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REVIEW ARTICLE

Turning the Spotlight to Cholinergic Pharmacotherapy of the Human Language System

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Abstract

Even though language is essential in human communication, research on pharmacological therapies for language deficits in highly prevalent neurodegenerative and vascular brain diseases has received little attention. Emerging scientific evidence suggests that disruption of the cholinergic system may play an essential role in language deficits associated with Alzheimer's disease and vascular cognitive impairment, including post-stroke aphasia. Therefore, current models of cognitive processing are beginning to appraise the implications of the brain modulator acetylcholine in human language functions. Future work should be directed further to analyze the interplay between the cholinergic system and language, focusing on identifying brain regions receiving cholinergic innervation susceptible to modulation with pharmacotherapy to improve affected language domains. The evaluation of language deficits in pharmacological cholinergic trials for Alzheimer's disease and vascular cognitive impairment has thus far been limited to coarse-grained methods. More precise, fine-grained language testing is needed to refine patient selection for pharmacotherapy to detect subtle deficits in the initial phases of cognitive decline. Additionally, noninvasive biomarkers can help identify cholinergic depletion. However, despite the investigation of cholinergic treatment for language deficits in Alzheimer's disease and vascular cognitive impairment, data on its effectiveness are insufficient and controversial. In the case of post-stroke aphasia, cholinergic agents are showing promise, particularly when combined with speech-language therapy to promote trained-dependent neural plasticity. Future research should explore the potential benefits of cholinergic pharmacotherapy in language deficits and investigate optimal strategies for combining these agents with other therapeutic approaches.

Key Points

To date, there is limited information on the role of cholinergic neurotransmission in human language.

Language deficits in Alzheimer's disease and vascular cognitive impairment, including post-stroke aphasia, are partially linked to reduced cholinergic signaling and may be attenuated with pharmacotherapy.

1 Introduction

Neurotransmitters play a crucial role in igniting and modulating the neural machinery of the brain, yet their influence on human language functions has only recently been explored [1–5]. Current language processing models are

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beginning to recognize the importance of the neuromodulator acetylcholine (ACh) in normal and abnormal language processing and its putative role in the recovery of language and communication deficits [4–7]. As the cholinergic system may be disrupted by diverse brain pathologies [8–10], studying its dysfunction in highly prevalent neurodegenerative and vascular brain diseases would provide insight into the role of cholinergic pharmacotherapy for language deficits and associated cognitive impairments [11–15]. Therefore, this review aims to investigate the current evidence on the association between language impairments in neurodegenerative and vascular brain disorders and the cholinergic system, which has yet to be comprehensively examined.

Notably, the ongoing reformulation of the cholinergic hypothesis of Alzheimer's disease (AD) is optimizing the use of acetylcholinesterase inhibitors (AChEIs), with early treatment initiation at therapeutic doses to achieve maximum benefits [14, 16] and exploring the interaction of cholinergic therapy with emerging pharmacological targets in AD, such as combinations of AChEIs with disease-modifying agents [14, 17]. Given that language deficits may be targeted with cholinergic agents in all stages of AD, even in severe phases [18–22], detecting language disturbances in typical AD early on, pre-empting the onset of other cognitive deficits [23, 24], can help anticipate diagnosis and initiate pharmacological treatment. In addition, the development of sensitive testing tools, such as automatic speech analysis of narrative discourse [25–27], could aid in the early identification of disruptions in language integrity and monitoring of response to pharmacological treatments. This approach would also enable the detection of isolated preclinical language deficits in patients with atypical AD in association with focal degeneration of the cholinergic basal forebrain (CBF) nuclei and their targeted white matter tracts and cortical language areas [15, 26, 28–30].

Deficits in cholinergic neurotransmission are not restricted to AD, as they have also been identified in vascular cognitive impairment (VCI) [31]. Therefore, this review also delves into the impairment of cholinergic neurotransmission in patients with language deficits associated with VCI, including post-stroke aphasia (PSA). A recent analysis of 404 patients evaluated 6 months post-stroke (GRECOG-VASC cohort) revealed mild cognitive impairment in 80% of patients, and the highest prevalence of cognitive disorders resulted from averaging performance in action speed, executive function, and language [32]. However, further research on language and communication in VCI still needs to be conducted. The present review is divided into two main parts. In the first part (Sects. 2, 3), we review the current knowledge of the human cholinergic system, its relationship with language, and how its function can be evaluated with non-invasive biomarkers. In the second part (Sects. 4–6), we examine the existing data on pharmacological approaches using cholinergic modulators to treat language deficits in neurodegenerative and vascular brain diseases.

In some non-AD dementias, the cholinergic system is also dysfunctional but is not the principal neurotransmitter affected. For example, Parkinson's disease is also associated with deficits in cholinergic neurotransmission. However, this condition is not analyzed herein because of the paucity of language deficits and because cholinergic deficits have mostly been linked to other clinical features [33]. In addition, Lewy body dementia is also related to cholinergic deficits, and recent cases of aphasic mild cognitive impairment [34] and progressive aphasia have been described [35, 36]. Nevertheless, as only a handful of patients have been treated with cholinergic agents, this information is not included [34, 37].

2 Cholinergic Innervation of Human Language Networks

In the central nervous system, ACh is a neuromodulator that plays a key role in regulating neuronal excitability, the presynaptic release of other neurotransmitters, and orchestrating neuronal group firing [38]. As a neuromodulator, ACh does not have strictly excitatory or inhibitory properties, but it has a role in modifying the state of groups of neurons to regulate their response to forthcoming stimulation [38]. Importantly, cholinergic neuromodulation contributes to normal cognitive functioning and may affect everyday language functioning [39–43].

Previous studies have suggested that cholinergic neuromodulation may contribute to language functions through different mechanisms such as modulation of sensory processing, enhancement and control of attention, learning and retention of tasks, and promoting experience-dependent neural plasticity and memory consolidation through long-term potentiation mechanisms [44–46]. Concerning learning, ACh may modulate the interaction between feedforward and feedback activity and synaptic plasticity, the molecular correlates of learning, in different cortical structures [38, 47, 48] related to language. For instance, Sajid and coworkers [5] proposed that disruption of cholinergic neuromodulatory control may explain alternate antagonism with paradoxical translation in bilingual aphasia, a situation in which the person alternatively shows severe anomia in one language but remains fluent in the other, accompanied by difficulties in translation from the fluent language to the temporarily poor language but not the other way around. That may be associated with the effect of ACh in sensory processing, increasing bottom-up signals, boosting selective and sustained attention [5, 46], and, therefore, allowing the execution of more adaptive responses to the demands imposed by complex tasks.

The cholinergic system does not have a single mechanism of action. This system has traditionally been conceptualized as a diffuse neuromodulator because of its broad and diffuse projections from the CBF and upper brainstem to the cortical mantle and deep gray nuclei [38]. However, molecular genetics and functional and quantitative anatomical studies have shown that corticopetal fibers from the CBF cannot rely solely on diffuse projections. Instead, the CBF has a specific, not diffuse, pattern of connectivity [49–52], innervating domain-specific regions, such as language-related areas, and domain-general networks [53–55] that support non-verbal cognition [56]. Thus, ACh may act rapidly and selectively on specific circuits, and its release can be coordinated in multiple brain regions that mediate cognitive processing. For example, cholinergic drugs increase task-related activity to external stimuli in frontal-parietal cortical areas [46], implicated in the recovery of language and cognitive control deficits in PSA [57]. In contrast, at the same time, these agents reciprocally deactivate the default mode network, probably in response to increased attentional demands [46].

Language is supported by large-scale, left perisylvian cortical networks that closely interact with subcortical circuits and are densely innervated by cholinergic projections [12, 58]. Modern anatomical models of language [59, 60] propose that cortical areas sustaining sensory-motor and lexical-semantic processes in the temporal lobe are coordinated with frontal areas through two pathways, a dorsal and a ventral pathway. The participation of extrasylvian frontoparietal domain-general areas related to attention or executive function is essential for monitoring speech and language functions [61, 62]. Histopathological, anatomical, and neuroimaging studies have revealed that cholinergic projections from the CBF nuclei are segregated into two well-defined discrete pathways, *medial* and *lateral* bundles [53, 58]. The medial cholinergic pathway travels within the gyrus rectus substance, surrounding the anterior corpus callosum and penetrating the cingulum. It then connects with the fibers of the lateral cholinergic pathway in the occipital lobe [63]. The medial cholinergic pathway innervates structures perfused by the anterior cerebral artery, which are usually spared by stroke lesions [64], but are affected early in AD, especially the posterior cingulum/retrosplenial area [65–67]. The lateral cholinergic pathway has two subdivisions: a capsular component traveling through the external capsule and uncinate fasciculus and a perisylvian component that passes through the claustrum. Both components are irrigated by branches of the middle cerebral artery [64], and these pathways supply 80% of the cholinergic innervation of the central language core, mainly through fibers emanating from the nucleus subputaminalis [68]. Specifically, the perisylvian component innervates areas such as the frontoparietal operculum, insula, superior temporal gyrus, and the underlying white matter of the inferior frontal gyrus, while the capsular component travels adjacent to the putamen [58, 68]. Therefore, depletion of cholinergic innervation in the left perisylvian cortex contributes to the dissolution of language in the logopenic subtype of primary progressive aphasia (PPA) and in strokes that cause aphasia. The cholinergic system is also represented in two upper brainstem constellations (Ch5–Ch6) that include the pedunculopontine nucleus, the lateral dorsal tegmental nucleus, a subset of thalamic nuclei, and striatum [53, 69–72]. Additionally, these brainstem nuclei diffusely project to the thalamus [70, 71] and striatum [73], but their potential role in the modulation of language functions remains unknown.

