

# Donepezil in the treatment of patients with Alzheimer's disease

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Alzheimer's disease (AD) is the most common cause of dementia and is characterized by an insidious onset and slow deterioration in cognition, activities of daily living (ADL), mood stability and social functioning. The cholinesterase inhibitors (ChEIs), developed based on the cholinergic hypothesis, are currently considered to be the best established treatment for AD, although the significant advances in the symptomatic pharmacotherapy of AD may be followed by disease-modification treatments. Donepezil is a mixed competitive and noncompetitive acetylcholinesterase inhibitor that shows a relative selectivity for acetylcholinesterase compared with butyrylcholinesterase. In many clinical trials of donepezil, beneficial effects on standard measures of cognitive function, ADL and behavior have been shown in patients with mild, moderate or severe AD. Although the pharmacological and pharmacokinetic profiles of the currently available ChEIs have notable differences that may affect efficacy, the clinical significance of these differences remains hypothetical in the absence of large, randomized trials that compare the ChEIs with each other.

**KEYWORDS:** Alzheimer's disease • cholinesterase inhibitor • donepezil • pharmacotherapy

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by an insidious onset and slow deterioration in cognition, activities of daily living (ADL), mood stability and social functioning. Epidemiological studies have indicated that in 2000 there were 25 million persons with AD worldwide, and this number is expected to increase to 114 million by 2050. Incidence of AD increases sharply and steadily after 65 years of age. It has been estimated that nearly 25% of people aged 85 years and older have AD or some form of dementia.

Alzheimer's disease is a slowly progressive disorder, with insidious onset and progressive impairment of episodic memory; instrumental signs include aphasia, apraxia and agnosia, with general cognitive symptoms, such as impaired judgment, disorientation and decline in ADL. Although neuroimaging, computed tomography and MRI, shows nonspecific findings of atrophy and ventricular dilatation, it plays an important role in the diagnosis of AD to exclude alternative causes of dementia, such as brain tumor and cerebral infarcts (i.e., vascular dementia). The pathological picture consists of neuronal cell loss, deposition of amyloid plaques, neurofibrillary tangles and secondary inflammation.

At this stage, the accumulation of amyloid plaques and neurofibrillary tangles in the brain has been damaging the medial temporal and neocortical areas, and has irreversibly affected synapses and neuron viability.

The goal of pharmacologic treatment for AD would be to stabilize or slow cognitive and functional decline, ameliorate behavioral symptoms, or reduce caregiver burden. Currently, the two classes of drugs approved for the treatment of AD are the cholinesterase inhibitors (ChEIs) and the NMDA receptor antagonist memantine. ChEIs are considered the first choice drug for the treatment for AD. This article reviews data on the use of the ChEI donepezil in the treatment of AD.

## Cholinergic hypothesis

The cholinergic hypothesis states that decreased cholinergic transmission plays a major role in cognitive dysfunction in AD. As a result of the pathological changes in the brain in AD, there are decreases in cholinergic neurons in the ventral forebrain. Several studies from the mid-1970s to the early 1980s suggested that the depletion of acetylcholine (ACh) induces the decrease or disruption of nerve transmission in the brain,

particularly in the temporal and parietal neocortex and hippocampus, that are associated with severity of cognitive decline [1–4]. These reports led to the hypothesis that it might be possible to develop therapeutic strategies similar to the levodopa treatment approach to Parkinson's disease. Subsequently, it has become obvious that other neurotransmitter abnormalities are also present in the brain in AD. For example, it has been suggested that the glutamate pathway is may also be involved in neuronal dysfunction and death. Memantine, an antagonist of NMDA, was produced by this exploration as a possible therapeutic strategy for AD.

### Mechanism of cholinesterase inhibitors

Cholinesterase inhibition is the only cholinergic strategy that has thus far proven to have beneficial effects in patients, although a number of therapeutic approaches have been tested for enhancing cholinergic and cognitive function in patients with AD. To date, four ChEIs have been approved in Europe, North America and Asia for the treatment of AD (FIGURE 1). These include tacrine (rarely used owing to hepatotoxicity), donepezil, galantamine and rivastigmine.

