CHOLINESTERASE INHIBITORS AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER AND NON-ALZHEIMER DEMENTIAS

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In aging societies, the morbidity and mortality of dementia is increasing at a significant rate, thereby imposing burden on healthcare, economy and the society as well. Patients' and caregivers' quality of life and life expectancy are greatly determined by the early diagnosis and the initiation of available symptomatic treatments. Cholinesterase inhibitors and memantine have been the cornerstones of Alzheimer's therapy for approximately two decades and over the years, more and more experience has been gained on their use in non-Alzheimer's dementias too. The aim of our work was to provide a comprehensive summary about the use of cholinesterase inhibitors and memantine for the treatment of Alzheimer's and non-Alzheimers's dementias.

Keywords: *dementia, therapy, treatment, cholinesterase inhibitors, memantine*

A KOLINÉSZTERÁZ-GÁTLÓK ÉS A MEMANTIN HASZNÁLATA ALZHEIMER- ÉS NEM ALZHEIMER EREDETŰ DEMENTIÁKBAN

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Az öregedő társadalmakban a dementia morbiditása és mortalitása jelentős ütemben növekszik, kifejezett terhet róva így az egészségügyre, a gazdaságra és a társadalom egészére egyaránt. A betegek és gondozóik életminőségét és életkilátásait a mihamarabbi diagnózis és az elérhető kezelések megkezdése nagymértékben meghatározza. A rendelkezésre álló kolinészteráz-gátlók és a memantin megközelítőleg két évtizede az Alzheimer-kór terápiájának alappillérei, de az évek során egyre több tapasztalat gyűlt össze a nem Alzheimer-kór okozta egyéb dementiát okozó kórképekben való alkalmazásról is. Munkánk célja, hogy átfogó összefoglalót adjunk a kolinészteráz-gátlók és a memantin használatáról, jellemzőiről és hatásairól Alzheimer- és nem Alzheimer eredetű dementiákban.

Kulcsszavak: *dementia, terápia, kezelés, kolinészteráz-gátlók, memantin*

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Dementia is becoming a highly prevalent chronic neurodegenerative disease in the rapidly ageing population. Approximately 45-50 million people lived with dementia worldwide in 2015, and this number is expected to increase to 130 million by 2050. In addition to its huge economic burden, it has harmful effects on patients' and caregivers' quality of life and life expectancy. Recognition and assessment of dementia together with the development of effective and comprehensive care plans are important in reducing the disease burden. The common feature of disorders with dementia is the acquired, progressive and irreversible neuronal loss. The etiology is diverse, abnormal protein accumulation, stroke or trauma-associated cell loss can also lead to dementia[1].

Dementia refers to a clinical syndrome characterized by progressive cognitive decline that interferes with the ability to function independently. Patients with an objective cognitive involvement

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Table 1. *Main symptoms of dementia[1]. These symptoms can be present individually, but commonly various psychopathological features co-occur simultaneously in the same patient. Different profiles of neuropsychiatric symptoms could emerge in each subtype of dementia, even at early stages*

Cognitive deficits	BPSD	Sleep	Physical
Short-term memory loss	Aggression	Altered sleep-wake cycle	Gait impairment
Long-term memory loss (later stages)	Disinhibition	Rapid eye movement (REM) behavior disorder	Parkinsonism
Executive dysfunctions	Agitation		Seizures
Visuospatial disabilities	Anxiety		Myoclonus
Language disorders: anomia semantic deficits aphasia (fluent, non-fluent, logopenic)	Elation		Dysarthria, dysphagia
	Irritability		Incontinence
	Depression		
	Apathy		
	Delusions		
	Hallucinations		
	Anosognosia		

BPSD: behavioral and psychological symptoms of dementia

but preserved daily activity are considered to have mild cognitive impairment (MCI)[2]. In addition to the cognitive deficit, behavioral and psychological symptoms (BPSD), sleeping and movement disorders may also be associated **(Table 1)**.

BPSD affects a notable proportion of patients with dementia, irrespective of its subtype and is associated with poor outcomes such as distress, both in the person with dementia and the caregiver, long-term hospital and institutional stays and admissions, and misuse of medications[3].