Asymmetry in the distribution of cholinergic neurons provides further evidence for the role of ACh in language function. There is a leftward asymmetry regarding the density of acetylcholinesterase (AChE)-containing pyramidal cells in layer III of the pars triangularis (Brodmann's area 45) in the frontal lobe [74–77] and in the left posterior temporal cortex, implicated in auditory processing of verbal stimuli, wherein the activity of choline acetyltransferase, the enzyme that synthesizes ACh, is higher than in its homolog in the right hemisphere [78]. Fibers innervating the perisylvian language cortex emanate from the Ch1–Ch4 sectors of the CBF [79]; among these, the posterior part of the nucleus basalis (Ch4) and the nucleus subputaminalis mostly innervates the inferior frontal gyrus [68], which is involved in language and cognitive control functions [80, 81].

The recovery of different language domains after neurodegeneration and focal brain injury relies on the compensatory activity of different neural networks [82], so it is conceivable that a pharmacological agent acting over a wide range of brain areas might improve one language deficit but may be ineffective or even worsen other language function by interfering with the activity of other regions [4, 82–84]. The fact that the release of ACh may be diffuse or region specific underscores the need for disentangling whether changes in language functions under cholinergic stimulation result from a generalized effect on brain structure [38] or whether there are specific "cholinergic circuitry hubs" [85] crucially participating in the recovery process of language deficits under cholinergic modulation [12, 86]. Hence, if the region-specific mechanism is further established [12, 86], obtaining information on the sites of cholinergic stimulation could be relevant because it would provide hints to guide pharmacotherapy to critical hubs and interconnecting pathways to optimize therapeutic effects and further amplify the beneficial effects of behavioral interventions tailored to act on these brain regions [86]. Although additional studies, including neuroimaging and other biomarkers are needed, the available information suggests that leveraging cholinergic neurotransmission with drugs may be an appropriate strategy for treating deficits in language functions, everyday communication, and behavior (mood, motivation) in

neurodegenerative and vascular diseases when used alone [11, 12, 20, 87–89] and combined with behavioral training [12, 86, 90–93]. Nevertheless, the role of ACh in the language domain has been overlooked, and studies exploring its role in different language components are scarce. Thus, whether ACh directly affects language functions requires further exploration.

3 Noninvasive Biomarkers

Biomarkers in neurology can inform clinical decisions, personalized medicine, and the generation of prevention actions in various ways [94]. Thus, biomarkers play a major role in developing precision medicine [95], an innovative approach to obtaining further knowledge of diseases using high-resolution technologies that refine diagnosis and improve treatments [96]. Precision medicine is a well-established practice in cancer and other conditions, and its use has been expanded to neuroscientific research targeting neurodegenerative disorders [97] and multifocal and focal vascular lesions [98, 99]. Such an endeavor includes an in vivo analysis of the cholinergic system with non-invasive methods that may allow the detection of cholinergic disruption in neurodegenerative diseases, such as AD, even in preclinical phases. In addition, their use is also incorporated to evaluate the status of the cholinergic system in vascular brain disorders [100] and traumatic brain injury [101, 102]. The relationship between cholinergic deficiency and impaired language functions is well established in healthy subjects treated with anticholinergic agents [103] and patients with AD [104–107]. However, biomarkers used to measure compromised cholinergic integrity should not necessarily be linked to the state of language functions. Instead, the main objective of predictive biomarkers is to help identify patients who are more likely to benefit from pharmacological modulation with cholinergic agents. Several biomarkers show a promising role in evaluating the cholinergic system, but further studies are necessary to confirm their utility. Newly investigated biomarkers include cognitive stress testing under scopolamine [14, 108, 109], pupillary light response [110–114], short-latency afferent inhibition [115–120], auditory sensory gating measured with P50 event-related potentials [101, 102, 121–123], and molecular, structural, and functional neuroimaging.

3.1 Molecular Neuroimaging

Brain cholinergic states can be quantified using positron emission tomography (PET) [124, 125]. Acetylcholinesterase is considered a valid marker for the integrity of the cholinergic neurons, and it was the first ligand measured with PET in humans [124–127]. This methodology is used for early diagnosis of cholinergic deficits in neurodegenerative conditions and for monitoring the effects of treatment with AChEIs (donepezil, rivastigmine, and galantamine). In addition, it might help define the clinical dosage of newly developed drugs targeting the cholinergic system [128]. The ligands for quantifying AChE activity with PET are 11C-MP4A [129] and 11C-PMP [130]. Other ligands such as ^{18}F-FEOBV and ^{123}I-IBVM quantify the vesicular ACh transporter, which is considered a robust marker of presynaptic cholinergic integrity [125].

The α4β2 nicotinic ACh receptor was examined with new radioligands and PET in healthy subjects and patients with AD [131–133]. Sabri et al. investigated the relationship between cognitive dysfunction in mild AD and α4β2-nAChR using (+)-[^{18}F]flubatine and PET. The authors reported a relationship between lower α4β2-nAChR availability in CBF, septo-hippocampal projections, and frontotemporal cortex and cognitive functioning (episodic memory and executive function/working memory). However, they found no significant differences in receptor availability between patients with mild AD and healthy control subjects related to language dysfunction (evaluated with the Boston Naming Test and category/letter fluencies) and cortical regions involved [131]. Similarly, Sultzer et al. [133] studied regional brain α4β2 nicotinic cholinergic receptor binding with 2-[18F]fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine and PET imaging, but they did not observe different involvement in mild cognitive impairment and AD relative to cognitively unimpaired subjects. Language functions were not evaluated in this study [133].

Positron emission tomography imaging markers capable of tracing donepezil and rivastigmine distribution are available [134]. Quantification and biodistribution tracing of donepezil can be achieved using [5-(11)C-methoxy]-donepezil ([(11)C]-donepezil), and these studies have revealed binding of the tracer in the striatum, thalamus, and cerebellum containing higher densities of AChE compared with the neocortex [135–137]. Furthermore, in small samples of patients with mild cognitive impairment and AD, [11C]-donepezil PET images show a progressive reduction in the radiotracer concentration when both groups were compared with healthy elderly subjects [135]. Importantly, this method helps predict the treatment response to donepezil in selected samples of patients with AD, PPA, and VCI, including PSA [29, 30, 138, 139]. However, this neuroimaging method for assessing human cholinergic function in vivo is expensive and not readily available in most centers.

3.2 Structural and Functional Neuroimaging

The relationship between the CBF nuclei and language functions has mainly been described in PPA [15, 29, 30, 140, 141]. Structural high-resolution magnetic resonance imaging

using voxel-based morphometry is a crucial tool for studying the volume of the CBF and its relationship to perisylvian areas and language functions [30]. In healthy controls, there is an association between the volume of the CBF, especially of the nucleus subputaminalis, and the gray matter volume of several areas of the perisylvian cortex. Volume loss of the CBF is a marker of AD [142] and PPA [29, 140], and in autopsied cases with PPA-AD, the depletion of CBF neurons was associated with cortical degeneration of cholinergic axons in the left-hemisphere language areas [15]. In PPA, this structural connectivity is shifted to right-hemisphere regions when the left dominant language network displays degeneration [140].

Early treatment with cholinergic agents appears necessary for diminishing atrophic changes in CBF. Long-term treatment with donepezil reduced CBF atrophy in subjects with prodromal AD [14, 143]. However, it should be noted that given that the basal forebrain region also contains non-cholinergic nuclei, further studies combining structural and molecular imaging are needed to establish whether CBF atrophy is associated with cholinergic depletion in diseases coursing with language deficits [30]. Future neuroimaging research may also examine the neuroanatomy of the CBF in VCI and PSA and its potential relationship with language functions. No prior research has explored the relationship between functional connectivity under cholinergic stimulation and language abilities. However, some studies have shown a complex reorganization of brain connectivity in response to donepezil treatment in healthy young and older individuals [144–148] and in patients with AD [149–153].