The ChEIs increase ACh levels at the synapses and presynaptic receptors and maintain some function in the cholinergic system. The general mechanism of action for this class of agents is to increase the availability of ACh by inhibiting ChE, the enzyme that degrades ACh in the synaptic cleft. ACh is hydrolytically destroyed in the brain by two ChEs, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AChE selectively hydrolyzes ACh and BuChE hydrolyzes other choline esters in addition to ACh. The role of BuChE in humans is not completely understood, although its inhibition may contribute to efficacy in treatment of AD.

### Pharmacology of donepezil

#### Pharmacodynamics

Donepezil is a mixed competitive and noncompetitive AChE inhibitor that shows a relative selectivity for AChE compared with BuChE (TABLE 1). The ratio of donepezil  $IC_{50}$  for BuChE to AChE from rodents and humans was found to be 1252:1 and 405:1, respectively [5,6]. This relative selectivity could be the reason for the low incidence of clinically relevant peripheral cholinergic side effects. There are also differences in inhibition of enzymes ( $IC_{50}$ ) isolated from various tissues, such as rat skeletal muscle, rat brain or human erythrocytes. The inhibition of the erythrocyte AChE is approximately 64% with donepezil 5 mg and 78% for doses under 10 mg in patients with AD.

Cholinesterase inhibitors for the treatment of AD vary in their pharmacological profiles and affinities for AChE and BuChE. Donepezil and galantamine are 1000- and 50-fold, respectively, more selective for AChE than for BuChE, whereas rivastigmine inhibits both enzymes with similar affinity [7]. Galantamine also allosterically modulates nicotinic receptors. Whether central activation of the nicotinic ACh receptor translates into cognitive benefits *in vivo* has yet to be definitively determined. The clinical relevance of these pharmacological differences remains unknown.

#### Pharmacokinetics

Donepezil is metabolized by the cytochrome P450 isoenzymes 2D6 and 3A4 in the liver. Donepezil may interact with drugs that inhibit these enzymes, such as cimetidine, ketoconazol, paroxetine, fluoxetine and fluvoxamine. Cimetidine and ketoconazol increase donepezil plasma concentrations. However, according to the current US FDA guidelines, these effects were not considered