Non-pharmacologic therapy primarily includes cognitive stimulation and rehabilitation, risk factor modification, social support, assistance with activities of daily living, long-term health care financial planning and providing support to caregivers. The currently available pharmacological treatments are only symptomatic, targeting neurotransmitter disturbances in the brain, aiming to slow the progression of dementia; disease-modifying pharmacotherapies are just entering to the clinical use with the approval of aducanumab by the Federal Drug Administration (FDA) in the USA in June, 2021[4].

Methods

Our aim was to summarize the effects and indications and recent experiences with cholinesterase inhibitors and memantine for the treatment of Alzheimer and non-Alzheimer dementias, by reviewing the existing literature using common online sources (eg, PubMed, Scopus). Recent available relevant studies were cited appropriately, but there was no aim to compile a systematic review.

Discussion

CHOLINESTERASE INHIBITORS

Alzheimer's disease (AD) is the most common cause of dementia, it accounts for 60-80% of all cases[5]. The main neurochemical alteration in AD is the damage of the cholinergic transmission **(Figure 1)** due to the progressive and excessive loss of cholinergic synapses and neurons, especially in the basal forebrain, as the main cholinergic center of the brain having heavy interconnections with the amygdala, hippocampus, entorhinal cortex and the neocortex, indicating a crucial role in modulation of memory- and attention-related processes[5]. Not only cognition but also psychiatric and behavioral symptoms have been associated with disturbances of the cholinergic transmission.

Due to the cell loss, acetylcholine (ACh) levels continuously decline as AD advances. In addition to the decreasing level of ACh, loss of pre- and postsynaptic nicotinic and muscarinic M_2 presynaptic receptors were found, while the number of postsynaptic M1 receptors did not change (but they were dysfunctional)[6, 7].

Anticholinergic drugs impair cognitive and memory functions and have a potential to induce psychotic symptoms, including hallucinations[3]. The negative cognitive effects of cumulative anticholinergic drugs in older adults may not be transient, cognitively normal adults taking anticholinergic medication had reduced total cortical and increased ventricular volumes. In addition, there is a significant longitudinal association between anticholinergic use and later progression to MCI or AD dementia[8].

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The possible ways to support the functioning of the affected cholinergic transmission are: (1) enhancing the synthesis of ACh (e.g. with precursors), (2) applying cholinergic receptor agonists or (3) prolonging the effect of ACh by inhibiting its elimination. The first two opportunities had no clinically meaningful benefits in AD and/or had been associated with high levels of adverse effects and poor tolerability[6, 9]. The third option is the group of cholinesterase inhibitors (ChEi).

Tacrine was the first ChEi used in clinical practice, but it is no longer available because of its side effects. Nowadays donepezil, rivastigmine and galantamine are the available drugs to treat AD **(Table 2)**. In addition, huperzine A is also licensed in China as an anti-AD drug with ChEi and non-cholinergic disease modifying effects, being also available as a nutraceutical in the USA[10].

In addition to AChE inhibition, donepezil has effects at molecular and cellular levels as well, including inhibition of glutamate-induced excitotoxicity, reduction of inflammatory effects through different mechanisms and induction of a neuroprotective isoform of AChE[11]. Galantamine is an allosteric potentiating ligand of the nicotinic ACh receptors, thereby has a potentiating role in learning and memory functions **(Figure 1)**[7, 11]. Rivastigmine also inhibits butyrylcholinesetrase[11].

ChEis have various dose-dependent cholinergic side-effects, including gastrointestinal (loss of appetite, nausea, vomiting and diarrhea), cardiac (bradycardia and heart blocks) and genitourinary (bladder outflow obstruction) symptoms, as well as insomnia, muscle cramps and weakness[11]. A slow titration dosing regimen is suggested to reach the recommended dose and minimize adverse effects. In case of intolerable side-effects, the drug should be discontinued and a different ChEi can be prescribed; there is no evidence of any differences between them in terms of efficacy in AD[1].

Alzheimer's disease

ChEis are approved for the treatment of mild and moderate AD dementia. In addition, donepezil and rivastigmine are also approved for use in severe stage of AD dementia[12, 13]. Use of ChEis in AD results improvement in cognitive functions, in global clinical state, and in activities of daily living (ADL)[14]. Cognitive function is usually assessed by using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) or Mini Mental State Examination (MMSE) tests. Compared to placebo, ChEis showed improvement on the ADAS-Cog (mean -2,7 points) and MMSE (mean 1,0 points) test scores after 6 months of treatment[15].

In addition to the cognitive improvement, ChEis have an influence on BPSD, especially on mood symptoms, apathy, and aberrant motor behavior[3]. Treatment with ChEis may delay admission to residential and nursing home care[14].

