect of tacrine.  Higher doses produce greater improvement on the ADAS-Cog scale over the 30 week study period. [21]*


DONEPEZIL

In 1997, Pfizer and Eisai received approval to market donepezil as the brand Aricept.  Donepezil offers several advantages over tacrine.  It is approved for mild to moderate stages of the disease. It is given once daily, at a starting dose of 5 mg and can be increased to 10 mg after 4-6 weeks.[22]   No hepatotoxicity has been demonstrated and no periodic lab monitoring is required.[22]  It is a piperidine, not an aminoacridine like tacrine, which probably contributes to its lack of toxicity.  Efficacy is good in about two thirds of patients treated, producing definite increases in cognition on ADAS-cog standard measurement (see Fig. 2). About one third of patients have little to no response.  It has also been shown using the NPI (Dr. Cumming's Neuropsychiatric Inventory)[23] to have effects on improving behavior, even in severe stages, and has three-year efficacy data.[24]   Like tacrine, it has been shown to delay the need for nursing home placement, and by as much as 21.4 months in one study where this was the primary outcome measure.[25]  It is typically given at bedtime to reduce GI side effects which affect under 5% of patients.[22]   Now accounting for the largest portion of the Alzheimer's

market, donepezil has enjoyed wide usage. Some reports have shown that it can have limited efficacy after two years, but this is quite variable in the author's experience. Cholinergic agents like other drugs can suffer from tolerance or reduced efficacy over time, which is compounded by the progression of the disease. As cholinesterase inhibitors like donepezil must act on the pool of available acetylcholine, it follows that as this pool contracts with cumulative loss of cholinergic neurons, the drugs will work less well over time. Note that doses in excess of 10 mg have been used clinically but are not safe for patients. Peripheral spillover effects of cholinesterase inhibition occur including bradycardia, syncope, and muscle cramps which are sometimes excruciating. Furthermore, no added benefit is seen with higher doses, and a labeled PET study shows 98% binding at 10 mg to all available brain sites.[26]
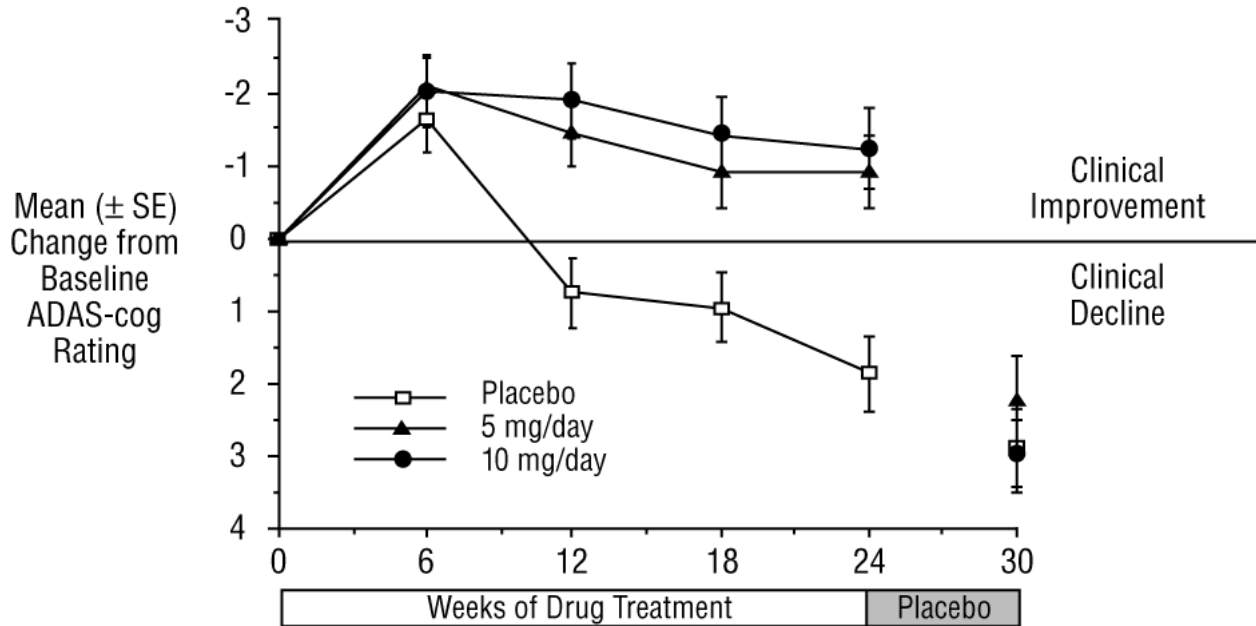