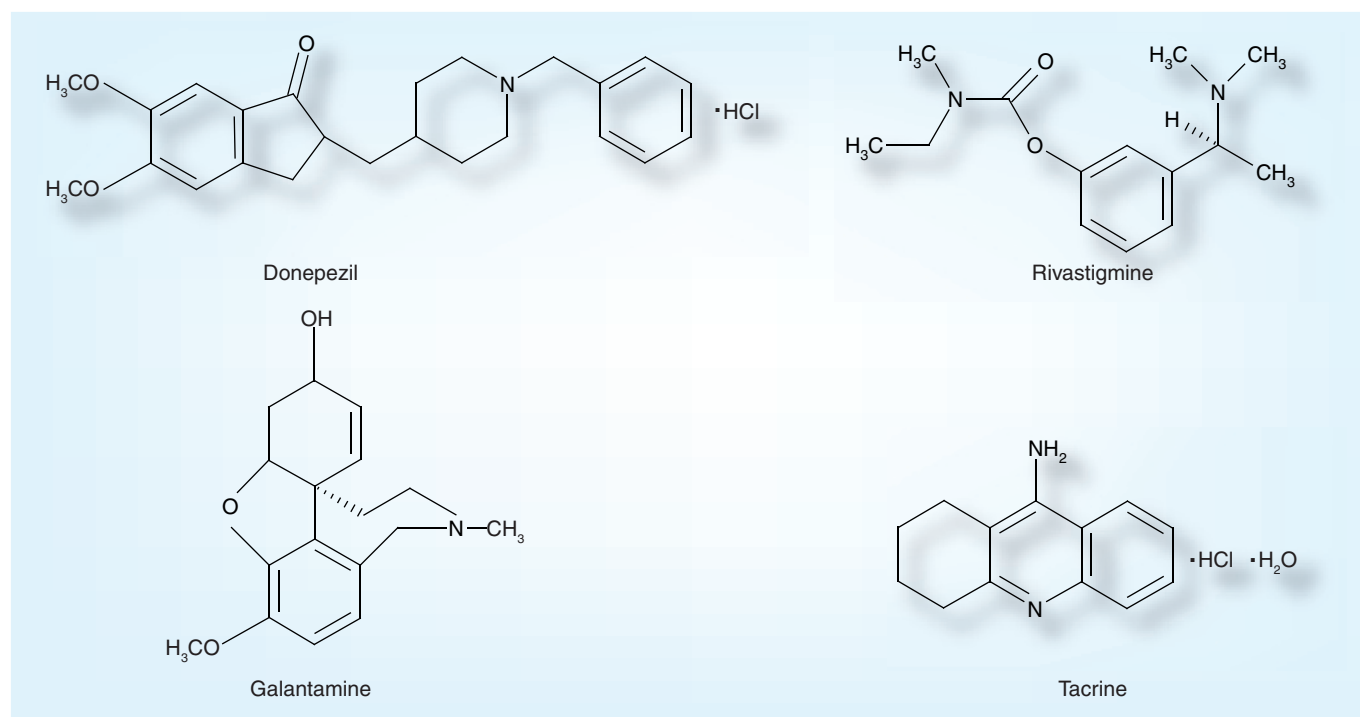


Figure 1. Structural formulae of cholinesterase inhibitors for the treatment of Alzheimer's disease.

Table 1. Pharmacologic profiles of currently available cholinesterase inhibitors.

Drug	Mode of action	ChE selectivity	Bio-availability (%)	Protein binding (%)	Metabolism	Elimination half-life (h)	Pharmacokinetic interactions	Pharmacodynamic interactions	Doses per day	Recommended therapeutic dose (mg/day)
Tacrine	Reversible ChEs	BuChE = AChE	17–37	75	CYP1A2 CYP2D6	1.3–7	Risk of elevated plasma levels in combination with theophylline	Risk of reduced heart rate in combination with $\beta$ -blocker, digoxin	4	80–160
Donepezil	Reversible ChEs	AChE > BuChE	43	93–96	CYP2D6 CYP3A4	70–80	Risk of elevated plasma levels in combination with ketokonazol (3A4), cimetidine, warfarin, digoxin	Risk of reduced heart rate in combination with $\beta$ -blocker, digoxin	1	5–10
Rivastigmine	Pseudo-reversible ChEs	AChE > BuChE	40	40	Cholinesterase Hydrolysis	0.6–2	No (low risk of interactions)	Risk of reduced heart rate in combination with $\beta$ -blocker, digoxin	2	6–12
Galantamine	Reversible ChEs	AChE > BuChE	85–100	18–34	CYP2D6 CYP3A4	6	Risk of elevated plasma levels in combination with ketokonazol (3A4), paroxetine (2D6), erythromycin (3A4)	Risk of reduced heart rate in combination with $\beta$ -blocker, digoxin	2, 3	24–32

AChE: Acetylcholinesterase; BuChE: Butyrylcholinesterase; ChE: Cholinesterase; ChEI: Cholinesterase inhibitor.

clinically significant. Although donepezil does not have a pronounced influence on the pharmacokinetic properties of digoxin, theophylline or warfarin in healthy subjects, minor alterations of theophylline, digoxin or warfarin plasma concentrations might become clinically relevant [8–13].

Donepezil undergoes an extensive hepatic first pass metabolism. Most of the metabolites are found in urine (e.g., 5-*O*-desmethyl donepezil, 6-*O*-desmethyl donepezil and donepezil-*cis*-*N*-oxide). Approximately 11–17% are excreted unchanged in urine [14]. Pharmacokinetic properties have been assessed in healthy subjects but not in patients with AD. The  $T_{max}$  and half-lives are longer, and the volume of distribution is larger in elderly than in younger volunteers [14].