4 Cholinergic Pharmacotherapy

4.1 Acetycholinesterase Inhibitors

Four agents, tacrine, donepezil, rivastigmine, and galantamine, with specific action on the cholinergic system, have been authorized worldwide and marketed for the symptomatic treatment of AD [154]. Nevertheless, tacrine is not currently in use because of hepatic adverse events. Donepezil hydrochloride (Aricept®) is a centrally acting reversible AChEI structurally unrelated to other anticholinesterase agents. The use of donepezil is authorized for mild-to-moderate AD (5–10 mg once daily, presented in tablets, for oral use and orally disintegrating tablets) and for severe AD (10–23 mg once daily, presented in tablets, for oral use).[1] Rivastigmine tartrate (Exelon®) is authorized for mild-to-severe AD, and it is available in capsules, liquid solutions, and transdermal patches. Rivastigmine is currently prescribed in patches to reduce gastrointestinal adverse events of capsules. Recommended doses of 4.6 and 9.5 mg, once daily, are available for mild-to-moderate dementia, whereas higher doses (13 mg once daily) are used for severe dementia. Galantamine hydrobromide (Razadyne®, Reminyl®) is a selective reversible inhibitor of AChE and an allosteric modulator of nicotinic cholinergic receptors. Galantamine is prescribed in tablets for oral use (4, 8, and 12 mg twice daily) and in solution (4 mg/mL). The use of these agents is associated with adverse events that are not uncommon in specific populations. A large retrospective cohort study ($n = 767{,}684$) in older adults (aged ≥ 65 years) with dementia showed that the use of AChEIs is associated with severe adverse events in 15% of patients within 6 months of drug prescription. However, the risk of adverse events varies by sex and pharmacological product [155]. Therefore, clinicians should exercise caution when prescribing AChEIs to old and oldest-old patients with AD, as they are at a high risk of developing gastrointestinal and cardiovascular adverse events [155, 156]. The beneficial effects of AChEIs are not confined to AD. Patients with VCI and PSA are also being treated with AChEIs. However, as AChEIs are not approved for treating these conditions, they are often prescribed off-label [4, 157] (see Sect. 5).

4.2 Healthy Aging

Healthy aging is generally defined as developing and maintaining the functional ability that enables well-being in older age [158]. Healthy aging also refers to preserving brain structure and function over time [159], although it may be associated with functional and structural changes, including decreased cholinergic activity [160, 161]. The cholinergic system probably plays a permissive role in phonological and lexical-semantic processing, as cholinergic blockade with scopolamine impairs performance in object naming, verbal fluency, reading, and spelling tasks in 25–60% of healthy young women [103]. The effects of cholinergic antagonists have also been investigated in other populations, with most studies [162, 163], but not all [164], reporting harmful effects in healthy aging and persons at risk for AD [162, 163], especially among apolipoprotein ε4 carriers [165].

The state of language varies with age, with some researchers considering it the most preserved cognitive function [166], whereas others have described deficits in verbal production affecting word-finding ability [167, 168]. Deleterious brain changes in aging include reduced cerebral perfusion and brain volume, which impair neural efficiency due to decreased integrity of ascending neuromodulators, eventually leading to network rearrangement [169–171]. Attenuation of neural activity causes inefficient processing and compels cognitively intact older adults to over-recruit brain tissue to comply with task demands and switch activity to

[1] High doses of donepezil (23 mg/day) are not authorized in Europe.

more efficient alternative networks to maintain a high level of performance [172, 173]. In older people, neuroimaging has revealed functional connectivity network compensation in tasks tapping phonemic fluency [174], semantic fluency [175], semantic processing of words [176], and narrative discourse [177, 178]. However, it should be noted that the neural mechanisms in aging are not always compensatory and may instead reflect neural decline [179]. For example, language failure complaints in community-dwelling subjects seemingly predict language deficits in long-term follow-up evaluations [180]. Moreover, intracerebral vascular changes, lacunes, and white matter microstructural abnormalities correlate with language and other cognitive deficits in elderly subjects without cognitive impairment [8], whereas these structural abnormalities are more severe in those with non-dementia cognitive impairment [181].

The results of pharmacological approaches to healthy aging using cholinergic agents have been inconclusive [182]. Most studies have used donepezil and yielded contradictory outcomes, with studies reporting no significant benefits [171, 183, 184]. These negative findings may have emerged from age differences and cognitive function and, presumably, because of the lack of fine-grained testing of language functions. Therefore, no recommendations can be provided regarding pharmacological augmentation with cholinergic drugs in individuals with subjective complaints of language decline or individuals who are concerned about age-related language changes [171]. However, as ACh diminishes in aging due to early CBF degeneration preceding the onset of AD symptoms [160, 161], the study of possible synergistic effects of combining AChEIs with intensive training in boosting language functions via strengthening experience-dependent plasticity may warrant the design of further studies.

4.3 Neurodegenerative Diseases

4.3.1 Typical Alzheimer's Disease (AD)

Typical AD is characterized by amnesia as the primary deficit resulting from symmetric affectation of medial temporal lobe structures [185, 186]. Deterioration of language and communicative ability in AD is also expected. It may herald the onset of psychological and behavioral symptoms, social exclusion, decreased quality of life, increased burden on caregivers, and the risk of mortality [187–192]. Furthermore, complaints of language failure are not infrequent in community-dwelling healthy older adults, and this population performs significantly worse than subjects without claims of language failure [180]. Language and functional communication deficits occur in the preclinical, prodromal, and mild cognitive impairment phases [193–195]. Therefore, the role of AChEIs in the early stages of AD, even in the preclinical phases, needs to be further investigated in patients with biomarker confirmation [17] using fine-grained language testing (e.g., connected speech) coupled, for instance, with automated text-level statistical and machine learning analyses [196, 197]. Language testing may focus on semantic content, syntactic complexity, verb fluency, vocal parameters, and pragmatic language [194, 196–202] to identify early linguistic markers that can be targeted through pharmacotherapy.

The etiology of AD is multifactorial and includes genetic predisposition, β-amyloid deposits, τ-protein phosphorylation, oxidative stress, mitochondrial dysfunction, vascular abnormalities, neuroinflammation, and dysfunction of ACh and other neurotransmitters [17, 203]. Despite the role of cholinergic deficits in cognitive and language impairments in AD, little research has been conducted on treating AD language deficits with AChEIs. However, novel strategies based on precision medicine support the re-evaluation of cholinergic agents in early AD [17] and propose analyzing the therapeutic effects of combining AChEIs with new disease-modifying agents [14, 17, 161]. Improvement or stabilization of language alterations have been described using AChEIs at usual doses [204, 205]. The relevance of cholinergic depletion in AD-related language deficits is not new. Post-mortem findings in patients with AD disclosed that perseverations correlate with low choline acetyltransferase [104] and that these reiterative verbal behaviors can be attenuated with AChEIs [6]. Donepezil and galantamine reduce perseverations, intrusions, self-referential tags, and non-productive verbal repetition in mild-to-moderate AD [6, 105–107]. Rivastigmine diminishes the production of "empty words" in spontaneous speech in early AD [206].

Although language deficits are common in AD, only two testing scales have primarily been used for evaluating these symptoms in pharmacological trials. Table 1 shows AChEIs trials in typical AD including evaluation of language functions with the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [207] in mild-to-moderate AD [208–212] (Mini-Mental State Examination score 21–24) or different versions of the Severe Impairment Battery-Language (SIB, 41 items, and SIB-Lang, 24 items) in moderate-to-severe AD (Mini-Mental State Examination score 0–20) [18, 19, 213, 214] . Overall, treatment with donepezil improved ADAS-Cog and SIB scores compared with baseline and placebo or induced cognitive stabilization (Table 1). A pilot study of patients with mild-to-moderate AD demostrated good safety and tolerability profiles of higher donepezil doses (15 and 20 mg/day) in comparison with the usual doses (10 mg/day) [215]. Two trials in moderate-to-severe AD showed that language domain scores for SIB improved more with standard doses of donepezil (10 mg/day) than with placebo [216, 217], while other trials found enhanced treatment response using higher doses of a slow-release donepezil formulation (23 mg/day). Changes in

Table 1 Trials of cholinergic pharmacotherapy in Alzheimer's disease and primary progressive aphasia

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Alzheimer's disease					
Donepezil					
Roger et al. [208] The Donepezil Study Group	14-week, randomized, multicenter, DB, placebo-controlled, parallel-group study Four groups: Placebo DP 1 mg/day DP 3 mg/day DP 5 mg/day Two phases: DB phase: 12 weeks SBPW phase: 2 weeks	$n = 161$ patients with mild-to-moderate AD ITT $n = 141$ Placebo ($n = 40$; female: 52.5%; mean age: 70.6 years) DP 1 mg/day ($n = 42$; female: 69.1%; mean age: 72.6 years) DP 3 mg/day DP ($n = 40$; female: 55%; mean age: 71 years) DP 5 mg/day ($n = 39$; female: 64.1%; mean age: 72.9 years)	ADAS-Cog[a,b]	Improvements were significantly greater in patients treated with DP 3 and 5 mg/day by week 3 than in placebo patients and maintained throughout the DB phase. The response was related to time and dose and was held at the end of the 2-week washout (DP 5 mg/day) At the DB phase endpoint mean change from baseline: on placebo group 0.7; on DP 1 mg/day − 0.9 ($p = 0.105$ vs placebo); on DP 3 mg/day − 1.4 ($p = 0.036$ vs placebo); on DP 5 mg/day − 2.5 ($p = 0.002$ vs placebo)	AEs with all three dosages (64–68%) were comparable to those with placebo (65%) The most frequent AEs with 5 mg/day compared with placebo were nausea/vomiting, diarrhea, dizziness, gastric upset, and constipation Most AEs were of mild-to-moderate intensity; in most cases, not related to the dose
Roger et al. [210] The Donepezil Study Group	30-week study, randomized, multicenter, DB, placebo-controlled, parallel-group study Three groups: Placebo DP 5 mg/day DP 10 mg/day Two phases: DB phase: 24 weeks SBPW phase: 6 weeks	$n = 473$ patients with mild to moderate AD ITT $n = 454$ Placebo ($n = 162$; female: 61%; mean age: 72.6 years) DP 5 mg/day ($n = 154$; female: 63%; mean age: 72.9) DP 10 mg/day ($n = 157$; female: 62%; mean age: 74.6 years)	ADAS-Cog[a,b]	Significantly greater improvements in patients treated with 5 mg/day and 10 mg/day from week 12 and maintained throughout the rest of the DB phase compared with placebo patients. Response was dose related At the DB phase endpoint, mean change from baseline: on placebo group 1.82; on DP 5 mg/day − 0.67 ($p < 0.0001$ vs placebo); on DP 10 mg/day − 1.06 ($p < 0.0001$ vs placebo). 80% of patients receiving DP did not experience cognitive worsening compared with 57.7% of patients in the placebo group At the end of SBPW phase, there were no significant differences between groups	The rate of patients discontinuing treatment due to AEs was similar between groups (7% in the placebo, 5% in the DP 5 mg/day, 16% in the DP 10 mg/day) Cholinergic AEs (primarily diarrhea, nausea, and vomiting) were significantly more often in DP 10-mg/day group and associated with a rapid dosage increase during titration. Most of these AEs were transient and of mild to moderate severity

