



Use of Cholinesterase Inhibitors in Non-Alzheimer's Dementias

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Abstract

Non-Alzheimer's dementias constitute 30% of all dementias and present with major cognitive and behavioral disturbances. Cholinesterase inhibitors improve memory by increasing brain acetylcholine levels and are approved symptomatic therapies for Alzheimer's disease (AD). They have also been investigated in other types of dementias with potential cholinergic dysfunction. There is compelling evidence for a profound cholinergic deficit in Lewy Body dementia (LBD) and Parkinson's disease dementia (PDD), even to a greater extent than AD. However, this deficit is difficult to objectivize in vascular dementia (VaD) given the increased comorbidity with AD. Furthermore, there is minimal to no evidence for cholinergic loss in frontotemporal dementia (FTD). Although cholinesterase inhibitors showed significant improvement in cognitive, behavioral, and functional measures in both LBD and PDD clinical trials, only rivastigmine is approved for PDD, due to the heterogeneity of the scales used, the duration of trials, and the limited sample sizes impacting data interpretation. Similarly, the interpretation of findings in VaD trials are limited by the lack of pre-defined inclusion criteria for 'pure VaD' and the wide heterogeneity of patients enrolled with respect to location and extent of cerebrovascular disease. In FTD patients, cholinesterase inhibitors were mostly associated with worsening of cognitive and behavioral symptoms. In non-AD dementias, cholinesterase inhibitors were well tolerated, with increased reports of mild to moderate cholinergic side effects and a non-significant trend for increased cardio and cerebrovascular events with rivastigmine in VaD, justifying their cautious use on a case-by-case basis, especially when there is evidence for cholinergic deficit.

1 Introduction

According to the World Health Organization (WHO), there are 50 million people living with dementia worldwide, and ten million new cases every year, costing 818 billion US dollars, and causing a substantial socio-economic burden [1]. In the most updated version of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), 'dementia' has been renamed 'major neurocognitive disorder—MNCD' and referred to as a significant decline from a previous level of performance in one or more cognitive domains (attention, executive functioning, learning and memory, language, perceptual-motor or social cognition), interfering with independence in activities of daily living (ADL) [2]. Subtypes of MNCDs include Alzheimer's disease (AD),

Key Points

Basic science and functional imaging studies provide evidence for cholinergic deficits in Lewy body dementia, Parkinson's disease dementia, and certain subtypes of vascular dementia. There is no strong evidence for cholinergic impairment in frontotemporal dementia.

In clinical studies, cholinesterase inhibitors show preliminary significant positive effects on cognitive and behavioral outcomes in Lewy body dementia and Parkinson's disease dementia, resulting in significant improvement of activities of daily living and functional status, but they were associated with worsening of cognition and behavior in frontotemporal dementia. Data from vascular dementia trials are mixed, depending on the population included and high comorbidity rates with Alzheimer's disease.

There is a need for large and better designed randomized controlled studies involving more homogeneous patient populations, followed for a longer period. Learning more about the pathophysiology of the cholinergic system in non-Alzheimer's dementias may improve our understanding of the role of cholinesterase inhibitors in the management of these disorders.

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vascular dementia (VaD), dementia with Lewy Bodies (DLB), frontotemporal lobe degeneration (FTD), Parkinson's disease dementia (PDD), traumatic brain injury (TBI)-related dementia and dementia due to Human Immunodeficiency Virus (HIV), but AD contributes to up to 70% of all dementia cases [1]. Hence, research into drug development for AD has been prioritized, hoping that what is learnt from these studies would be generalized to other MNCDs that share the same pathophysiology of toxic proteins' aggregation and cell injury [3]. Despite enormous research funds, no disease-modifying pharmacotherapies have been developed yet. Current US Food and Drug Administration (FDA)-approved therapies are symptomatic in nature, targeting neurotransmitter disturbances in the brain [4]. The cholinergic hypothesis in AD describes presynaptic loss of cholinergic neurons and underlies the approval/use of cholinesterase inhibitors (ChEIs) [5]. These medications work as cognitive enhancers by inhibiting the enzymes acetylcholinesterase (AChE) and/or butyryl cholinesterase (BuChE) responsible for the catabolism/breakdown of acetylcholine in the brain [6]. They include donepezil, rivastigmine, and galantamine, all equally effective for the treatment of cognitive and neuropsychiatric symptoms in AD [7]. However, rivastigmine has the unique property of dual 'pseudo-irreversible' inhibition of both AChE and BuChE, which can last for up to 12 h [6]. BuChE is thought to hydrolyze excess acetylcholine, especially when acetylcholinesterase levels are depleted, which has been seen with progression of dementia [8]. Therefore, its inhibition may further enhance cholinergic neurotransmission in the brain. Given the fame surrounding the cholinergic hypothesis in AD and the lack of development of newer therapies, researchers attempted to explore the effectiveness and safety of cholinergic therapies in other forms of MNCDs with potential underlying presynaptic cholinergic dysfunction [9]. This led to the FDA approval of rivastigmine as a symptomatic treatment for mild to moderate PDD in 2007 [10].

The aim of this paper is to update the readers about the evidence behind ChEIs' use in non-AD MNCDs. For this purpose, we summarized the evidence behind cholinergic impairment in other forms of dementias and reviewed relevant efficacy/tolerability and safety clinical data of these therapies in DLB, PDD, VaD, and FTD. PubMed and MEDLINE databases were searched for articles published up to January 2019 using the following keywords: vascular dementia, frontotemporal (lobar) degeneration, frontotemporal dementia, parkinson disease (dementia), cholinesterase inhibitor, acetylcholinesterase, butyrylcholinesterase, rivastigmine, donepezil, galantamine, and non-alzheimer's dementia.