*Fig 2. Donepezil effect on cognition. Active treatment is associated with clinical improvement compared to placebo. 10 mg/day is modestly superior to 5 mg/day. Placebo washout at week 24 was associated with reduction in performance of treatment groups to the same level as placebo group, implying a lack of effect on the underlying condition.[22]*

RIVASTIGMINE

The third cholinesterase inhibitor to be approved is rivastigmine, marketed by Novartis as Exelon, it was approved in 2000.[27] It is a carbamate, selective for the C4 isoform of acetylcholinesterase, which is present to a greater degree in cortex and hippocampus, which suggests that the compound has anatomic selectivity. Rivastigmine is approved for mild to moderate stages of the disease and is given twice daily, starting at 1.5 mg bid. Advancing 1.5 mg every two weeks appears to be well-tolerated, but faster titration schedules tend to result in nausea and gastric distress, which occurred in more than a third of patients in the original registration trials. However, no laboratory monitoring is required. The maximum dose is 6 mg bid; higher doses are associated with more GI distress and other peripheral spillover effects as the drug loses central selectivity. It shares with tacrine an affinity for butyrylcholinesterase, which may be beneficial in that butyrylcholinesterase is not present in brain normally, but

increases with Alzheimer's disease, brought in by activated microglia in plaque.[28]   There is some question about whether inhibition of this other sink for acetylcholine has a clinical benefit, as this has not been established clearly, nor has it been established that a drug which only has butyrylcholinesterase inhibitory effect has efficacy on its own.   Figure 3 shows the cognitive effect using the ADAS-Cog test over two years in the original registration trials of rivastigmine. There is also data using the NPI to suggest that rivastigmine has a superior profile for control of behavior.[29]
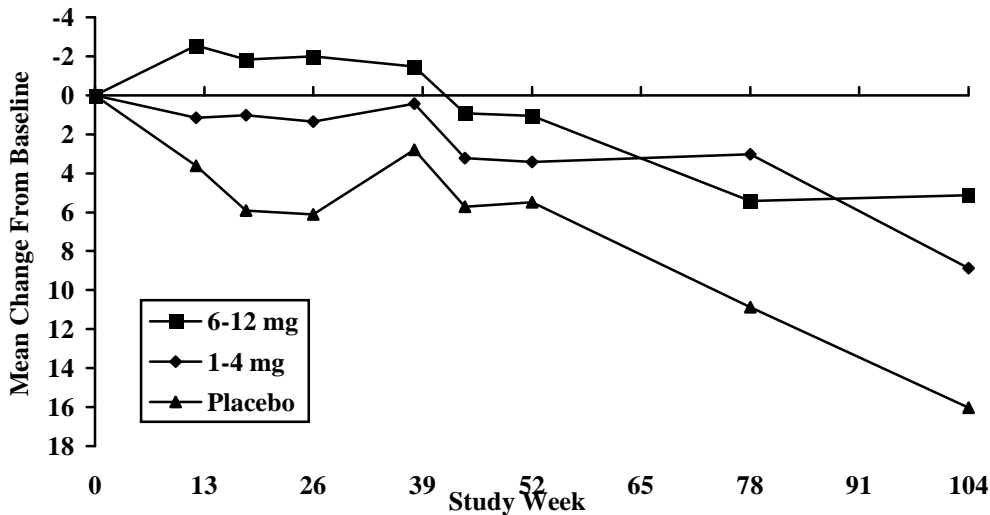