AD is a genetically, pathologically and clinically heterogeneous syndrome, therefore only approximately 40% of patients taking ChEis have a good response; however, it is difficult to predict who will respond to the drugs[16]. The pathological damage caused by the tau-containing neurofibrillary tangles (NFT) in the nucleus basalis of Meynert (nbM) might be a critical element determining this response. Depending on the involvement of the lim-

Table 2. *Main features of cholinesterase inhibitors*[1, 11]

Drug	Mechanism of action	Form	Dosage Minimum effective dose	Recommended dose	Metabolism Elimination (plasma half-life)
Donepezil	reversible AChE inhibitor + molecular and cellular level	tablet	1×5 mg	1×10 mg 1×23 mg*	CYP450 renal (70h)
Rivastigmine	pseudo-irreversible AChE and BChE inhibitor	capsule, oral solution	2×3 mg	2×6 mg	non-hepatic renal (1h)
		transdermal patch	–	9.5 mg/24h 13.3 mg/24h*†	
Galantamine	competitive reversible AChE inhibitor	capsule	1×16 mg	1×24 mg	CYP450 hepatic (8-10h)
	+ nicotinic receptor allosteric potentiating ligand	tablet, oral solution	2×8 mg	2×12 mg	

*treatment for moderate to severe AD, †: mild to moderate Parkinson's disease dementia[12, 13]

AChE: acetylcholinesterase, BChE: butyrylcholinesterase

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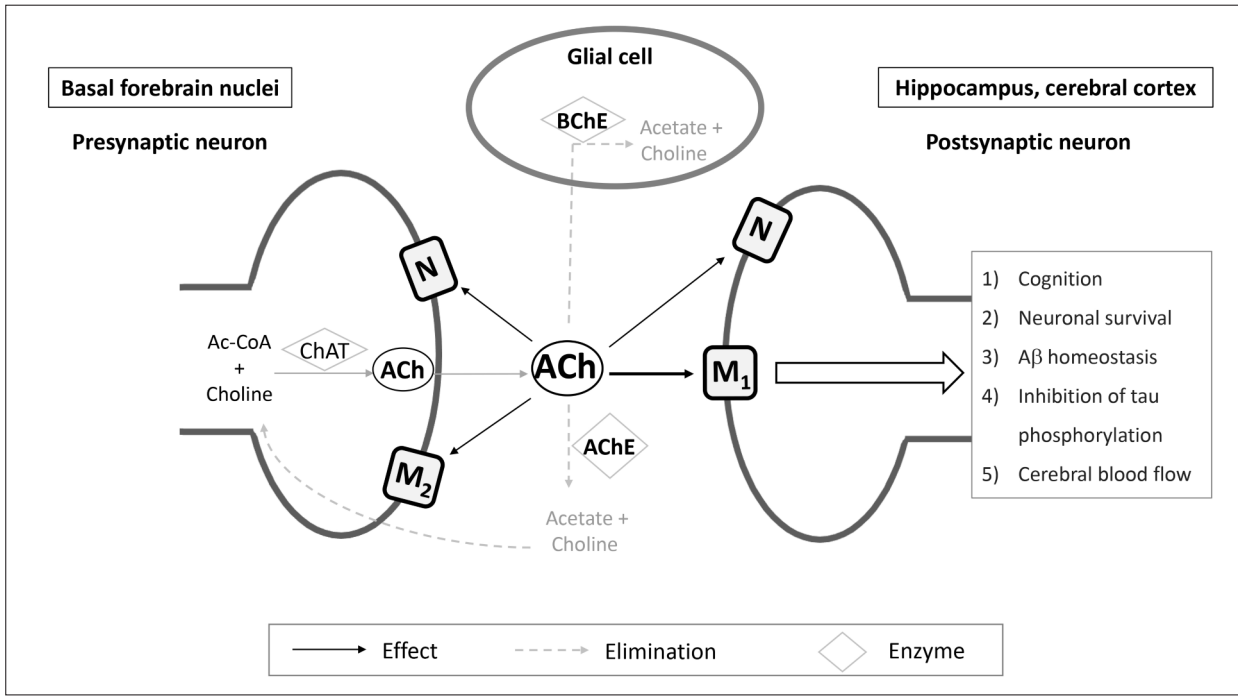