### Tolerability

The predominant adverse effects of donepezil occur in the gastrointestinal tract, resulting in nausea, vomiting or diarrhea, and can be attributed to the cholinergic action of the drugs. The occurrence of the most common cholinergic adverse events is most pronounced in the first few weeks after initiating treatment. The incidence of side effects is higher during initiation of treatment or when doses are increased before steady-state is achieved. There is some evidence taken from an open-label titration study that a 6-week treatment period with donepezil preceding the escalation to donepezil 10 mg decreases the rate of adverse events [15]. Initiating treatment with a low dose and then escalating the dose slowly can usually reduce the incidence of adverse events.

Drug absorption rate is another factor that affects the incidence of side effects. Drugs with short half-lives show a rapid change in blood level. Certain side effects are more strongly related to changes in blood levels than to absolute blood levels. Therefore, side effects are often considerably worse during increasing or decreasing blood levels of the medication. Rivastigmine and galantamine have short half-lives and are rapidly absorbed. Drugs with short half-lives may cause cholinergic side effects more often than those with long half-lives. Coadministration of drug with food delays absorption and can lower the incidence of its side effects. Donepezil has a long half-life and probably does not require coadministration with food.

Particular caution should be used when administering ChEIs to patients with cardiovascular disease, such as sick sinus syndrome. However, no consistent patterns of clinically significant treatment effects in cardiovascular indices have been reported in the clinical trials of donepezil published to date, with no increase in serious arrhythmias found [15–21].

### Dosage & administration

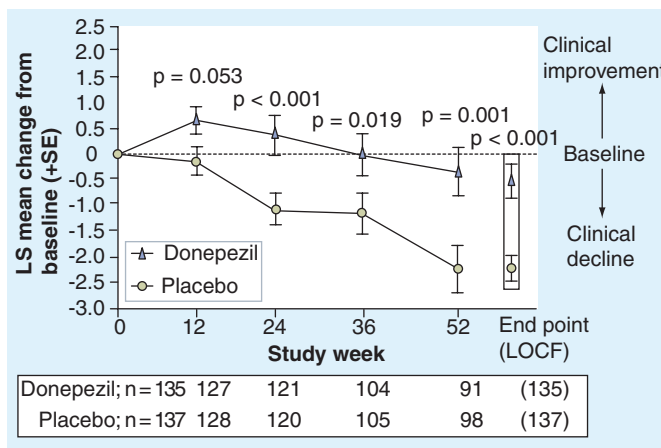
Donepezil is administered once daily in a dose of 5–10 mg, beginning with a dosage of 5 mg/day. An initial dose should be maintained for 4–6 weeks before increasing to 10 mg. In Japan, the recommended dose was lower than in other countries (3 mg daily increasing to 5 mg after 2–3 weeks) because of the higher incidence of poor metabolizers. However, according to an extension of the donepezil label to severe stage of AD in 2007, a dose of 5–10 mg has been approved in Japan.

**Clinical evidence supporting the use of donepezil**

Since 1996, several fully published, randomized, double blind, placebo controlled, multicenter studies have been conducted in the USA and Europe, enrolling approximately 3000 patients [15–18,20–22]. The studies covered a period of 12, 24 or 52 weeks and the donepezil dosage ranged from 1, 3 or 5 up to 10 mg/day. Patients in the studies had mild-to-moderate disease. Available outcome data covered domains including cognitive function, ADL, behavior, global clinical state and adverse events.

As primary efficacy measure, the Alzheimer’s Disease Assessment Scale-cognitive subscale score (ADAS-cog) or the Mini Mental State Examination (MMSE) was chosen in these studies. The ADAS-cog comprises 11 individual tests: spoken language ability (0–5), comprehension of spoken language (0–5), recall of test instructions (0–5), word finding difficulty (0–5), following commands (0–5), naming objects (0–5), construction drawing (0–5), ideational praxis (0–5), orientation (0–8), word recall (0–10) and word recognition (0–12). The total score ranges from 0 to 70, a high score indicating greater impairment. The MMSE has a maximum score of 30 points, with different domains: orientation to time and place; registration of three words; attention and calculation recall of three words; language; and visual construction. For cognition, patients treated with donepezil showed statistically significant improvements compared with placebo groups on the ADAS-cog or the MMSE score in these studies (FIGURE 2).