*Fig 3.  Rivastigmine effect on cognition using the ADAS-Cog.  Placebo controlled through week 26, then all patients receive rivastigmine, so placebo line following week 26 is projected.[27]*


GALANTAMINE

The fourth and last cholinesterase inhibitor to be approved for mild to moderate Alzheimer's disease in the US, galantamine is actually an old drug in European formularies, going back to the 1950s where it was used to reverse the effects of succinylcholine.  It is marketed by Janssen under the brand name Reminyl.  The drug is a tertiary alkaloid, a natural product now produced synthetically, derived originally from daffodils and snowdrops.  The starting dose is 4 mg bid and it can be increased 4 mg per week to a maximum approved dose of 12 mg bid.  It was in fact studied up to 16 mg bid and is safe at that dose in the author's clinical experience, but was not shown to be statistically superior to 12 mg bid.  The 16 mg bid dose is associated with more bradycardia as a peripheral spillover effect.  Figure 4 shows the effect of galantamine on cognition using the standard ADAS-cog primary outcome measure.[30]

There is a documented nicotinic effect of galantamine of uncertain clinical benefit, but interesting pharmacologically.[31]   Briefly, galantamine acts as an allosteric modulator of the presynaptic nicotinic receptor in a manner similar to the effect of benzodiazepines on the GABA receptor.  When galantamine is present, acetylcholine binding has a roughly tenfold increased effect.[31]
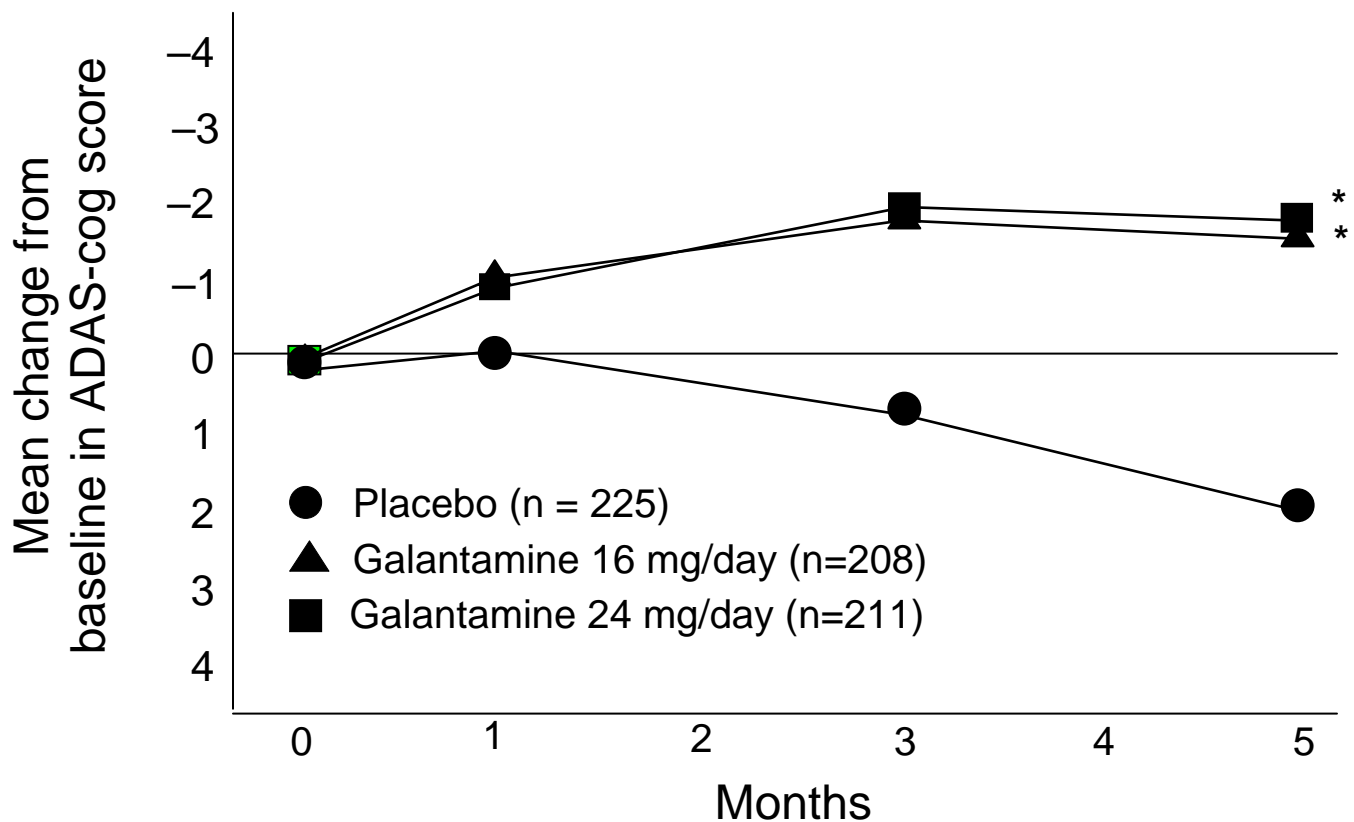
*Fig. 4. Effect of galantamine on cognition. \*p<0.001. Treatment is associated with improvement compared to placebo. There was not much difference is noted between 16 mg/day and 24 mg/day in the grouped analysis*[32]