Figure 1. *The schematic representation of the cholinergic system of brain. Basal forebrain fibers originating from distinct neuron clusters differentially innervate separate areas of the cerebral cortex, hippocampus and amygdala. ACh is synthesized from two precursors, acetyl coenzyme A and choline by the enzyme ChAT, stored in vesicles and released by biochemical signals to the synaptic cleft, where it acts on different pre- and postsynaptic receptors. The main effects are mediated through M1 receptors. M2 receptor is the main inhibitory auto-receptor, contributing to the suppression of presynaptic ACh release. Among the N receptors, the homomeric α7 N receptor is one of the most abundant in the nervous system. Postsynaptic α7 N receptor enhances the neuronal firing rates contributing to the hippocampal long-term potentiation, a neuronal-level component of learning and memory. Activation of presynaptic nicotinic ACh receptors has been shown to augment the release of a number of neurotransmitters including ACh, monoamines, and glutamate. ACh is eliminated by the AChE and partially and especially in the the glial cells by the BChE. BChE activity is prominent in hippocampus, temporal cortical regions and it is attached to senile plaques in AD*[5-7]

Ac-CoA: acetyl coenzyme A, ChAT: choline acetyltransferase, ACh: acetylcholine, AChE: acetylcholinesterase, BChE: butyrylcholinesterase, Aβ: β-amyloid, M1 and M2: muscarinic receptors subtypes 1 and 2, N: nicotinic receptors

bic structures (including the nbM), three different subtypes of AD were described: (1) hippocampal sparing (relatively spared hippocampal formation compared to the neocortex), (2) limbic predominant (severely involved hippocampus compared to the relatively spared neocortex) and (3) typical AD pattern, where NFT pathology is balanced between the two forms. Greater NFT accumulation and the lowest number of surviving nbM neurons were observed in the hippocampal sparing type, compared to the typical AD and limbic predominant subtypes[17]. As a result of this, different patterns of NFT accumulation in the nbM are associated with different responses to ChEis. In addition to the neuropathological variations (including comorbid neuropathologies), environmental factors, cognitive profile at baseline, the degree of autonomy of the patients at the beginning of therapy and lifestyle might also affect the long-term response to ChEI treatment as well[16].

Mild cognitive impairment

There is uncertainty about the treatment of MCI with ChEis as the neuropathological heterogeneity of MCI makes it difficult to analyze the effect of ChEis. ChEis do not result in clinically significant improvement in cognitive functions and global clinical state of patients with MCI, although it is difficult to measure changes in mild symptoms, and side-effects were present[18]. Donepezil has been shown to reduce the progression of hippocampal atrophy in patients with mild and moderate AD and in patients in prodromal stage as well[19], raising the

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possibility of a disease-modifying effect of ChEis and a meta-analysis by *Matsunaga* et al[18] suggests that ChEis may reduce the MCI-dementia progression. However, these outcomes are not sufficient to recommend ChEis for MCI patients and ChEis are not approved in this indication. Emphasis should be placed on screening and regular monitoring of MCI patients to detect MCI-dementia conversion earlier and to start the treatment as soon as possible.

Non-Alzheimer dementias

In addition to AD, rivastigmine is also approved for the treatment of mild to moderate Parkinson's disease dementia (PDD) by the FDA and the European Medicines Agency[1]. However, ChEis could be beneficial in other types of dementias with proven cholinergic deficit, such as dementia with Lewy bodies (DLB) and vascular dementias (VaD)[20, 21]. Hereinafter the outcomes with ChEis in different types of dementia are summarized.

Dementia with Lewy bodies

In AD with concomitant Lewy bodies (LB), NFT pathology in the nbM is relatively milder compared to pure AD, however the loss of large cholinergic neurons is similar, suggesting the role of α-synuclein (the main constituent of LBs) in the process. The neuronal loss of the nbM is similar or more extensive in Parkinson's disease (PD) than in AD and even more pronounced in PDD and DLB cases[20].