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Roger et al. [209] The Donepezil Study Group	15-week, randomized, multicenter, DB, placebo-controlled, parallel-group study Four groups: Placebo DP 5 mg/day DP 10 mg/day Two phases: DB phase: 12 weeks SBPW phase: 3 weeks	$n = 468$ patients with mild-to-moderate AD ITT $n = 412$ Placebo ($n = 153$; female: 61%; mean age: 74.0 years) DP 5 mg/day ($n = 157$; female: 69%; mean age: 73.8) DP 10 mg/day ($n = 158$; female: 61%; mean age: 73.4 years)	ADAS-Cog[a,b]	Greater significant improvements were observed in both DP-treated groups by week 3 and maintained throughout the DB phase compared with the placebo group At the DB phase endpoint, LS mean change from baseline, ITT-LOCF analysis: on placebo group 0.4; on DP 5 mg/day − 2.1 ($p < 0.001$ vs placebo); on DP 10 mg/day − 2.7 ($p < 0.001$ vs placebo) At the end of the SBPW phase, DP-treated patients showed a similar rate of decline than the placebo group; however, the improvement remained statistically significant ($p < 0.001$) compared with the placebo group	The proportion of any AE was 68% at 5 mg/day, 78% at 10 mg/day, and 69% at placebo. Most AEs were mild (92%) and transient (1 or 2 days) AEs significantly more common with DP than placebo were nausea and insomnia ($p < 0.001$), which appeared to be dose related The proportion of severe AEs was similar between both treated groups and placebo
Burns et al. [211] The International Donepezil Study Group	30-week, randomized, multicenter, DB, placebo-controlled, parallel-group, study Three groups: Placebo DP 5 mg/day DP 10 mg/day Two phases: DB phase: 24 weeks SBPW phase: 6 weeks	$n = 818$ patients with mild-to-moderate AD patients (from 9 countries) ITT $n = 631$ Placebo ($n = 274$; female: 55%; mean age: 71.0 years) DP 5 mg/day ($n = 271$; female: 61%; mean age: 72.0 years) DP 10 mg/day ($n = 273$; female: 57%; mean age: 72.0 years)	ADAS-Cog[a,b]	Significantly greater improvements in both DP-treated groups by week 6 and maintained throughout the DB phase compared with the placebo group. These outcomes were consistent and independent of the populations studied (US vs multinational). There was a dose-response effect with better outcomes with DP 10 mg/day than DP 5 mg/day At the endpoint, LS mean change for both DP-treated groups was statistically significant ($p < 0.01$ vs baseline), and the DP vs placebo differences were 1.5 with 5 mg/day and 2.9 with 10 mg/day. The primary efficacy analysis was based on ITT (ITT and ITT: LOCF analyses were similar)	Patients with AEs with both dosages (9–18%) were comparable to placebo (10%) Digestive cholinergic AEs (diarrhea, nausea, vomiting, anorexia) were more often in the 10-mg/day group and associated with a rapid dosage increase during titration AEs were transient and generally mild in severity

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Homma et al. [212]	24-week, multicenter, DB, placebo-controlled comparative trial Two groups: Placebo DP 5 mg/day	$n = 268$ patients with mild to moderate AD ITT $n = 263$ Protocol compatible $n = 228$ Placebo ($n = 112$; female: 66%; mean age: 69.4 years) DP 5 mg/day ($n = 116$; female: 68%; mean age: 70.1 years)	ADAS-Cog (Japanese version)	Cognitive improvement was significantly better in the DP group compared with placebo Mean change from baseline, ITT analysis: on placebo group: 0.11; on DP 5 mg/day: − 2.43 ($p < 0.0001$ vs placebo)	Drug-related AEs were similar between groups: 10% in the DP group and 8% in the placebo group ($p = 0.587$) Discontinuity due two AEs was of 1% in the DP and 5% in the placebo group The main drug-related adverse events in the DP group were gastrointestinal symptoms including 3 cases of diarrhea (2%), 3 with nausea (2%), 2 with constipation (1%), 1 with abdominal pain (1%), 1 with vomiting (1%), 1 with anorexia (1%), and 1 with abdominal distension (1%)
Winblad et al. [216] The Donepezil Nordic Study Group	6-month study, randomized, DB, placebo-controlled study Two groups: Placebo DP 10 mg/day	$n = 248$ patients with severe AD ITT $n = 194$ Placebo ($n = 120$; female: 74%; mean age: 85.3 years) 10 mg/day DP ($n = 128$; female: 79%; mean age: 84.5 years)	SIB[b]	At the endpoint, patients treated with DP significantly improved more than patients in the placebo group Global SIB score LS mean change from baseline, ITT analysis: on placebo group − 1.8; DP group 4.0 ($p = 0.008$ vs placebo) Individual SIB language domain scores improve more with DP than with placebo ($p < 0.05$) in the ITT population	Between-groups comparable AEs (DP: 82% [$n = 105$] vs placebo: 76% [$n = 91$]) with most being transient and mild to moderate in severity There were no between-group differences in severe AEs during the study or within the 30-day study lag period (DP: 24% [$n = 31$] vs placebo: 26%) More patients treated with DP than controls discontinued their treatment because of adverse reactions (DP: 16% vs placebo: 7%)
Black et al. [217]	24-week, randomized, multinational, DB, placebo-controlled study Two groups: Placebo DP 10 mg/day (5 mg/day 6 weeks, and 10 mg/day after that)	$n = 343$ patients with severe AD (from 5 countries) ITT $n = 244$ Placebo ($n = 167$; female: 67.7%; mean age: 78.0 years) DP 10 mg/day ($n = 176$; female: 72.7%; mean age: 78.0 years)	SIB[b]	DP-treated patient had better outcomes than patients in the placebo group At the endpoint, global SIB score LS mean change change from baseline, ITT-LOCF analysis: on placebo group − 5.13; DP group 0.19 ($p = 0.0001$ vs placebo). 63.3% of patients receiving DP improved or did not experience cognitive worsening compared with 39.4% of placebo patients At the endpoint, DP-treated patients improved vs their baseline in the language domain in the ITT population	The proportion of any AE was 79.5% at DP and 70.1% at placebo. Most AEs (73.6%) were mild or moderate. Severe (15.6% placebo vs 10.8% DP) or serious (15.0% placebo vs 11.4% DP) AEs were higher in the placebo group AEs related to the study medication (diarrhea, nausea, vomiting, anorexia, and agitation) were 42.0% at DP vs 30.5% at placebo. The DP group had twice the rate of diarrhea, insomnia, nausea, infection, urinary incontinence, and pain vs the placebo group