MEMANTINE

In October 2003 the US Food and Drug Administration approved memantine as the first of a new class of drugs for Alzheimer's disease, the selective NMDA receptor antagonists. It is licensed for distribution to Forest Pharmaceuticals under the brand name Namenda. Memantine is an unusual drug derived from adamantane and related to amantadine. It is structurally unrelated to the cholinesterase inhibitors and in fact has no pharmacological interaction or effect on

cholinesterases, in the presence or absence of cholinesterase inhibitors like donepezil. It is voltage-sensitive low to moderate affinity uncompetitive antagonist at the NMDA receptor, meaning that it is a 'polite molecule', binding and blocking only pathological levels of glutamate activation. It is surmised that since glutamate levels are dysregulated in AD—an effect thought to be mediated by beta-amyloid-pathological activation of the NMDA receptor leads to excitotoxicity and ultimately death of neurons. It is known that memantine interferes with the toxic effect of amyloid on neurons, which is thought to occur at the NMDA receptor.[33]

Memantine can be given with or without food. Dosing is best accomplished by titration first with a standardized titration kit, which takes the patient from 5 mg qAM to 10 mg bid at 5 mg per week increments. Using the titration kit is the easiest way to achieve the recommended maintenance dose of 10 mg bid.[34] Three trials were proposed for registration, including a monotherapy trial in moderate to severe AD,[35] a combination trial with donepezil in moderate to severe AD,[36] and in severe stage nursing home patients with dementia.