PDD and DLB are clinically and pathologically overlapping disorders, also named as LB-associated dementias. The core clinical features of probable DLB are: (1) fluctuating cognitive functions, especially alertness and attention; (2) well-formed and detailed recurrent visual hallucinations; (3) REM sleep behavior disorder; (4) one or more spontaneous cardinal features of parkinsonism (bradykinesia, rigidity or resting tremor). The diagnosis is supported by (1) severe sensitivity to antipsychotics; (2) postural instability; (3) repeated falls; (4) syncope and other transient non-responsive episodes; (5) severe autonomic dysfunction; (6) hypersomnia; (7) hyposmia; and (8) BPSD signs, such as non-visual hallucinations, systematized delusions, apathy, anxiety or depression[22]. In general, PDD is diagnosed when cognitive impairment develops in the setting of well-established PD[23]. For the diagnosis of DLB, cognitive impairment must precede parkinsonian motor signs or it develops within one year after the parkinsonism[22]. LB mixed with AD pathology is common and direct biomarker evidence of LB pathology is not yet available for clinical diagnosis, therefore many DLB cases are missed or misdiagnosed.

In LB-associated dementias the use of ChEIs to treat cognitive decline, psychiatric disturbances, ADL, and global functions was effective without detrimental effects on motor function. For cognitive functions, donepezil was the most effective while galantamine did not have substantial effect. Behavioral symptoms (apathy, visual hallucinations and delusions) were significantly improved by rivastigmine[22, 24].

Vascular dementia

VaD, as the second most common cause of dementia, covers a broad spectrum of cognitive impairment caused by cerebrovascular diseases, including small vessel disease and territorial and strategic infarcts. It often occurs in conjunction with AD pathology resulting in mixed dementia[14], leading to difficulty in the differentiation of the origin of the cholinergic deficit seen in VaD. The cholinergic deficit found in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a pure form of VaD, suggests that cholinergic transmission is damaged in VaD as well[21]. Patients with donepezil (5 and 10 mg) or galantamine (16 and 24 mg) therapy showed improvement in cognitive tests, while rivastigmine had no substantial effect on cognition[25]. Examining a wider range of outcomes, the meta-analysis of *Jin* and *Liu*[26] found, that the effect of ChEis on cognitive functions was similar, but without improvement on ADL and BPSD domains. The clinical heterogeneity of VaD limits the general validity of outcome data, the effect of treatment on specific patients or subgroups might be different.

Frontotemporal dementia (FTD)

FTD is the second most common dementia subtype under 65 years of age, accounting about 10% of all dementia cases, encompassing diseases with heterogeneous clinical and pathological phenotypes. The cholinergic system is relatively preserved in FTD. Evidence suggests that ChEis are not effective in FTD or they might even worsen the condition by exacerbating behavioral symptoms[27].

Other conditions

In addition to the most common forms of dementia, there are several studies (most of them with small sample sizes) about the use of ChEis in other conditions with cognitive impairment.

In patients with Huntington's disease, medium-term use of ChEis improved the results of the verbal fluency tests, but short-term effect was not seen[28].

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Table 3. *Effects of memantine on different neurotransmitter systems[7, 32, 34]. Main effect of memantine is to antagonize an overactive glutaminergic system (causing neuronal cell loss) through the NMDA receptors. The other mechanisms of action are not fully elucidated but they probably have positive effects on learning and cognitive functions*

Neuro-transmitter	Normal function	Pathological function	Target receptor	Mechanism of action	Effect
Glutamate	Main excitatory system Learning, memory neuronal plasticity	Ca2+ influx induced cell death Increased amyloid production	NMDA	Uncompetitive antagonist	Reduce cell death Reduction of tau phosphorylation May upregulate NMDA receptor expression
Serotonin	Mediate fast excitatory synaptic transmission	Inhibition of LTP and memory	5-HT3	Non-competitive antagonist	Facilitates learning, cognitive performance Antiemetics
Acetyl-choline	Learning, memory, LTP Augment release of neurotransmitters, e.g. glutamate	Inhibition of LTP and memory	α7N	Non-competitive antagonist	Nicotinic receptor upregulation Paradox facilitation of LTP

LTP: long-term potentiation, NMDA: N-methyl-D-aspartate glutamate receptor, 5-HT3: 5-hydroxytryptamine 3 serotonin receptor; α7 N: homomeric α7 nicotinic acetylcholine receptor

Approximately 70% of patients with multiple sclerosis are affected by cognitive deficits at all stages and in all subtypes of the disease. ChEis did not result in improvement in memory or BPSD domains[29].

In the chronic phase of traumatic brain injury (TBI), hypocholinergic state contributes to cognitive decline. An attempt was made to perform a meta-analysis of the studies using ChEis in TBI, but because of their low number and the methodological weaknesses, no convincing evidence was concluded[30].