2 Cholinergic Impairment in Neurodegenerative Disorders

The cholinergic system is a complex network of projections from cholinergic nuclei into different brain areas. The first group of cholinergic neurons is in the basal forebrain and corresponds to nuclei in the medial septum (Ch1), ascending and horizontal limbs of the diagonal band of Broca (Ch2 and 3), and the nucleus basalis of Meynert (NBM) (Ch4). They project to the cortex, hippocampus, olfactory bulb, and amygdala and are thought to be implicated in the pathophysiology of AD [11, 12].

A second group of cholinergic neurons consists of the large, aspiny cholinergic interneurons of the caudate nucleus and putamen, whereas a third group is localized in the brainstem and involves Ch5, 6, 7, and 8, projecting mostly to the thalamus, hypothalamus, globus pallidus, and the forebrain cholinergic nuclei [12].

Patterns of cholinergic degeneration across non-AD MNCDs are presented below.

2.1 Dementia with Lewy Bodies (DLB)

DLB is the second most common, pure MNCD after AD, and is characterized by the accumulation of α -synuclein proteins in the cytoplasm of brainstem nuclei, subcortical regions, and cerebral cortices [13]. The revised core features of DLB include fluctuating cognition, recurrent visual hallucinations, rapid-eye-movement (REM) sleep behavior disorder that may precede the cognitive decline, and one or more spontaneous parkinsonian signs such as bradykinesia, rest tremor or rigidity [14]. It is usually diagnosed when cognitive decline occurs before or concurrently with parkinsonian features [13]. There is evidence regarding a significantly increased cholinergic deficit in DLB compared with AD, affecting not only the basal forebrain (Ch1–4) but also mid-pontine cholinergic nuclei Ch5 and 6 neurons as demonstrated by MRI and AChE and vesicular acetylcholine transporter positron emission tomography (PET)-imaging studies [12, 15]. These findings were further confirmed using choline acetyltransferase immunohistochemistry staining: greater cholinergic depletion in the brainstem was found in DLB brains in comparison with AD or control brains, independent of the presence of a REM sleep behavior disorder [16]. Perry et al. were able to demonstrate extensive reduction in choline acetyltransferase activity in the temporal cortices of DLB patients with visual hallucinations [17]. Surprisingly, profound cholinergic neuronal loss and choline acetyl transferase depletion occur very early in DLB compared with later stages in AD [18]. Moreover, there are significant reductions in α 4 β 2 nicotinic acetylcholine receptor binding in the frontal, temporal and cingulate cortex, and

striatum of patients with DLB, contrasting with an increase in the occipital lobe, the latter correlating with the occurrence of visual hallucinations in these patients [19].

2.2 Parkinson's Disease Dementia (PDD)

PDD is a late complication of Parkinson's disease, with an estimated point prevalence of 25–30%. Up to 90% of patients will develop dementia if they survive beyond 10 years after the diagnosis [20]. In addition to α -synuclein pathology, β -amyloid deposits seem to play a pivotal role in up to one-third of patients with PDD, leading to an earlier and more rapid cognitive decline [20].

Evidence for both pre- and post-synaptic cholinergic deficits in PDD have been demonstrated using PET and single-photon emission computed tomography (SPECT) imaging with radioligands for cholinergic markers [21]. Presynaptic cholinergic dysfunction is greater in PDD compared with AD as reflected by cortical and thalamic decrease in AChE activity [22]. Due to denervation hypersensitivity, there is also an increase in postsynaptic cortical muscarinic acetylcholine receptors [23]. Interestingly, neocortical cholinergic deficit was found to be more pronounced with an increased duration of PD prior to dementia diagnosis [24].

2.3 Vascular Dementia (VaD)

VaD is one of the most common MNCDs after AD, accounting for approximately 15% of all dementia cases [25]. It results from different vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease) that damage blood vessels, reducing their ability to supply sufficient oxygen and nutrients to the brain [26]. It was previously thought that only large cortical infarcts were responsible for vascular cognitive impairment, however, other subtypes of VaD have been identified including subcortical VaD (sVaD) of the Binswanger's type (lacunar infarcts/extensive white matter lesions) and mixed vascular pathology with AD [25].

The biggest question is whether cholinergic dysfunction reported in VaD cases stems from concomitant AD pathology (mixed dementia) or is related to pure vascular changes in the absence of pathological evidence for AD in the brain. This has been difficult to assess since the cholinergic system and cerebral blood flow seem to be inter-related: acetylcholine, as a vasodilator, is known to regulate cerebral blood flow, but also reduced blood supply due to ischemic infarcts leads to hypoperfusion of cholinergic neurons/projections in a pattern that is largely dependent on the localization of the infarct [27].