[34] Figure 5 shows the effect of memantine in monotherapy using the Severe Impairment Battery (SIB), a cognition scale which is more suited to the population with late AD. The drug also had good impact on activities of daily living and although no statistically significant effect was noted on the NPI total score between active and placebo groups, there were significant differences in favor of memantine for reducing delusions and agitation/aggression.
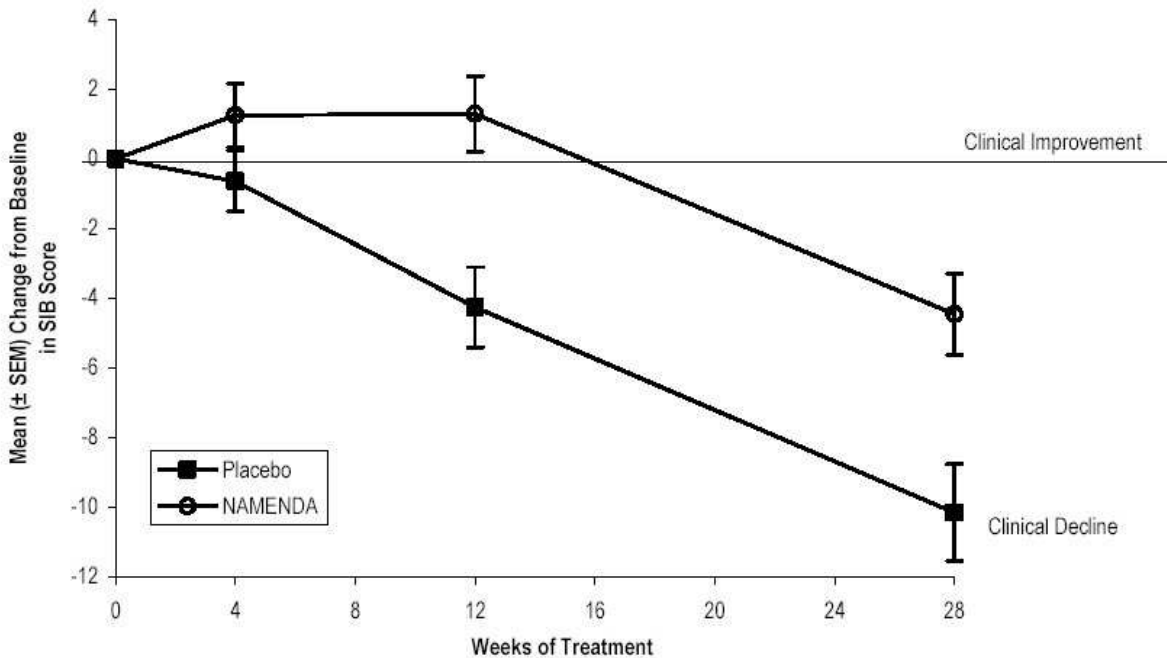


Fig 5. *Effect of memantine (Namenda) monotherapy on cognition using the Severe Impairment Battery (SIB).[34]*

Given its favorable interaction profile, it is only natural to wonder if memantine will have synergistic effects in patients already on a cholinesterase inhibitor. This has only been formally studied with donepezil, with favorable effects depicted in figure 6. There was also good effects on activities of daily living, caregiver burden was reduced in comparison to patients on donepezil

alone, and there was a statistically significant difference in total NPI scores in favor of combination therapy, indicating superior efficacy for behavioral control.[34]

As memantine has not been studied with rivastigmine or galantamine (or tacrine), use with those cholinesterase inhibitors would be off-label. Much of the author's own clinical experience has indicated that memantine is safe with galantamine or rivastigmine, and some combinations work well anecdotally, especially memantine/galantamine.
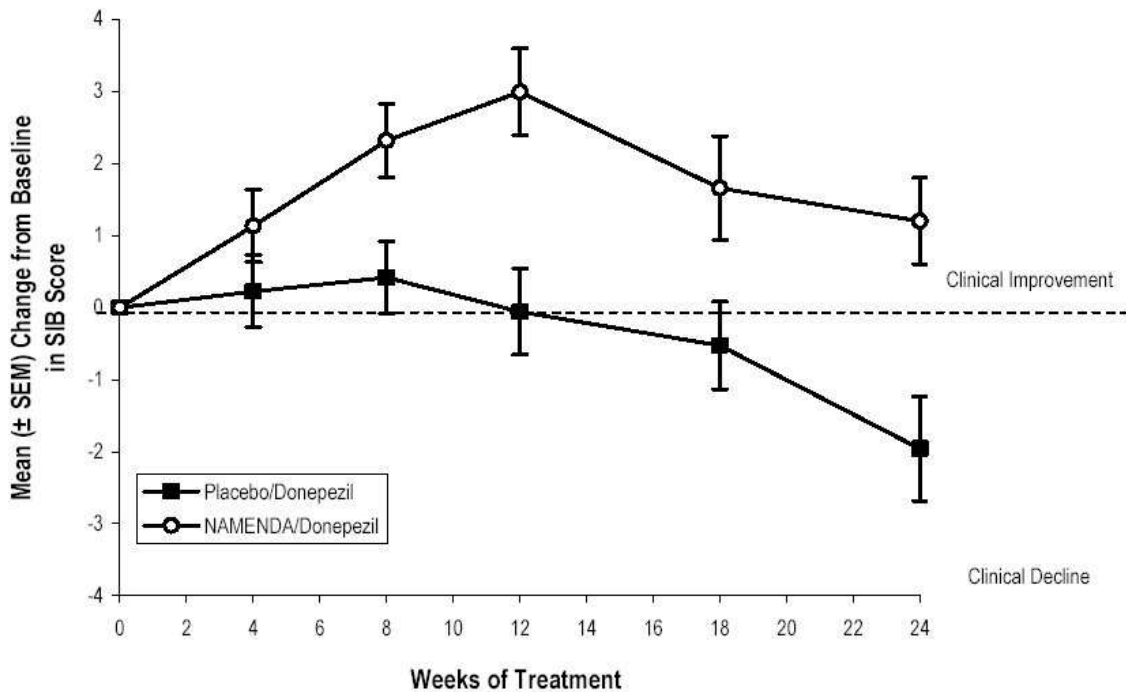