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Farlow et al. [18]	24-week, randomized, multinational, DB, parallel-group, double-dummy trial Two groups: DP 10 mg/day DP 23 mg/day	$n = 1467$ patients with moderate-to-severe AD (from 23 countries) ITT $n = 1434$ DP 10 mg/day ($n = 471$; female = 62.4%; mean age: 73.8 years) DP 23 mg/day ($n = 963$; female = 63%; mean age: 73.9 years)	SIB[b]	Significant greater benefit in cognition with 23 mg/day in comparison with 10 mg/day At the endpoint, global SIB score LS mean change from baseline, ITT-LOCF analysis: on DP 10-mg/day group 2.6; on DP 23-mg/day group 0.66 ($p < 0.001$).	More AEs were reported with 23 mg/day (73.7%) than 10 mg/day (63.7%). Doses of 23 mg induced mild (30.8%), moderate (34.5%), and severe (8.4%) AEs, whereas doses of 10 mg/day induced mild (31.2%), moderate (25.3%) and severe (7.2%) AEs
Ferris et al. [20] Post-hoc language analysis of a multinational trial (Farlow et al. [18])	24-week, randomized, multinational, DB, parallel-group study Two groups: DP 10 mg/day DP 23 mg/day	$n = 1467$ patients with moderate-to-severe AD ITT $n = 1.371$ DP 10 mg/day ($n = 462$; female = 62.1%; mean age: 73.8 years) DP 23 mg/day ($n = 909$; female = 63.1%; mean age: 73.8 years)	SIB language subscale (SIB-L) SIB-Lang (a new 21-item version derived from principal components factor analysis)[c]	Significantly greater improvement of language functions with DP 23 mg compared with DP 10 mg At the endpoint, language functions decline from baseline in the DP 10-mg/day group but improved in the DP 23-mg/day group (SIB-L treatment difference 0.8, $p = 0.0013$; SIB-Lang treatment difference 0.8, $p = 0.0009$)	More AE were reported 23 mg/day (73.7%) than with 10 mg/day (63.7%). Doses of 23 mg induced mild (30.8%), moderate (34.5%), and severe (8.4%) AE, whereas doses of 10 mg/day induced mild (31.2%), moderate (25.3%), and severe (7.2%) AEs The most reported AEs probably related to the 23-mg/day dose were nausea (6.1 vs 1.9% with the 10-mg/day dose), vomiting (5.0 vs 4 0.8%), and diarrhea (3.2 vs 1.5%)
Rivastigmine					
Winblad et al. [224] IDEAL study	24-week, multicenter, DB, parallel-group, double-dummy, placebo- and active-controlled trial Four groups: Placebo 9.5 mg/24 h RV patch 17.4 mg/24 h RV patch 12 mg/day RV capsule	$n = 1195$ patients with AD ITT $n = 1053$ Placebo group ($n = 302$; female: 66.6%; mean age 73.9 years) 9.5 mg/24 h RV patch group ($n = 291$; female: 68%; mean age 73.6 years) 17.4 mg/24 h RV patch group ($n = 303$; female: 66%; mean age 74.2 years) RV 12-mg/day capsule group ($n = 294$; female: 65.6%; mean age 72.8 years)	ADAS-Cog[a,b]	Beneficial treatment effects of RV compared with placebo At the endpoint, mean change from baseline, ITT-LOCF analysis: on placebo 1.0; on 9.5 mg/24 h RV patch − 0.6 ($p = 0.005$ vs placebo); on 17.4 mg/24 h RV patch − 1.6 ($p < 0.001$ vs placebo); on RV capsule group was − 0.6 ($p = 0.003$ vs placebo) 17.4 mg/24 h and 9.5 mg/24 h RV patches showed non-inferiority to RV capsule	AEs were higher in the 17.4 mg/24 h patch and capsule groups compared with the placebo group. No statistically significant differences were found between the 9.5 mg/24 h patch and placebo groups The most frequent AEs were nausea and vomiting. Other AEs were diarrhea, weight decreased, dizziness, decreased appetite, headache, and asthenia. Most AEs were moderate or mild The proportion of patients who reported no, slight, or mild skin irritation was 90–98% across the patch's groups

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Cummings et al. [21] OPTIMA study	72- to 96-week, randomized, multi-center, parallel-group study Two phases: IOL phase: 24–48 weeks DB phase: 48-week randomized, DB, parallel-group phase Two groups: 9.5 mg/24 h RV patch 13.3 mg/24 h RV patch	n = 1.584 patients with mild-to-moderate AD IOL phase: 9.5 mg/24 h RV patch Evaluations at weeks 24, 36, and 48 (n = 1584; female: 62.3%; mean age 74.9 years) DB phase (n = 567). ITT n = 536 9.5 mg/24 h RV patch group (n = 287; female: 62.4%; mean age 75.9 years) 13.3 mg/24 h patch group (n = 280; female: 66.1%; mean age 75.6 years) ITT(DB)-LOCF: n = 271 (9.5 mg/24 h patch group); n = 265 (13.3 mg/24 h patch group)	ADAS-Cog[a,b]	Cognitive decline was less in the RV 13.3 mg/24 h treated group compared with the RV 9.5 mg/24 h group at DB phase week 24 (p = 0.027) but not at week 48 (p = 0.227) LS mean change from baseline during the DB phase, ITT-LOCF analysis: on RV 9.5 mg/24 h: 2.2 at 24 weeks and 4.9 at 48 weeks; on 13.3 mg/24 h RV: 1.0 at 24 weeks 4.1 at 48 weeks	In the DB, phase AEs were reported in greater proportion in the 13.3 mg/24 h patch group than in the 9.5 mg/24 h patch group. The most frequent AEs in this phase were gastrointestinal, psychiatric, and nervous system disorders Specific cholinergic AEs were also more frequently reported in the 13.3 mg/24 h patch group than in the 9.5 mg/24 h patch group. The most common were vomiting, nausea, weight and appetite decreased, and upper abdominal pain. The percentage of patients with these AEs decreased over time in both groups (exception for weight decrease) No differences were reported in application site skin AEs between both groups, this symptom decreased over time The proportion of severe AEs was similar between both groups in the DB phase. The most frequent severe AEs were infections and infestations and nervous system disorders The incidence of AEs and severe AEs leading to interruption in the DB phase was lower in the 13.3 mg/24 h patch than in the 9.5 mg/24 h patch group
Alva et al. [22] Factor analysis of individual items of the ADAS-Cog from the OPTIMA study (Cummings et al. [21])	Same as the DB phase from the OPTIMA study 48-week, randomized, multi-center, DB, parallel-group study	Same as the OPTIMA study (Cummings et al. 2012)	ADAS-Cog[a,b]	The 9.5 mg/24 h RV patch group showed a higher decline in the memory domain than the 13.3 mg/24 h RV patch group (p < 0.05; observed cases) at weeks 12, 24, and 48 It is worth noting that in this study, the “memory” domain encompasses language-related tasks such as object naming and following commands	Same as the OPTIMA study (Cummings et al. 2012)

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Galantamine					
Tariot et al. [228]	5-month, randomized, multicenter, placebo-controlled, DB, parallel-group trial Four groups: Placebo GAL 8 mg/day GAL 16 mg/day GAL 24 mg/day	$n = 978$ patients with mild-to-moderate AD ITT $n = 887$ Placebo ($n = 286$; female: 178; mean age: 77.1 years) GAL 8 mg/day ($n = 140$; female: 90; mean age: 76.0 years) GAL 16 mg/day ($n = 279$; female: 174; mean age: 76.3 years) GAL 24 mg/day ($n = 273$; female: 183; mean age: 77.7 years)	ADAS-Cog[a,b]	Beneficial effect of GAL 16 and 24 mg/day on the ADAS-Cog compared with placebo Significantly greater benefits in the two higher doses of GAL than the lower dose group Mean change baseline, ITT analysis: on placebo group: 1.7; on GAL 8 mg/day: 0.4 (p = ns vs placebo); on GAL 16 mg/day: −1.4 ($p < 0.001$ vs placebo; $p < 0.01$ vs GAL 8 mg/day); on GAL 24 mg/day: −1.4 ($p < 0.001$ vs placebo; $p < 0.01$ vs GAL 8 mg/day)	Proportion of any AEs (72% in the placebo, 75.7% in the GAL 8-mg/day group, 73.8% in the GAL 16-mg/day group and 80.2% in the GAL 24-mg/day group), any serious AEs (10.8% in the placebo, 10% in the GAL 8-mg/day group, 10% in the GAL 16-mg/day group and 12.8% in the GAL 24-mg/day group) and deaths (1.4% in the placebo, 0.7% in the GAL 8-mg/day group, 1.1% in the GAL 16-mg/day group, and 1.1% in the GAL 24-mg/day group) was similar between GAL-treated patients and those in the placebo group The rate of patients discontinuing treatment because of adverse events was also similar between groups (7% in the placebo, 6% in the 8 mg/day, 7% in the 16-mg/day group and 10% in the 24-mg/day group) The most frequent adverse events were nausea, vomiting, anorexia, agitation, and diarrhea
Raskind et al. [229]	6-month, randomized, multicenter, placebo-controlled, DB, parallel-group trial followed by a 6-month, open-label phase Three groups: Placebo GAL 24 mg/day GAL 32 mg/day	$n = 636$ mild to moderate AD patients ITT $n = 606$ Placebo ($n = 213$; female: 131; mean age: 75.3) 24 mg/day GAL ($n = 212$; female: 139; mean age: 75.9) 32 mg/day GAL ($n = 211$; female: 224; mean age: 75.0)	ADAS-Cog[a,b]	Significant improvements on ADAS-Cog compared with placebo Mean change from baseline, ITT LOCF analysis: on placebo group: 2.0; on GAL 24 mg/day GAL: 1.9 ($p < 0.001$ vs placebo); on GAL 32 mg/day: −1.4 ($p < 0.001$ vs placebo)	AEs were mostly mild to moderate in severity. The proportion of severe AEs was comparable across groups (13–16%). The proportion of patients that discontinued treatment because of AEs during the DB phase was higher in GAL-treated groups than in the placebo group (8% in the placebo group, 23% in the GAL 24-mg/day group, 32% in the GAL 32-mg/day group). Only 16% of patients withdrew from the open-label phase because of AEs Most reported AEs were nausea, vomiting, anorexia, dizziness, diarrhea, weight loss, and abdominal pain