In hypertensive, stroke-prone rat models of VaD, there is a significant reduction in acetylcholine concentrations in the cerebrospinal fluid (CSF) compared with normal rats [28], in

addition to a reduction in choline acetyltransferase responsible for acetylcholine synthesis in the cortex, hippocampus, and striatum [29]. Postmortem human studies yielded mixed results: in patients with dementia of the Binswanger type and multiple small infarct dementia, acetylcholine CSF concentrations were shown to be significantly reduced compared with controls ($p < 0.001$), but significantly higher compared with levels in patients with AD ($p < 0.001$) [30]. In one study involving 9 VaD cases, 10 mixed cases, 10 AD cases, and 12 controls, patients with mixed dementia had evidence of greater cholinergic deficits compared with controls and pure VaD ($p = 0.001$) [31]. In another larger study involving 13 cases of infarct brain tissue, 11 with sVaD, 29 with concurrent VaD and AD, 12 AD brains and 23 controls, there was evidence of cholinergic loss only in mixed dementia brains compared with controls, as reflected by significant reductions in choline acetyltransferase activity measured in Brodmann areas 9 and 20/21. Paradoxically, there was a significant 27% increase in choline acetyltransferase activity (increase in cholinergic transmission) in those with pure infarct dementias [32].

These findings contrast with autopsy results of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a purely genetic form of VaD showing evidence for cholinergic neuronal deficit and denervation, in patterns that vary, however, from those with AD [33, 34]. More recently, using diffusion tensor imaging (DTI), researchers were able to demonstrate impairment in white matter fibers mapping to the cholinergic system in patients with early vascular cognitive impairment. However, no atrophy of the NBM was identified, unlike what is typically seen in patients with AD [35]. Improved knowledge of the anatomy of the cholinergic pathways and their relation to the vascular territories where an interruption can occur may consequently improve our understanding of specific cholinergic deficits in certain types of VaD [36]. Additionally, the 'cholinergic anti-inflammation pathway' has been proposed as another hypothesis underlying the efficacy of cholinesterase inhibitors in VaD, due to the presence of nicotinic receptors on immune cells, modulating cytokine release and ischemic injuries [37]. Rivastigmine might theoretically be beneficial for the sVaD subtype, since imaging studies have shown that this drug significantly improves blood flow in cerebral frontal areas known to be associated with subcortical executive function and behavior [38].

2.4 Frontotemporal Dementia (FTD)

FTD describes a cluster of neurocognitive syndromes that present with impairment of executive functioning, changes in behavior, and a decrease in language proficiency associated with degeneration of the frontal and anterior temporal lobes [39]. Its underlying pathology consists of neurotoxic

deposition of either microtubule-associated protein tau (MAPT) or TAR DNA-binding protein weight 43 kDa (TDP-43) or the fused-in sarcoma (FUS) protein aggregates [40]. To date, there is a lack of evidence for consistent cholinergic deficit in FTD patients in the absence of another comorbid MNCD. Despite some evidence for loss of cholinergic neurons in the nucleus basalis, cholinergic pathways to the cortex seem to be intact. In addition, although levels of choline acetyl transferase and acetylcholinesterase may be reduced in the NBM, they are preserved or even increased in the frontal, temporal, and parietal cortex [41, 42]. However, cholinergic deficit may be relatively more pronounced in the primary progressive aphasia and cortico-basal syndrome subtypes when compared with the behavioral FTD subtype [42]. More recently, in a progranulin-deficient FTD mouse model, treatment with a nicotinic $\alpha 7$ acetylcholine receptor agonist was shown to reduce neuroinflammation and compulsive behavioral disturbance. This compelling new role of the cholinergic system in brain inflammation merits further exploration [43].

3 Efficacy of Cholinesterase Inhibitors (ChEIs) in Non-Alzheimer's Disease (AD) Dementias

3.1 DLB

3.1.1 Galantamine

One open-label study investigated the efficacy of galantamine (8–24 mg daily) on cognition, behavior, and global functioning in 25 patients with mild–moderate DLB, at 12 and 24 weeks of treatment [44, 45]. At 12 weeks, galantamine was associated with a statistically significant improvement in cognition as measured by the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog) (– 6.63 points, $p=0.004$), but not the Mini-Mental State Examination (MMSE) ($p=0.05$). It also improved neuropsychiatric symptoms with a 5.04-point decrease ($p=0.003$) in the Neuropsychiatric Inventory (NPI)-4 (delusions, hallucinations, apathy, and depression) score, as well as sleep disturbances, as measured by the Pittsburgh Sleep Quality Index (PSQI) (– 6 points; $p=0.016$). Global functioning was also improved with a significant 0.95-point decrease in the Clinical Global Impression of Change scale (CGIC) ($p=0.02$), but there was no change in ADL evaluated using the Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL). Fluctuations in alertness assessed by the clinician, and one-day fluctuation scales were shown to improve significantly ($p=0.0006$ and 0.0003 , respectively).

Similarly, at 24 weeks, there was an 8.2-point improvement in the NPI-12 ($p=0.01$), especially in the hallucinations and the night behaviors components, in addition to sleep symptoms on the PSQI ($p=0.015$). Global functioning assessed through the ADCS-CGIC improved significantly from 3.9 to 3.4 ($p=0.01$), but without a change in the ADL. Statistically significant beneficial effect on cognition was only evidenced with the ADAS-cog ($p=0.02$), and not the MMSE. One-day fluctuations and clinical fluctuations also improved significantly ($p=0.025$ and $p=0.001$, respectively).