In a randomized controlled trial of rivastigmine (preferred due to its lower risk of interactions with antiretroviral drugs) in HIV-associated neurocognitive disorder (HAND), psychomotor speed was improved, but no significant influence on cognitive functions was seen[31].

MEMANTINE

In addition to the cholinergic hypothesis, overstimulation of the glutamatergic system (with chronic activity of the N-methyl-D-aspartate (NMDA) receptors) leading to excitotoxicity and subsequent neuronal degeneration, is also implemented in the pathogenesis of AD[32]. The primary mechanism of action of memantine is its NMDA receptor antagonism, however it also acts on other ion channel receptors of the serotonergic and the cholinergic systems with supportive effects in memory and learning processes and on its therapeutic tolerability[32] **(Table 3)**. In animal models, memantine treatment caused reduction in Aβ brain levels and amyloid plaque burden, with decrease in the neuroinflammatory biomarkers too[33].

Memantine is approved for the treatment of moderate to severe AD[34]. It is usually a second-line treatment when progression of symptoms is observed in patients with already on ChEi therapy, or it can be the first option in patients with initial evaluation in moderate to severe dementia stage or in those cannot tolerate ChEis[1]. In memantine add-on cases (i.e. in patients already using ChEis), continuation of the ChEi is recommended, since combination of the agents is more effective on cognitive, ADL and BPSD symptoms than their isolated use[35]. Fixed combination formulation is also available, containing memantine and donepezil[1] and there are recently designed memantine-ChEi and memantine-antioxidant hybrid small molecules in experimental phase for multitarget approaches as well[36]. To minimize side effects, a slow titration dosing over 4 weeks is recommended to reach the target dose of 20 mg/day. Memantine is mostly well tolerated, the most common side-effects are headache and constipation[1].

In clinical studies, a small, but significant benefit was observed in moderate and severe AD, but not in mild AD[34]. Patients taking memantine showed less decline in language and memory subscales but not in praxis on the ADAS-Cog[37]. Memantine also had a beneficial effect on BPSD

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Table 4. *Summary of the indications of available antidementia drugs*

Drug	Indication Approved	Not approved (off-label)
Donepezil	Mild to moderate AD	PDD
	Severe AD*	DLB
		VaD
		Huntington's disease
	Mild to moderate AD	DLB
Rivastigmine	Severe AD*	HAND
	Mild to moderate PDD	Huntington's disease
Galantamine	Mild to moderate AD	VaD
Memantine	Severe AD	PDD
		DLB
		VaD
		FTD
		HAND

It is a non-exhaustive list, limited to the diseases aforementioned in our work.
*not approved in all countries, but e.g. in USA
AD: Alzheimer's disease, PDD: Parkinson's disease dementia, DLB: dementia with Lewy bodies, VaD: vascular dementia, HAND: HIV-associated neurocognitive disorder, FTD: frontotemporal dementia

complications, such as delusion, agitation, aggression, disinhibition and possibly on hallucination and irritability, especially in moderate cases. Patients with combination therapy (ChEi+memantine) may have more benefits on agitation and aggression and the time to nursing home admission was delayed[38]. Furthermore, no deterioration was observed in case of negative symptoms (e.g. apathy and depression) with memantine treatment, so there is no need to stop the therapy when negative symptoms appear[39]. Moreover, due to the 5-HT_3 receptor antagonistic properties of memantine, it can reduce the gastrointestinal side-effects caused by the ChEis[32].

As with the ChEis, there were attempts with memantine in other indications than AD, however much less experience is available. In patients with PD, PDD and DLB, memantine showed positive impact on global impression, but no effect on cognition and ADL[40]. On non-cognitive symptoms, no significant benefit was found[14].

Memantine probably has a small positive effect on cognition, global functions, behavior and mood without effect on ADL in VaD patients[26, 34]. In FTD and HAND, studies have shown that memantine has a mild, but not significant clinical effect[34].

Conclusion

In the last twenty years, a lot of experience has been gained about the use of ChEis and memantine in Alzheimer and non-Alzheimer dementias. They are approved for the treatment of Alzheimer dementia, while rivastigmine is also approved for PDD. However, their use in other disorders with cognitive decline are important too **(Table 4)**. In rarer types of dementia, further studies with larger sample sizes are necessary to reach reliable evidences. Accurate diagnosis of the type of dementia is essential in order to provide effective and safe treatment with ChEis and memantine.

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