*Fig 6. Effect of memantine (Namenda) in combination with donepezil (Aricept) on cognition using the Severe Impairment Battery.[34]*

ANTIPSYCHOTIC AGENTS FOR ALZHEIMER'S DISEASE

Psychosis in AD is uncommon, but when present can be difficult to treat. The cholinesterase inhibitors and memantine do have antipsychotic effect in clinical trials. This effect is sometimes sufficient, but when agitation is considerable or hallucinations are threatening, it is appropriate to employ a second agent. The atypical antipsychotics are much preferred in this setting, as drugs like haloperidol are likely to exacerbate the cholinergic deficit and worsen the patient clinically. Moreover, D1-receptor antagonist effects will produce marked parkinsonian reactions in some patients with Alzheimer's disease.[37] The preferred antipsychotic agent in these patients is quetiapine, which is, in the author's experience, safe and efficacious in low doses starting at 12.5 mg bid, but is not approved for this use by the FDA. It has side effects of sedation and weight gain, which are actually desirable in patients with moderate and severe stages of the disease.

Ziprasidone and aripiprazole may be worthwhile where sedation is not wanted or is present too strongly with quetiapine. The author has not found risperidone or olanzapine to be safe in this population due to parkinsonian side effects, especially worrisome in patients who also have Lewy Body pathology. Because Lewy Bodies can only be detected at autopsy and have up to 40% overlap with AD, it is difficult to predict who may do poorly, hence quetiapine is preferred. [38]

HYPNOTIC AGENTS FOR ALZHEIMER'S DISEASE

Quetiapine is a good choice for insomnia in AD due to its great safety and strong sedative effect. This can even have the effect of synchronizing the patient's day-night cycle, at least from the viewpoint of the caregiver. Doses of 25 mg qhs are often sufficient. Also useful in this context are non-benzodiazepines, like zolpidem and zaleplon, typically at low doses. Benzodiazepines are used very frequently, but are not preferred due to lingering sedation and tolerance. A large National Institute on Aging multicenter trial of melatonin for sleep disturbance in Alzheimer's showed no significant benefit.[39] Diphenhydramine, while often used, tends to add to confusion as it is anticholinergic; the same applies to low-dose opiates.[40]

Chloral hydrate is effective for short courses but tolerance develops rapidly.[41] Its exact mechanism of action is unknown, but its principal active metabolite is trichloroethanol which may mediate its sedative-hypnotic effect. The starting dose is 500 mg qhs, but many patients need as much as 2000 mg for good control of insomnia. The drug has been shown to be carcinogenic in mice with lifetime exposure, but this is of unclear clinical significance.[42]

CONCLUSION

Clinicians who care for patients with Alzheimer's disease now enjoy a rich armamentarium which can provide significant positive impact to quality of life. It remains to be seen whether newer agents like memantine, perhaps in combination with a cholinesterase inhibitor, will lead to enhanced longevity.

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