3.1.2 Rivastigmine

The most important study that investigated the use of rivastigmine in DLB is a multicenter, double-blind, randomized, placebo-controlled trial (RCT) published in 2000 in which 120 participants with mild to moderately severe DLB received 12 mg/day of rivastigmine for 20 weeks [46]. The drug was associated with a statistically significant improvement in the behavioral symptoms, notably apathy, indifference, anxiety, delusions, hallucinations, aberrant motor behavior, depression/dysphoria, and agitation/aggression assessed using the NPI-4 and -10. There was also a non-significant trend of improvement in cognition assessed through the Clinical Global Change-Plus (CGC-plus) and the MMSE ($p=0.085$ and $p=0.072$, respectively). However, a 96-week open-label trial involving 29 patients on rivastigmine 6 mg daily demonstrated that the early benefits on behavioral disturbances and cognition obtained at weeks 12 and 24 were not significantly maintained long-term (beyond 36 weeks) [47].

A small case series also showed beneficial effects of rivastigmine on neuropsychiatric symptoms and cognition in seven of the eight patients described, as measured by the NPI and the Modified MMSE scores. Fluctuation of cognition and independence in ADL were also subjectively reported to be improved in these patients. Additionally, six patients had an improvement of daytime somnolence and/or nocturnal sleep disturbance [48], which was also corroborated in another study showing a trend into normalization of the sleep pattern with this drug [49]. In a larger case series (30 DLB patients), rivastigmine (average dose 7.6 ± 2.9 mg/day) was shown to enhance cognition (increase in the MMSE score from 21.6 to 23.5; $p=0.03$) and improve behaviors (decrease in the NPI score from 25.7 to 16.1; $p=0.003$), especially hallucinations ($p=0.003$), anxiety ($p=0.01$), and sleep disorders ($p=0.01$) [50].

3.1.3 Donepezil

In a 14-week double-blind RCT including 140 patients with DLB, donepezil at the doses of 3, 5, and 10 mg/day

significantly improved cognition measured by the MMSE ($p < 0.001$, $p < 0.001$, $p = 0.001$, respectively) [51]. On the behavioral outcome measures, donepezil was found to improve the NPI-2 and -4, but not the NPI-10 with doses of 5–10 mg daily. Global functioning improved in all groups as shown by a significant increase in the Clinician's Interview-Based Impression of Change, plus carer interview (CIBIC-plus) ($p < 0.001$ in all active groups) and the improvement was not dose-dependent. Caregiver burden measured by the Zarit Burden Interview (ZBI) only showed a significant decrease in the 10-mg active group ($p = 0.004$), but this result was not significant after baseline value adjustment. The 52-week extension open-label study with donepezil 3–5 mg/day demonstrated lasting effects on cognition and neuropsychiatric symptoms but not on caregiver burden [52].

In a second double-blind RCT, 142 DLB patients were randomized to receive donepezil 5 or 10 mg/day or placebo for 16 weeks [53]. In the Full Analysis Set (FAS), MMSE scores improved in those who were on 10 mg/day (mean difference 1.6; $p = 0.016$), and in the Per-Protocol Set (PPS) analysis, they improved in both the 5- and the 10-mg/day groups ($p = 0.025$ and $p = 0.004$, respectively). The subsequent 36-week extension open-label trial included 110 patients on donepezil 10 mg/day and showed sustained cognitive improvement for 52 weeks ($p < 0.001$). Participants who received placebo in the RCT showed an improvement in their MMSE scores after starting active treatment. NPI scores also improved in all participants, including those who were previously on placebo. Increasing the donepezil dose from 5 mg in the RCT to 10 mg in the open-label trial showed a remarkable impact on both cognition and behavioral measures [54].

To explore this dose-dependent improvement in cognition, a follow-up pharmacokinetic analysis showed a significant positive correlation between plasma donepezil concentration and changes in MMSE scores ($p = 0.04$), in addition to a non-statistically significant trend for correlation between the dose and the NPI scores [55]. Moreover, Mori et al. used pooled data from these studies to investigate changes in MMSE subitem scores from baseline to week 12 [56]. They found a statistically significant positive impact on orientation to time ($p < 0.001$), place ($p = 0.026$), serial sevens test ($p = 0.022$), repetition ($p = 0.045$), three-step command ($p = 0.018$), and copying ($p = 0.03$). The best responders to donepezil in terms of MMSE score were patients with specific baseline scoring on MMSE subitems: serial sevens ≥ 1 and delayed recall ≥ 1 , serial sevens ≥ 1 and copying = 0, delayed recall ≥ 1 and copying = 0, serial sevens ≤ 3 and delayed recall ≥ 1 and copying = 0. In these subgroups, MMSE improved by 3.5 ± 3.1 as compared with 2.19 ± 3.25 for the overall population. The higher the number of these conditions, the higher the likelihood to benefit from the donepezil treatment ($p = 0.001$).

Several small open-label trials (ranging between 4 and 22 participants) reported similar positive results on cognition and behaviors using donepezil (5–15 mg/day) in DLB patients [57–60].

As for REM-sleep behavior disorder, it was particularly investigated in a recent open-label trial including 16 patients with mild to moderate DLB, of whom 50% had at least one sleep disturbance at baseline [61]. This number decreased to 37.5% with donepezil 5 mg/day. On actigraphy measurements, donepezil was also found to improve Average Activity Count (AAC) per minute from 31.3 to 23.9 ($p = 0.044$) and Wake After Sleep Onset (WASO) from 73.3 to 58.6 ($p = 0.03$). However, in another case report, donepezil 5 mg/day was associated with decreased sleep efficiency, increased sleep latency, and decreased slow-wave sleep yielded by polysomnography measures, contrasting with subjective reports of improvement in insomnia by the patient, and a concordant decrease in the PSQI score from 12 to 9 [62].