The Clinician’s Interview Based Assessment of Change-Plus (CIBIC plus) was often applied as a second primary efficacy in trials of treatment for AD. It provides a global rating of patient function in four areas: general, cognitive, behavior and ADL. Information is obtained from the caregiver and patients. The clinician then assesses the CIBIC plus, being blind to all other measures. As with the ADAS-cog, the CIBIC plus exhibited statistically significant improvement in global clinical state in subjects treated with donepezil compared with the placebo group. Although none of the studies routinely reported the effects of donepezil on ADL, benefits of treatment were seen on measures of ADL and behavior.



**Figure 2. Least-squares mean changes from baseline in the Mini-Mental State Examination score for patients treated with donepezil and placebo.**

LOCF: Last observation carried forward; LS: Least squares; SE: Standard error. Data from [21].

Donepezil appears to have a beneficial impact on behavioral and neuropsychiatric symptoms, such as hallucinations, distractibility, aberrant motor behavior and apathy [18,23,24]. The use of ChEIs, including donepezil, has also been reported to reduce caregiver burden and to delay nursing home placement [24–26].

Recently, several studies have suggested the efficacy of donepezil in patients with severe AD residing in the community or in nursing homes (TABLE 2) [27–29]. A multinational study comparing donepezil to placebo in severely ill patients still in the community showed similar findings [30]. It is therefore clear that there may be measurable benefits in treating patients suffering from severe AD with donepezil if they have never had a therapeutic trial with a ChEI. The question is whether these benefits are clinically relevant in late-stage AD. Several newer instrumentals may prove useful if adapted to the more severe stages of AD [31].

**Table 2. Selected randomized-controlled trials of donepezil in patients with severe Alzheimer’s disease.**

Study (year)	Subjects (n)	MMSE Range	Dose (mg/day)	Duration	Outcome measures	Main outcome	Ref.
Feldman <i>et al.</i> (2005)	290	5–12	5–10	24 weeks	CIBIC plus	Significant positive effect on CIBIC plus in donepezil group	[27]
Winblad <i>et al.</i> (2006)	248	1–10	5–10	6 months	SIB, ADCS-ADL-severe	Significant improvements on SIB and ADCS-ADL-severe scores in donepezil group	[29]
Black <i>et al.</i> (2007)	343	1–12	10	24 weeks	SIB, CIBIC plus	Significant improvements on SIB and CIBIC plus scores in donepezil group	[30]
Homma <i>et al.</i> (2008)	325	1–12	5 or 10	24 weeks	SIB, CIBIC plus	Significant improvements and significant dose-responses with SIB and CIBIC plus in donepezil group	[28]

ADCS-ADL: Alzheimer’s Disease Cooperative Study Activities of Daily Living scale; CIBIC plus: Clinician’s Interview-Based Impression of Change; MMSE: Mini-Mental State Examination; SIB: Severe impairment battery disease.

**Table 3. Comparative studies: donepezil versus galantamine or rivastigmine.**

Study (year)	Subjects (n)	Donepezil versus	Dose (mg/day)	Duration	Outcome measures	Main outcome	Ref.
Wilcock <i>et al.</i> (2003)	182	Galantamine	Donepezil: 10 Galantamine: 24	52 weeks	BrADL, MMSE, ADAS-cog/11, NPI	No statistical differences in BrADL. Significant differences favoring galantamine on ADAS-cog and MMSE scores in a subgroup of patients with moderate AD	[33]
Ancoli-Israel <i>et al.</i> (2005)	63	Galantamine		8 weeks	Sleep efficacy (measured by actigraphy)	No significant differences in sleep measures	[32]
Bullock <i>et al.</i> (2005 and 2006)	994	Rivastigmine	Donepezil: 5–10 Rivastigmine: 3–12	2 years	SIB, NPI, GDS, MMSE, ADCS-ADL	No significant differences in SIB, MMSE and NPI. Significant benefits favoring rivastigmine on GDS and ADCS-ADL. Younger patients showed greater responses to rivastigmine than donepezil	[34,35]

ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living scale; BrADL: Bristol Activities of Daily Living Scale; GDS: Global Deterioration Scale; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatric Inventory; SIB: Severe impairment battery disease.