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Wilkinson and Murray [231]	12-week, randomized, multicenter, placebo-controlled, DB, parallel trial Four groups: Placebo GAL 18 mg/day GAL 24 mg/day GAL 36 mg/day	$n = 285$ with suspected AD Placebo ($n = 87$; female: 59%; mean age: 74.2) 18 mg/day GAL ($n = 88$; female: 56%; mean age: 72.7) 24 mg/day GAL ($n = 56$; female: 59%; mean age: 72.9) 36 mg/day GAL ($n = 54$; female: 57%; mean age: 75).	ADAS-Cog[a,b]	Greater improvements in the ADAS-Cog were observed after treatment with GAL 24 mg/day than placebo, and a tendency to significance was found for GAL 24 mg/day compared with placebo Mean change from baseline, ITT LOCF analysis: on placebo group: 1.6; on GAL 18 mg/day: -0.1 (p = ns vs placebo); on GAL 24 mg/day: −1.4 ($p < 0.01$ vs placebo); on 36 mg/day GAL: −0.7 ($p < 0.08$ vs placebo)	Most AEs were mild and transitory and occurred mainly during the dose-escalation phase (5 days to 2 weeks). The rate of AEs was dose related (placebo 43.7%; 18 mg/day GAL 55.7%; 24 mg/day GAL 58.9%; 36 mg/day GAL 70.4%) The most frequent AEs were nausea, vomiting, diarrhea, headache, decreased appetite, and dizziness
Rockwood et al. [232]	3-month, randomized, multinational, placebo-controlled, single-blind trial Two groups: Placebo GAL 24-32 mg/day	$n = 386$ patients with probable AD placebo ($n = 125$; female: 67; mean age: 74.6) 24-32 mg/day GAL ($n = 261$; female: 148; mean age: 75.2)	ADAS-Cog[a,b]	Beneficial effect of GAL compared to placebo was observed Mean change from baseline, ITT LOCF analysis: on placebo group 0.6; on GAL 36 mg/day: −1.1 ($p < 0.01$ vs placebo)	GAL was well tolerated. AEs during the dose-escalation phase were more frequent in the GAL group than in the placebo group. Most AEs were mild and were reduced in the maintenance phase. The rate of serious AEs was comparable across groups (6% in the placebo and 8% in the GAL group). Discontinuations because of AEs were more common in the GAL than in the placebo group AEs that occurred at least 5% more often in GAL-treated patients than placebo were: nausea, dizziness, vomiting, anorexia, somnolence, abdominal pain, and agitation
Wilcock et al. [230]	6-month, randomized multinational, DB, placebo-controlled, parallel-group trial Three groups: Placebo GAL 24 mg/day GAL 32 mg/day	$n = 653$ mild to moderate AD Placebo group ($n = 215$; female: 132; mean age: 72.7) 24 mg/day GAL ($n = 220$; female: 139; mean age: 71.9) 32 mg/day GAL ($n = 218$; female: 138; mean age: 72.1)	ADAS-Cog[a,b]	Significantly better outcome on ADAS-Cog in the GAL groups than in the placebo group was observed Mean change from baseline, ITT analysis: on placebo group: 2.4; on GAL 24 mg/day: −0.5 ($p < 0.001$ vs placebo); on GAL 32 mg/day: −0.8 ($p < 0.001$ vs placebo)	AEs were mainly mild to moderate in severity, and the proportion of serious AEs was similar across groups (12–13%). Discontinuation because of AEs was more common in patients receiving GAL (18%; 79/438) than among the placebo group (9%; 19/215) AEs that occurred at least 5% more often in GAL-treated patients than placebo were: nausea, vomiting, diarrhea, dizziness, headache, anorexia, and weight loss

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Pirttilä et al. [236]	24-month, GAL 24-mg/day open-label extension study of two previous 12-month trials	$n = 491$ probable AD patients (female: 216; mean age: 73.1)	ADAS-Cog[a,b]	Beneficial effects of prolonged treatment with GAL 24 mg/day. Worsening on ADAS-Cog was lower than expected in 75.6% of patients under continuous treatment with GAL for 36 months (no change in ADAS-Cog in 15.3% of patients, 48.8% increase ≤ 10 points, 75.6% ≤ 20 points)	GAL 24 mg/day was well tolerated. Most AEs were mild to moderate in severity and unrelated to the study The most common AEs were agitation (17.5%), insomnia (14.7%), depression (12.4%), fall (11.2%), and urinary tract infection (10.2%)
Raskind et al. [237]	24-month, GAL 24-mg/day, open-label extension study of two previous 12-month trials	$n = 194$ patients (female: 56.7%; mean age: 76.1)	ADAS-Cog	Patients who received uninterrupted treatment of GAL for 36 months experienced an average increase of 10.2 points on the ADAS-Cog. This increase indicates a significantly lower cognitive decline (approximately 50%) than the expected for patients who did not receive treatment.	GAL was well tolerated. Most AEs observed were transitory and mild to moderate in intensity The AEs 10% more common in GAL-treated patients than placebo patients were agitation, urinary incontinence, fall, depression, insomnia, anorexia, injury, urinary tract infection, weight decrease, dizziness, and confusion
Suh et al. [233]	Randomized, DB, parallel-group, 16-week study Four groups: Community control group GAL 8 mg/day GAL 16 mg/day GAL 24 mg/day	$n = 300$ mild to moderate AD Community control group ($n = 66$; female: 75.8%; mean age: 76.8) GAL 8 mg/day ($n = 76$; female: 65.8%; mean age: 75.2) GAL 16 mg/day ($n = 78$; female: 84.6%; mean age: 74.4 years) GAL 24 mg/day ($n = 80$; female: 77.5%; mean age: 73.8 years)	ADAS-Cog/11-K[a,b] (Korean version of the ADAS-Cog/11)	Beneficial effects in all 3 GAL treated groups relative to baseline and compared with the control group in the ADAS-Cog/11-K (mixed model, $p < 0.001$) ADAS-Cog/11-K scores in the GAL 24-mg/day group were significantly higher than in the GAL 8-mg/day group	The incidence of AEs was similar in the combined treatment and control groups. The most reported AEs were dizziness, nausea, headache, weight loss, appetite loss, and vomiting. The only AE significantly higher in the treatment groups than the control group was nausea

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Lyketsos et al. [238]	12-month, GAL 24-mg/day, open-label extension of an earlier 5-month, DB, placebo-controlled trial with a 6-week withdrawal phase [228] Three phases: DB phase Withdrawal phase Open-label phase	$n = 699$ patients with mild to moderate AD GAL/GAL/GAL group ($n = 288$; female: 61.5%; mean age: 76.5 years) GAL/placebo/GAL group ($n = 189$; female: 66.7%; mean age: 77.0 years) Placebo/placebo/GAL group ($n = 204$; female: 64.2%; mean age: 77.1 years)	ADAS-Cog/11[a,b]	Patients from the GAL/GAL/GAL group maintained ADAS-Cog scores at or above baseline for 12 months, indicating sustained cognitive benefits	50.8% of AEs were mild, and 39.6% were moderate. The most frequent AEs, in order, were agitation, nausea, depression, anorexia, falls, diarrhea, urinary tract infection, confusion, dizziness, and insomnia. The incidence of AEs was similar in all groups
Brodaty et al. [234]	6-month, randomized, DB, placebo- and active-controlled, parallel-group trial Three groups: Placebo GAL 8 or 12 mg twice daily GAL PRC 16 or 24 mg/day	$n = 971$ patients with mild-to-moderate AD ITT $n = 715$ Placebo ($n = 320$; female: 64%; mean age: 76.3 years) GAL group ($n = 326$; female: 64%; mean age: 76.5 years) GAL PRC group ($n = 319$; female: 64%; mean age: 76.6 years)	ADAS-Cog/11[a,b]	GAL and GAL PRC groups showed significant better outcomes compared with the placebo group Mean change from baseline, ITT-LOCF analysis: on placebo group: 1.2; on GAL: −1.6 ($p < 0.001$ vs placebo); on GAL PRC: −1.3 ($p < 0.001$ vs placebo)	Patients in the GAL PRC, GAL, and placebo groups presented with at least 1 AE (79%, 72% and 70%, respectively). The most frequent AE was nausea, which occurred more frequently in both GAL groups than in placebo; vomiting and anorexia were also more frequently reported in both. Other reported AEs in the three groups were: psychiatric disorders, nervous system disorders, respiratory system disorders, nutritional disorders, and urinary system disorders
Rockwood et al. [235] VISTA study	4-month, randomized, multi-center, DB, placebo-controlled, parallel-group trial followed by a 4-month open-label phase Two groups: Placebo GAL 16–24 mg/day	$n = 130$ patients with mild-to-moderate AD Placebo group ($n = 64$; female: 62%; mean age: 78 years) GAL 16–24 mg/day ($n = 66$; female: 64%; mean age: 77 years)	ADAS-Cog	Significant better outcomes at 4 months in the GAL group compared with the placebo group ($p = 0.04$)	In the placebo-controlled phase, the proportion of any AEs was higher in the GAL group than in the placebo group (84.4 vs 62.1%) AEs that were at least 5% more often in GAL-treated patients than placebo were: nausea, vomiting, upper respiratory tract infection, and anorexia