On the other hand, visual hallucinations were reported to have improved with a small dose of donepezil 1.5 mg daily, and to have recurred upon discontinuation of treatment [63]. Two other small open-label studies reported similar improvement in visual hallucinations with different doses of donepezil starting at 3 mg daily up to 10 mg daily, with a possible dose-dependent effect [64, 65].

3.2 PDD

3.2.1 Rivastigmine

Rivastigmine in both oral and transdermal/patch formulations is FDA-approved for PDD: The EXelon in PaRkinson's disEaSe dementia Study (EXPRESS), a 24-week, multicenter RCT included 501 mild/moderate PDD patients on rivastigmine 3–12 mg/day. It showed a statistically significant improvement in cognition, behaviors, global functioning, and ADL as reflected by the ADAS-cog ($p < 0.001$), the MMSE ($p = 0.03$), the Cognitive Drug Research computerized assessment system power of attention tests (CDR power of attention) ($p = 0.009$), the Delis–Kaplan Executive Function System D-KEFS ($p < 0.001$), the clock drawing test ($p = 0.02$), the NPI-10 ($p = 0.02$), the ADCS-CGIC ($p = 0.007$), and the ADCS-ADL ($p = 0.02$) compared with placebo [66]. The 48-week treatment extension study that included 273 patients showed that upon switching to rivastigmine, patients in the original placebo group experienced a 2.8-point improvement in their ADAS-cog scores between weeks 24 and 48. This improvement in cognition was of a similar magnitude to that seen in the original rivastigmine group during weeks 0–24. Thus, the original placebo group appeared to catch up with those patients who had been receiving rivastigmine for the entire study (double-blind and active treatment extension). The effects on cognition and

behaviors reported at week 24 in the original rivastigmine group were also maintained at week 48 [67].

3.2.2 Galantamine

In an 8-week, open-label study including 16 patients with PDD [68], galantamine (8–16 mg daily) was associated with a statistically significant improvement on the clock-drawing test ($p=0.016$) but a non-significant trend for improvement on the MMSE ($p=0.09$) and verbal fluency ($p=0.16$). The treatment was, however, beneficial for hallucinations: 78% of patients with hallucinations at baseline reported improvement and 33% reported complete resolution. Interestingly, 6 out of 13 patients (46%) reported an improvement of parkinsonian symptoms with the treatment and 50% of them had marked improvement with a decrease of Hoehn and Yahr from stage 4 to stage 2.

In a similarly designed 24-week study including 41 patients with PDD [69], galantamine 16 mg daily was associated with a significant improvement in the MMSE and ADAS-cog at weeks 12 and 24 ($p<0.05$), and a significant decrease in the NPI-12 at weeks 12 ($p=0.03$) and 24 ($p=0.009$), especially for the hallucinations component ($p=0.0002$). Galantamine also improved anxiety ($p=0.04$), apathy ($p=0.006$), and daytime drowsiness ($p=0.044$). This resulted in a significant improvement of caregiver burden at weeks 12 ($p=0.03$) and 24 ($p=0.007$), as well as an improvement of the Disability Assessment for Dementia (DAD) scores ($p=0.003$ at weeks 12 and 24). Interestingly, the mean changes in the Frontal Assessment Battery (FAB), and the clock drawing test were greater in patients with hallucinations at baseline compared with those without ($p=0.03$ and $p=0.048$, respectively).

3.2.3 Donepezil

Several small open-label trials involving 11–35 patients with PDD investigated the use of donepezil (5–10 mg daily) for up to 20 weeks [60, 70–72]. All but one [70] demonstrated significant improvement in the MMSE, ADAS-cog, NPI, as well as specific measures of central processing speed and attentional measures [60, 71, 72].

RCTs yielded conflicting findings: in an 18-week RCT including 16 PDD patients, donepezil (10 mg/day) failed to show significant improvement in cognitive measures using the MMSE and ADAS-cog, or behavioral measures (NPI) [73]. However, in another 10-week crossover RCT including 22 subjects with PDD [74], donepezil 10 mg/day was associated with a statistically significant improvement of the MMSE ($p=0.0044$) and of the CGI ($p=0.0056$), but not the ADAS-cog ($p=0.18$). The largest multinational RCT investigating the efficacy and safety of donepezil (5 and 10 mg daily) included 550 PDD patients followed for

24 weeks [75]. The study failed to demonstrate a statistically significant improvement of the ADAS-cog in the primary intention-to-treat analysis ($p=0.05$ and $p=0.76$ for donepezil 5 and 10 mg/day, respectively), and only showed a statistically significant change in the CIBIC-plus, a coprimary endpoint, with the dose of 10 mg daily ($p=0.04$). However, when alternative statistical analyses were conducted given the imbalance in enrollment among participating countries, significant improvements in the ADAS-cog were demonstrated for both doses compared with placebo ($p<0.002$ and $p<0.001$, respectively). Additionally, there was a significant dose-dependent benefit affecting the MMSE, D-KEFS test, and the Brief Test of Attention (BTA) between baseline and week 24 ($p<0.001$, $p<0.007$, and $p<0.007$, respectively). But donepezil failed to show a significant change in the functional status of patients (measured by the DAD and the Shwab and England scales), as well as the behavioral symptoms of PDD (measured by the NPI).