TABLE 3 shows studies of comparative effectiveness between ChEIs. Two studies compared donepezil with galantamine in 245 patients. One study was a pilot trial undertaken primarily to evaluate the potential of galantamine to affect sleep in patients with AD and lasted only 8 weeks [32]. Neither galantamine nor donepezil were associated with decrements in sleep measurements. However, mean scores in all measures of sleep showed a tendency for minimal improvements in galantamine-treated patients and minimal decrements in the donepezil-treated patients. The same tendencies were present in caregiver sleep measures. Global function either improved or remained stable in a higher percentage of patients treated with galantamine than with donepezil. However, the trial was insufficiently powered because of the small sample size. The second study showed no statistical differences in the primary outcome of ADL function [33]. Changes in secondary outcomes of cognition, measured with the ADAS-cog and the MMSE, showed statistical differences favouring galantamine only in a subgroup of patients with moderate AD (MMSE scores between 12 and 18). This study showed differences in scores on the screen for caregiver burden and global function favoring galantamine over donepezil. Both studies reported that galantamine and donepezil did not differ with respect to serious adverse events. One large trial compared donepezil with rivastigmine in patients with AD over 2 years [34,35]. Measures of cognition and behavioral symptoms did not show statistically significant differences. Significant differences in global function and ADL favored rivastigmine. Rivastigmine provided significant benefits in a subgroup of patients younger than 75 years of age in some measures of behavior and function compared with older patients. Patients receiving rivastigmine reported more adverse events than those receiving donepezil, but serious events did not significantly differ.

The rivastigmine patch is the first transdermal treatment to be recently approved for AD in the USA and Europe. When given by once-daily rivastigmine patch, transdermal administration of rivastigmine prolongs  $T_{max}$ , lowers  $C_{max}$  and reduces fluctuation compared with a similar level of exposure obtained with oral administration. A randomized controlled trial has demonstrated that the target dose 9.5 mg/day rivastigmine patch provided similar efficacy to the highest rivastigmine capsule doses, yet with a threefold reduction in reports of nausea and vomiting [36]. The potential of a patch to improve the tolerability of rivastigmine, while permitting greater exposure, may result in improved treatment efficacy.

In general, although the pharmacological and pharmacokinetic profiles of the most widely used ChEIs have notable differences that may affect efficacy, the clinical significance of these differences remains hypothetical in the absence of large, randomized trials that compare the ChEIs with each other [37].

### Expert commentary

Over recent years, donepezil has shown favorable efficacy and tolerability in the treatment of AD [38], although most trials have some flaws in methodological assessment [39]. Patients with mild, moderate or severe AD treated with donepezil experienced benefits in cognitive function, ADL and behavior. There is also some evidence that the use of donepezil is neither more nor less expensive compared with placebo when assessing total health care resource costs [25,40]. A recent randomized controlled trial from the UK concluded that treatment of mild-to-moderate AD with donepezil was neither efficacious nor cost effective [41]. This study has some flaws which question the validity of these conclusions because the actual recruitment of 566 patients was far short of the intended recruitment of 3000, and was underpowered for achieving the original objectives. Birks reported that taking into

consideration the better tolerability of donepezil 5 mg/day compared with the 10 mg/day dose, together with the lower cost, the lower dose might be the better option [42]. Cost–benefit data are limited and require further investigation.