Table 1 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs
Primary progressive aphasia					
Kertesz et al. [255]	26 weeks, DB, placebo-controlled, randomized withdrawal study Two phases: IOL phase: 18 weeks (with a 4-week titration GAL 4 mg/day phase and a 14-week GAL 8–12 mg/day maintenance phase) DB phase: 8-week DB, placebo-controlled randomized withdrawal (two groups: GAL 8–12 mg/day and placebo group)	Open-label phase $n = 39$ FTD-bv/PPA patients (FTD-bv = 17; PPA = 22) Open-label phase ITT $n = 36$ Open-label phase (female: 38%; mean age: 63.3 years) DB phase $n = 36$ DB phase ITT-LOCF $n = 34$ GAL 8–12 mg/day ($n = 18$; female: 11%; mean age: 63.6 years) Placebo group ($n = 18$; female: 56%; mean age: 63.1 years)	WAB-AQ[b]	No significant differences in behavior or language were found for the entire group. A significant treatment effect for GAL ($p = 0.009$) over placebo was found in the PPA subgroup in the placebo-withdrawal phase, but it did not survive after correction for multiple comparisons On WAB-AQ, GAL demonstrated significant advantages compared with placebo. However, these differences did not reach statistical significance once baseline differences among the groups were corrected	Patients who discontinued treatment because of AEs: three in the IOL phase, one in the GAL group, and one in the placebo group in the DB phase The most frequent AEs in the IOL phase included: nausea, diarrhea, headache, abdominal pain, dizziness, fatigue, dyspepsia (13%), vomiting, and agitation There were no significant differences in the proportion of AEs between the GAL-treated and placebo groups in the DB phase

AD Alzheimer's disease, *ADAS-Cog* Alzheimer's Disease Assessment Scale-Cognitive Subscale [10], *AE* adverse event, *DB* double-blind, *DP* donepezil, *FTD-bv* behavioral variant of frontotemporal dementia, *GAL* galantamine, *IOL phase* initial open-label phase, *ITT* intent-to-treat population, *LOCF* last observation carried forward, *LS* least-squares, *ns* not significant, *PPA* primary progressive aphasia, *PRS* prolonged-release capsule, *ns* non-significant, *RV* rivastigmine, *SBPW* single-blind placebo washout, *SD* standard deviation, *SE* standard error, *SIB* Severe Impairment Battery, *SIB-Lang* Severe Impairment Battery-derived language scales, *WAB-AQ* Aphasia Quotient of the Western Aphasia Battery

Ranges are shown in brackets

[a]Negative change indicates improvement

[b]Indicates that the battery/measure was used as a primary outcome measure. Domain-specific analysis of ADAS-Cog was not reported in these studies

[c]Indicates that SIB and SIB-L were used as co-primary endpoints. See text for further details

the language domain were specifically assessed only in three trials, two of them treating patients with the usual donepezil doses (10 mg/day) [216, 217] and another trial comparing low (10 mg/day) with high doses (23 mg/day) [20, 218] (Table 1). Analysis of language domains revealed that donepezil-treated patients (10 mg/day) improved in comparison with placebo [216] and with their baseline scores [217], and the other trial showed greater language benefits in patients with moderate-to-severe AD receiving donepezil 23 mg/day than in those receiving donepezil 10 mg/day [20]. Donepezil 23 mg (Aricept®) was approved in 2010 by the US Food and Drug Administration for advanced AD. Nevertheless, concerns have been raised regarding a higher rate of adverse cholinergic effects with donepezil 23 mg/day compared with lower doses [18, 214, 219, 220], although dropouts because of adverse events (cholinergic-related gastrointestinal events) with donepezil 23 mg/day usually decline after the first month of therapy [221]. Dose manipulation using intermediate titration strategies (10 mg and 23 mg on alternate days for 4 weeks or 15 mg for 4 weeks) before escalating to donepezil 23 mg/day showed better safety in terms of cholinergic adverse events (ODESA study) [222]. These data show that establishing the appropriate donepezil dosage is required. The availability of measuring cerebrospinal fluid/plasma concentration of donepezil would enable optimal adjustment of doses [223].

Table 1 also shows drug trials of the safety and efficacy of transdermal patches of rivastigmine on general cognition, including language deficits in AD, using the ADAS-Cog [21, 22, 224–226]. These studies were, in part, devised to examine whether this formulation contributes to overcoming the well-known central gastrointestinal adverse events of oral presentation [227]. Better responses were found with all rivastigmine doses (4.6 mg, 9.5 mg, and 13.3 mg) than with placebo, and patients receiving higher doses showed less decline than those receiving lower doses (see Table 1). The use of high doses of rivastigmine (transdermal delivery system, 13.3 mg/day) was approved by the US Food and Drug Administration in 2012 for the treatment of patients with mild-to-moderate AD who are experiencing a decline in overall function and cognition. In contrast, in the European Union, there was a change in 2013 from the previous application that concerned an extension of the indication to allow the 13.3 mg/24-h transdermal patch to be used to treat patients with severe AD. However, only one study reported data on the effect of rivastigmine on the language domain in AD [204] (Table 1). A sub-analysis of the OPTIMA study (a 24- to 48-week initial open-label phase followed by a 48-week, randomized, double-blind, parallel-group phase including 657 patients [205]), compared the efficacy of rivastigmine patches of 13.3 mg/24 h versus 9.5 mg/24 h on individual items and newly derived domains from the ADAS-Cog [22, 207]. This study showed greater efficacy of rivastigmine (13.3 mg/24 h vs 9.5 mg/24 h) on memory than language, but this result should be interpreted with caution because two subtests evaluating language (following commands and naming objects) were classified as memory subdomains [22]. In addition, rivastigmine at high doses was more effective in the language domain in patients with severe but not mild or moderate AD [22].

Beneficial effects of the prolonged-release galantamine formulation (16 and 24 mg/day) on the ADAS-Cog have been reported in comparison with placebo, with more significant benefits under higher doses of galantamine groups compared with lower doses [228–235] (Table 1). Moreover, the benefits of prolonged treatment (36 months) with galantamine 24 mg/day on the ADAS-Cog have also been reported [236–238]. A subdomain analysis of the ADAS-Cog was performed in a 52-week, open-label, observational clinical trial that included 66 patients with mild-to-moderate AD treated with galantamine (24 mg/day) [204]. Responders to galantamine showed significantly better scores than non-responders in memory and language subdomains but not in praxis and executive function [204].

In summary, studies have demonstrated that donepezil, rivastigmine, and galantamine can improve, stabilize, or slow down language functions decline in patients with AD, even in severe stages when high doses are used [20, 22, 228]. Innovative clinical trial designs explore combining AChEIs with non-pharmacological therapies such as speech and language therapy or non-invasive brain stimulation to enhance language and communication improvements [90, 239, 240]. This approach strengthens cholinergic learning-induced plasticity [241]. Responder analysis could guide treatment modification or cessation to optimize treatment for individual patients [11, 17, 240].

4.3.2 Down syndrome

Individuals with Down syndrome (DS) have a high risk of premature aging (> 40 years of age), and subsequent cognitive decline inexorably progresses to AD [161, 242]. Down syndrome is associated with many developmental impairments, including language abnormalities that progress throughout life [243]. As cholinergic neurotransmission is impaired in DS, the role of pharmacological cholinergic enhancement has been studied [244]. However, the quality of evidence from pharmacological interventions with AChEIs for treating cognitive decline in DS is low, thus precluding drawing consistent conclusions about the effectiveness of any of these interventions [245]. The treatment of language deficits in DS has been examined in a 24-week open-label clinical trial of donepezil in a small sample (n = 6) of young (age range 20–41 years, mean age: 29 years) individuals without dementia with low intellectual function (IQ range 40–60, mean IQ: 52) [246]. More benefits were

found in expressive than receptive language in individuals with higher language skills and IQ at baseline [246]. Further studies are strongly needed.

4.3.3 Atypical AD: The Aphasic Variant

Symptoms of AD can also atypically emerge with the slow dissolution of speech and language functions [247, 248], so that affected individuals meet the diagnostic criteria for PPA-AD. Neuropathological data on PPA-AD show asymmetric cortical involvement with more severe loss of AChE-positive cholinergic axons in the left-hemisphere's language regions than in other areas [15]. A meta-analysis of 1.251 patients with PPA analyzed the prevalence of amyloid β deposition (a biomarker for AD) using PET/cerebrospinal fluid biomarkers, neuropathological examinations, or different combinations of them. Amyloid β deposition was significantly more prevalent in logopenic PPA (86%) than in both non-fluent (20%) and semantic variants (16%) of PPA ($p < 0.001$), and these percentages increased with age and in apolipoprotein E ε4 carriers [249]. More than 50% of these patients had positive AD amyloid biomarkers [250], which increased to more than 95% for the logopenic PPA variant [251–253]. To advance the differential diagnosis in the initial stages of PPA variants, evaluation of connected speech using computerized methods can identify subtle language deficits in PPA [26, 197, 254]. Therefore, in comparison to other subtypes of PPA, the logopenic variant specifically warrants a stronger rationale for the utilization of AChEIs treatment.