3.3 VaD

3.3.1 Donepezil

In a 24-week RCT including 616 patients with probable or possible VaD according to criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN), donepezil at doses of 5 and 10 mg/day showed statistically significant improvement in cognition as measured by the ADAS-cog ($p=0.003$ and $p=0.0002$, respectively) and the MMSE ($p<0.01$ and $p<0.001$, respectively) when compared with placebo [76]. Global functioning was also significantly improved, as shown by the CIBIC-plus at week 24 ($p=0.008$). The authors reported that effect sizes were though smaller than those observed in similar AD studies.

A similarly designed multicenter RCT including 603 patients with probable or possible VaD according to the NINDS/AIREN criteria [77] confirmed the previous findings: there was a significant improvement in cognition, as measured by the ADAS-cog ($p=0.001$ and $p<0.001$ for donepezil 5 mg and 10 mg, respectively). Global functioning was also improved with a significant change in the CIBIC-plus with donepezil 5 mg ($p=0.014$) and a significant change in the sum of the boxes of the CDR with donepezil 10 mg ($p=0.007$). The Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) showed a significant mean change from baseline score with an effect size at week 24 of -1.31 ($p=0.02$) for donepezil 5 and 10 mg/day. In the subgroup analysis, both probable and possible VaD subgroups showed similar patterns of improvement, but only the group with probable VaD reached statistically significant results.

As a follow-up on these significantly positive results, an open-label extension study evaluated both RCTs' outcomes at 54 weeks from initiation of donepezil treatment in 707 patients. This study found a sustained improvement in cognition at week 54, regardless of the initial dose taken (5 or 10 mg/day). However, patients who initially received placebo didn't experience any improvement in their ADAS-cog scores but a simple stabilization over time [78].

In another large, 24-week RCT including 974 patients with possible or probable VaD, donepezil 5 mg/day was associated with a significant improvement of the ADAS-cog scores ($p < 0.01$), but not the CIBIC or the carer interview. Compared with placebo, donepezil stabilized cognition in the subgroup of patients with hippocampal atrophy ($p = 0.01$), and improved cognition in those without hippocampal atrophy ($p = 0.04$) [79].

One multicenter open-label study included 24 patients diagnosed with sVaD of the Binswanger type with ischemia scores of 12 or more according to the rule of Junque on brain MRI (reflecting severe ischemic changes), receiving donepezil 5–10 mg daily for 24 weeks. This study showed improvement in measures of attention, language, visuospatial function, memory, and executive functions, as reflected by the Seoul Neuropsychological Screening Battery—Dementia Version SNSB-D ($p < 0.05$). On the MMSE, there was only significant improvement in the subitems of immediate and delayed recall, word recognition, delayed recall of visual memory, and naming ($p < 0.05$). No significant changes were observed on the Short form Samsung Dementia Questionnaire (S-SDQ), Barthel ADLs, Korean version of instrumental activities of daily living (K-IADL), Korean version of Neuropsychiatric Inventory Questionnaire (K-NPI), or the Global Deterioration Scale (GDS) [80].

3.3.2 Galantamine

In one study, 592 patients with a diagnosis of probable VaD according to the NINDS/AIREN criteria or possible AD with cerebrovascular disease were randomized to receive either galantamine 24 mg daily or placebo for 6 months. In the subgroup of patients with probable VaD, ADAS-cog improved from baseline by 2.4 points in those assigned galantamine ($p < 0.0001$), whereas those assigned placebo did not differ significantly from baseline. In the subgroup of patients with mixed dementia, ADAS-cog scores of the galantamine-group patients significantly improved when compared with their baseline ($p = 0.024$), but also when compared with placebo (treatment difference 2.7 points, $p = 0.0006$). No statistically significant change in CIBIC-plus scores was observed between galantamine and placebo in those with VaD ($p = 0.238$), whereas an improvement was noted in those with mixed dementia ($p = 0.019$). Galantamine

was also found to have favorable effects in maintaining patients' ADL ($p = 0.0006$) and on behavioral symptoms ($p = 0.016$) when both subgroups were combined together [81]. Erkinjuntti et al. also investigated the effect of a more prolonged treatment (additional 6-month extension trial) in 459 patients. Sustained improvements in cognition (ADAS-cog scores) and functional ability (DAD scores) were obtained at month 12 in both the galantamine/galantamine group and the placebo group switched to galantamine in the open-label trial. Greater improvements of the ADAS-cog mean scores particularly occurred in those with a baseline MMSE score ≥ 18 in both groups. However, no statistically significant difference was seen on the NPI compared with baseline in either group [82].

To enhance diagnostic accuracy over previous trials with VaD patients, Auchus et al. adopted the following strict inclusion criteria for participants' enrollment. In addition to a diagnosis of VaD according to the NINDS/AIREN criteria, MRI findings including multiple large vessel infarcts, a single strategically located infarct, multiple basal ganglia and frontal white matter lacunes or extensive white matter lesions involving at least 25% of cerebral white matter were required. The trial involved 788 participants randomized to receive galantamine 8 mg twice daily or placebo for 26 weeks. Galantamine was associated with an improvement of one co-primary endpoint, the ADAS-cog score ($p < 0.001$), but not the ADCS-ADL ($p = 0.783$). No significant improvement in global functioning on CIBIC-plus was found ($p = 0.069$), but executive functioning improved significantly as reflected by the Executive Interview 25 (EXIT 25) ($p = 0.041$). Interestingly, cognitive improvement seen with galantamine was greater than placebo in all types of cerebrovascular lesions except single strategic infarcts, and those with a recent onset of VaD (< 6 months). This was attributed by authors to the spontaneous resolution of symptoms due to the natural history of recovery after a stroke [83].