Although ChEIs are the current standard of care for AD, there is less agreement on how long patients should be treated with ChEIs. Long-term, open-label extensions of randomized controlled clinical trials with donepezil suggest sustained benefits for up to 5 years, in comparison with the expected decline of the natural course of the disease [43,44]. These possible disease-modifying effects have been further reinforced by a naturalistic study in which patients who were treated with ChEIs were found to be 2.5-times more likely to have slower progression of AD and also had a significantly reduced rate of nursing home admission than patients who never received ChEIs [45]. However, it is important to bear in mind that studies with open-label extensions have several biases, including selective dropout and survivor effects, and the results may not be generalizable to patients at large. Further studies are needed to prove the efficacy of donepezil for long-term prognosis of AD.

### Five-year view

In the coming years, significant advances in new therapeutic agents will enable us to offer more comprehensive and individualized pharmacotherapy at all stages of AD. In the USA and Europe memantine was the first approved treatment for severe AD. Memantine partially blocks NMDA receptors and prevents excess stimulation of the glutamate system, which influences learning and memory. The effects of memantine on cognition, behavior and ADL in moderate-to-severe AD have been studied in a number of controlled trials. A memantine monotherapy placebo-controlled trial in outpatients with moderate-to-severe AD reported slower rates of decline with memantine versus placebo in cognition and ADL function. Furthermore, there is some evidence that combination therapy with memantine and donepezil may have greater efficacy than donepezil alone [46,47].

The production and accumulation of amyloid- $\beta$  (A $\beta$ ) peptide is considered by many to be the key factor in the pathogenesis of AD. Currently, the main disease-modifying treatments target amyloid deposition. The development of active or passive immunization against A $\beta$  is still in developmental stages. The first human trial on immunotherapy was halted owing to the development of meningoencephalitis in 6% of the treatment group [48]. Currently, a Phase II trial involving a monoclonal antibody against A $\beta$  is in progress [101]. Other possible gateways of pursuit include immunoglobulin and immunization with shorter fragments of A $\beta$ , which may avoid the complication of meningoencephalitis.

Although the amyloid hypothesis has been confirmed in pre-clinical research, the ultimate validation of this hypothesis will require treatments that reduce amyloid levels and cause concomitant neurological clinical improvement in patients with AD. Furthermore, nonimmune methods to reduce A $\beta$  levels, such as those targeted to proteases that induce toxic A $\beta$  peptides, might ultimately be used in combination with immune approaches.

In clinical practice settings of dementia care, utilizing an individualized combination of pharmacologic and nonpharmacologic therapies leads to improved quality of life for both the patients and the caregiver. Recently, some studies suggested that psychosocial intervention, such as reality orientation, enhanced the effect of donepezil treatment alone [49–51]. In the coming years, significant development of combination therapies, including psychosocial intervention, will enable us to offer a more comprehensive approach to the treatment of patients with AD.

### Financial & competing interests disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Key issues

- Alzheimer's disease (AD) is the most common cause of dementia, and is characterized by an insidious onset and slow deterioration in cognition, activities of daily living, mood stability and social functioning. The pathological picture consists of neuronal cell loss, deposition of amyloid plaques, neurofibrillary tangles and secondary inflammation.
- The cholinergic hypothesis in AD states the degeneration of cholinergic neurons in the ventral forebrain causes disturbance in presynaptic cholinergic terminals in the temporal and parietal neocortex and hippocampus, which is important for memory disturbances and other cognitive symptoms.
- Cholinesterase inhibitors (ChEIs) increase the availability of acetylcholine by inhibiting acetylcholinesterase (AChE), the enzyme that degrades acetylcholine in the synaptic cleft.
- Donepezil is a mixed competitive and noncompetitive AChE inhibitor that shows a relative selectivity for AChE as compared with butyrylcholinesterase. Selective inhibition of central as opposed to peripheral cholinesterase might be expected to reduce the incidence of adverse events associated with ChEIs.
- Clinical trials have shown that donepezil produces clinically meaningful improvements of cognitive and global function, especially in patients with mild-to-moderate AD.
- Direct comparisons among ChEIs are limited and do not suggest important differences.
- Research advances in the molecular pathogenesis of AD have also led to new drug candidates with disease-modifying potential, which have now come to testing in clinical trials.

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