3.3.3 Rivastigmine

In one 22-month open-label study involving 16 patients with a diagnosis of probable VaD, rivastigmine 3–6 mg daily showed significant improvement in cognitive functioning on the MMSE, the Ten-Point Clock test (TPC), and word fluency ($p < 0.05$), as well as behavioral symptoms on the NPI ($p < 0.05$), global functioning on the Clinical Dementia Rating (CDR) ($p < 0.05$), and caregiver stress on the Relatives Stress Scale (RSS) ($p < 0.05$) [84].

However, RCTs yielded mixed findings with respect to rivastigmine's efficacy in VaD.

In one small, 26-week, placebo-controlled RCT including 40 patients with sVaD (according to standardized diagnostic criteria combining clinical and radiologic findings, extensive white matter lesions, and at least one lacunar infarct on brain CT or MRI), no cognitive benefits were demonstrated and there was only a trend favoring the rivastigmine 6 mg/day group in NPI sub-scores of irritability ($p=0.066$) and aberrant motor behavior ($p=0.068$) [85]. On the other hand, studies with longer duration of follow-up showed positive findings with respect to cognition and/or neuropsychiatric symptoms: the first one included 208 patients with a diagnosis of probable VaD who received rivastigmine 3–6 mg/day or cardioaspirin 100 mg/day for a year. There was a significantly less prominent deterioration of cognition and executive function in the rivastigmine group ($p<0.05$) as well as an improvement of behavioral symptoms (except for delusions) on the Behavioral Pathology in Alzheimer's Disease rating scale (BEHAVE-AD) ($p<0.05$). Depression significantly improved with rivastigmine, as measured by the Geriatric Depression Scale (GDS) ($p<0.001$) [86]. In a 14-month prospective study, 100 patients with multi-infarct dementia (MID) and 100 patients with sVaD received either rivastigmine 6 mg/day or nimodipine 60 mg/day. The trial's results were in favor of rivastigmine with a significant improvement of behavioral symptoms compared with baseline measured using the BEHAVE-AD, while patients on nimodipine deteriorated significantly ($p<0.0001$). Affective disturbances in MID were stabilized by treatment ($p=0.003$) as compared with deterioration with nimodipine. Cognitive function assessed using the CDR, MMSE, and 10-point clock drawing scores deteriorated slightly with both drugs in MID and sVaD, with a more pronounced deterioration in sVaD with nimodipine ($p<0.0001$). The study also found a 35% reduction of concomitant need for using neuroleptics and benzodiazepines with rivastigmine, compared with a 37% increase in their use with nimodipine [87]. Finally, a more recent 24-week RCT showed that rivastigmine 3–12 mg/day led to a statistically significant improvement of cognitive functioning measured using the Vascular Dementia Assessment Scale (VaDAS), the ADAS-cog, and the MMSE as compared with placebo ($p<0.05$), but not on behavioral measures or ADL. However, in a subgroup analysis, these results were only proven to be significant in older patients (≥ 75 years old) who were assumed more likely to have a concomitant AD pathology compared with their younger counterparts [88].

3.4 FTD

Given the lack of a consistent cholinergic deficit in FTD, clinical studies exploring the use of cholinergic therapies in this type of dementia are scarce and of a low level of evidence.

Only one open-label study involving 40 patients followed for a year on rivastigmine 3–9 mg/day showed a statistically significant reduction of 15.1 ± 4.2 points on the NPI ($p<0.001$ vs baseline and control) and 4.4 ± 3.3 points on the BEHAVE-AD ($p<0.001$ vs baseline and control). Rivastigmine also reduced caregiver burnout at 12 months of treatment reflected by a reduction of 16 ± 7.1 points on the RSS scores ($p<0.001$ vs baseline and control). However, no benefits on cognitive decline were shown using the MMSE [38]. Other studies using galantamine 16–24 mg/day and donepezil 5–10 mg/day failed to show any clinical benefits on cognition or behavioral disturbances. Those two medications were even associated with inducing confusion and worsening of behavioral symptoms that were reversible in few instances after discontinuation of treatment [89–91].

4 Tolerability and Safety of ChEIs in Non-AD Dementias

In addition to their expected cholinergic side effects, ChEIs have been particularly explored with respect to the potential worsening of parkinsonian features in both DLB and PDD studies, as anticholinergics have been traditionally used to treat PD motor symptoms [92].

In DLB studies, only mild and transient adverse events were seen with galantamine [44, 45] and donepezil [51] that were most commonly cholinergic and comparable to placebo groups. Only rivastigmine was associated with mild–moderate adverse events including nausea, vomiting, anorexia, and somnolence more significantly reported in comparison with placebo [46]. In one study, only four out of 60 patients discontinued the treatment because of side effects, mostly cholinergic [50].

No worsening of parkinsonian symptoms as evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) was found with either of the three drugs [44–46, 51, 93].

Similarly, in PDD studies, both donepezil and galantamine were well tolerated: side effects reported were mild [68], included nausea, a non-significant increase in tremor ($p=0.3$) that did not affect withdrawal rates when compared with placebo [68, 69], and no worsening of parkinsonian features on the UPDRS [68, 69, 73, 74]. Nausea and vomiting were significantly more reported with rivastigmine versus placebo in the EXPRESS trial ($p<0.001$), but no statistically significant difference in reported serious adverse events was found [66]. In the extension study, cholinergic adverse events were mild or moderate in severity; however, 17.1% of participants reported serious adverse events [67].

Emerging mild or moderate tremor more frequently reported with rivastigmine was usually a transient phenomenon during up-titration, and this adverse event was not reflected by a significant change in UPDRS scores [94].

Given that the patch formulation is usually better tolerated compared with the oral form [95], a 76-week prospective trial randomized 583 patients aged 50–85 years with mild to moderately severe PDD (according to DSM-IV criteria) to rivastigmine capsules 6 mg twice daily and rivastigmine patch 9.5 mg/24 h with a primary objective of assessing tolerability and safety [96]. Discontinuation due to worsening of motor symptoms was comparable between the two groups (4.4% and 2.4% for capsules and patch, respectively), with tremor more commonly reported with the oral form. The incidence of adverse events was also comparable in both groups (36.1% and 31.9% for capsules and patch, respectively). However, nausea was more commonly reported with the capsule (40.5%) than the patch (8.3%), while the patch was more commonly associated with increased incidence of falls (20.1%) and application-site erythema (13.9%). Cases of application-site erythema were mild and led to discontinuation in only 1.4% of patients. Safety profile due to deaths and serious adverse events was similar in both groups: 11 deaths were reported in each group. Only one death was attributed to the study drug in the patch group (myocardial infarction). The incidence of serious adverse events was 29.6% with capsules and 28.8% with the patch. There was a 2.1-point deterioration on the UPDRS-III scores in both groups, which was similar to the expected rate of decline due to natural disease progression [96].

In VaD trials, donepezil was well tolerated with no significant difference between treatment groups and placebo with respect to laboratory studies, reports of serious adverse events or vital signs and drop-out rates for up to a year of follow-up [78, 79]. No increased mortality was reported with galantamine either, and both cardiovascular and cerebrovascular events occurred at similar rates seen with placebo [83]. Gastrointestinal side effects more frequently reported with galantamine versus placebo were attributed to the rapid initiation and titration schedule of the treatment [81, 82]. Similarly, rivastigmine treatment was well tolerated with reports of transitory cholinergic side effects (nausea, anorexia) during the titration phase that didn't lead to treatment discontinuation [86]. No serious adverse events or clinically significant changes in laboratory tests were reported [87]. Only in the most recent RCT, rivastigmine capsules were associated with non-statistically significant increased rates of mortality, adverse events of cerebrovascular accidents, and hypertension in younger patients (aged < 75 years old); the reason behind this finding was not clear [88].

5 Conclusions

Except for rivastigmine, which is FDA approved for PDD, no other drugs have yet shown sufficiently robust evidence to be integrated in the standard guidelines for the management

of non-AD MNCDS. In DLB and PDD, cholinesterase inhibitors yielded significant improvements in cognitive function and behavioral symptoms, particularly psychotic features and sleep disturbances as well as ADL, without worsening of parkinsonian symptoms [97]. They were overall well tolerated, although rivastigmine may warrant more careful monitoring as it has been associated with increased occurrence of adverse events (generally mild to moderately severe) [97, 98]. In a recent meta-analysis, none of the three drugs was shown to prevent the risk of falls, as a safety measure in DLB/PDD [98]. These positive results confirm the presence of cholinergic deficits in these two types of MNCDS, even to a greater extent than what is seen in AD, as was reflected by a numerically higher effect size of rivastigmine in PDD compared with AD on ADAS-cog measures [99]. However, the great heterogeneity in the questionnaires/scales used and the difference in duration of trials and sample sizes impact data interpretation and comparability among different studies. Hence, better designed trials for the future are warranted for DLB and PDD patients to move these drugs forward in the FDA regulatory process.

On the other hand, despite their relatively larger sample sizes, VaD trials are limited by the lack of pre-defined and homogeneous criteria to distinguish pure VaD from mixed dementia (with comorbid AD). In addition, heterogeneous populations in terms of type, extent, and location of cerebrovascular disease were included, limiting interpretation of findings regarding which subtype of VaD might benefit from cholinergic therapies or whether the benefits are attributed to a comorbidity with AD pathology. Finally, except for a couple of follow-up studies, most trials were limited by a relatively short duration (6 months). The great challenge for future trials is to optimize the design by refining inclusion criteria and duration to obtain more meaningful and interpretable results. Although ChEIs were well tolerated with no statistically significant increased mortality risk, caution is always warranted given the cardiovascular comorbidities in these patients and non-significant trends observed for increased cardio and cerebrovascular events in certain trials [100]. ChEIs also failed to show a consistent benefit in FTD patients. They are not recommended to be used given the fact that they have been associated with worsening of cognitive and behavioral disturbances.

Finally, a better characterization of cholinergic pathways and dysfunction in the brain is key to better account for patterns and extent of cholinergic loss in non-AD dementias. Neuroimaging techniques using newer *in vivo* acetylcholine ligands have been utilized more recently [101]. Furthermore, pupillometry is believed to be a fast, low-cost, non-invasive technique used in the monitoring of the central cholinergic system. It consists of the assessment of changes in pupil size and mobility during the constriction phase, which is regulated by acetylcholine [102]. In addition to the use of

subjective scales/questionnaires, incorporating those innovative techniques as biomarkers for cholinergic loss in clinical trials may be useful to enhance diagnostic accuracy in inclusion of eligible research subjects and further ascertain findings.

Compliance with Ethical Standards

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