Although the evidence above refutes the argument against using AChEIs for treating PPA-AD [9], only a single trial of galantamine in PPA has been performed to date [255]. Kertesz et al. [255] enrolled 36 patients with the behavioral variant of frontotemporal dementia or PPA in an open-label period of 18 weeks and a randomized placebo-controlled phase for 8 weeks with galantamine (Table 1). A trend for stabilization in language scores was found in the galantamine-treated group at drug withdrawal, whereas language performance in the placebo group deteriorated [255]. Future studies should further evaluate the role of AChEIs in selected samples of patients with PPA with evidence of cholinergic depletion (AD, Lewy body dementia) [37, 256]. In addition, the potential contribution of adding speech-language therapy and non-invasive brain stimulation to pharmacotherapy should also be evaluated [257].

5 Vascular Cognitive Impairment

Vascular brain abnormalities are frequent contributors to dementia, mainly owing to synergistic interactions with neurodegenerative pathologies (AD and others) [258, 259]. Increasing evidence indicates that various neuropathological pathologies often coexist in the older and oldest-old populations (mixed dementia) [260]. However, VCI may occur as an independent disorder [258, 261, 262] encompassing a continuum of cognitive phenotypes (subcortical ischemic vascular dementia, post-stroke dementia, multi-infarct dementia) [263] and severities, from subjective cognitive decline, and mild cognitive impairment to full-blown dementia [258].

Research on language disturbances in VCI still needs to be conducted [264]. The paucity of studies explicitly dealing with language and communication impairments in VCI possibly relies on focusing testing on previous studies on non-verbal cognitive deficits [265], whereas the assumed lack or mildness of language disturbances additionally prevents identifying subtle preclinical impoverishment in discourse and everyday communication. To further complicate matters in the mild-to-moderate VCI continuum, language deficits are very heterogeneous depending on the clinical subtypes and lesion locations. Nevertheless, language deficits in VCI seem to be very frequent [266]. Indeed, language deficits, defined either by aphasia, reduced verbal fluency, or abnormal auditory or written comprehension, were observed in more than 55% of participants in a drug trial of donepezil in VCI [266].

Post-mortem studies report that the loss of cholinergic function is only evident in VCI concurrent with AD [267–269]. However, the relevance of these negative data is uncertain because choline acetyltransferase was measured in a few cortical regions [268, 269]. In contrast, neocortical cholinergic denervation after multiple subcortical infarctions, sparing the CBF, but interrupting the ascending cholinergic pathways, was described in a young patient with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and impairments in language, memory, and visuospatial orientation [270]. This finding aligns with the involvement of long-distance white matter pathways in mild-to-moderate VCI [271], subjective cognitive impairment [272, 273], and cognitively unimpaired older people [8]. Cognitive deficits in VCI (psychomotor slowing, decreased attention, and impaired language and executive functions) can likewise result from lesions in deep gray nuclei (basal ganglia, thalamus) [274, 275] disrupting cholinergic innervation [276, 277].

Three pharmacological agents acting on ACh have been investigated to treat VCI with variable safety and efficacy profiles [11, 278]. Table 2 shows trials of AChEIs in VCI. An outcome analysis is focused on changes in language functions. Positive effects of donepezil were found in three trials [266, 279, 280] evaluating possible or probable vascular dementia, but not in another trial evaluating patients with CADASIL [281]. Results from rivastigmine trials were mixed with a lack of efficacy in two studies [282, 283] and positive outcomes in ADAS-Cog in another study [284].

Table 2 Trials of cholinergic pharmacotherapy in vascular cognitive impairment

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs (Alzheimer's disease)
Donepezil					
Wilkinson et al. [280] The Donepezil 308 Study Group	Randomized, double-blind, placebo-controlled, parallel-group, 24-week study	$n = 616$ patients with possible or probable VaD Female: 40.1%; mean age: 75.0 years ± 0.3 SD DP 5 mg/day ($n = 208$); DP 10 mg/day ($n = 215$); placebo ($n = 193$)	ADAS-Cog[a,b]	Positive effects on ADAS-Cog with DP 5 and 10 mg/day. LS mean change ± SE from baseline to week 24 ITT LOCF compared with placebo, on ADAS-Cog: placebo − 0.10 ± 0.39; DP 5 mg/day, − 1.75 ± 0.33 ($p < 0.01$); DP 10 mg/day − 2.19 ± 0.44 ($p < 0.001$)	The proportion of AEs was similar in the DP and placebo groups. At least one AE was reported in 86.5% of the placebo group, 90.4% of the DP 5-mg/day group, and 91.6% of the DP 10-mg/day group AEs with greater frequency in the DP 5-mg/day group than placebo were: accidental injury, insomnia, leg cramps, and rhinitis. The DP 10-mg/day group presented with diarrhea, nausea, abnormal dreams, leg cramps, and rhinitis more frequently than controls
Black et al. [279] The Donepezil 307 Vascular Dementia Study Group	Randomized, multinational, double-blind, placebo-controlled, parallel-group, 24-week study	$n = 603$ patients with possible or probable VaD Female: 44.8%; mean age: 73.9 ± 0.3 SD DP 5 mg/day ($n = 198$); DP 10 mg/day ($n = 206$); placebo ($n = 199$)	ADAS-Cog[a,b]	Improvements on ADAS-Cog with DP 5 and 10 mg/day. LS mean change ± SE from baseline to week 24 ITT LOCF compared with placebo, on ADAS-Cog: placebo 0.72 ± 0.40; DP 5 mg/day − 0.96 ± 0.39 ($p = 0.01$); DP 10 mg/day − 1.52 ± 0.40 ($p < 0.001$)	A high incidence of AEs was reported in all groups. Most AEs were mild to moderate and resolved without discontinuing treatment. The proportion of patients experiencing AD was similar between the placebo (88.4%) and the DP 5-mg/day group (88.9%). A higher incidence was reported in the DP 10-mg/day group than in the placebo group (94.7%, $p < 0.03$) DP (both doses) was more frequently associated with cramps and anorexia than placebo. Diarrhea and headache were more frequent in the DP 5-mg/day group, and nausea, vomiting, and abnormal dreams in the DP 10-mg/day group than in the placebo group

Table 2 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs (Alzheimer's disease)
Dichgans et al. [281]	Randomized, multinational, double-blind, placebo-controlled, parallel-group, 18-week study	$n = 168$ patients with CADASIL Female: 46.4%; mean age: 54.8 years DP 10 mg/day ($n = 86$); placebo ($n = 82$)	V-ADAS-Cog[a,b] ADAS-Cog[a]	DP 10 mg/day has no significant effect on V-ADAS-Cog, ADAS-Cog, or MMSE. LS mean change ± SE from baseline to week 18 LOCF compared with placebo, on V-ADAS-Cog: placebo − 0.81 ± 0.59; DP − 0.85 ± 0.57 ($p = 0.956$); on ADAS-Cog: placebo − 0.78 ± 0.51; DP − 0.72 ± 0.49 ($p = 0.932$)	The proportion of AEs was higher in the DP group (81%) than in the placebo group (71%). Generally, AEs were mild to moderate and resolved without discontinuing treatment. The frequency of AEs as a reason for discontinuation was similar in both groups, but for nausea and vomiting, which were higher in the DP group (3 vs 0%). Commonly occurring AEs included gastrointestinal, musculoskeletal, nervous system, and psychiatric disorders
Román et al. [266]	Randomized, multinational, double-blind, placebo-controlled, 24-week study	$n = 974$ patients with possible or probable VaD Female: 41%; mean age: 73 years DP 5 mg/day ($n = 648$); placebo ($n = 326$)	V-ADAS-Cog[a,b] ADAS-Cog[a]	Improvements on V-ADAS-Cog, ADAS-Cog with DP 5 mg/day. LS mean ± SE change from baseline to week 24 LOCF compared with placebo, on V-ADAS-Cog: placebo 0.12 ± 0.35; DP 5 mg/day − 1.03 ± 0.25 ($p < 0.001$); on ADAS-Cog: placebo − 0.33 ± 0.29; DP 5 mg/day − 1.04 ± 0.21 ($p = 0.046$)	The proportion of AEs was similar between groups (80.7 vs 77.6%, DP and placebo groups, respectively). AEs were generally mild to moderate, with transient symptoms. Severe AEs were reported in 12.7% of patients receiving DP and 11% of the placebo group. A greater rate of patients in the DP group discontinued treatment because of AEs (11%) than in the placebo group (5.5%) More frequent AEs included: nausea, anorexia, abdominal pain, diarrhea, abnormal dreams, hypertonia, and leg cramps
Rivastigmine					
Moretti et al. [282]	22-month, open-label study	$n = 16$ patients with dementia and probable VaD Female: 37.5%; mean age, 72 years RV 3–6 mg/day ($n = 8$); cardio-aspirin 100 mg/day ($n = 8$)	Phonological and semantic word fluency (WFp and WFs)	No effect of RV 3–6 mg/day on word fluency compared with cardio-aspirin 100 mg/day. Mean change ± SD from baseline to month 22	All patients completed the study. No severe AEs were reported AEs in the RV group included: transitory nausea, muscle contraction, anorexia, syncope, and postural hypotension. In the cardio-aspirin group, AEs included: nausea, anorexia, heartburn, constipation, and dizziness

Table 2 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs (Alzheimer's disease)
Ballard et al. [284]	Randomized, multi-center, double-blind, placebo-controlled, parallel-group, 24-week study	$n = 710$ patients with probable VaD Female: 37.7%; Mean age: 72.8 years RV 3–6 mg/day ($n = 365$); placebo ($n = 345$)	VaDAs (ADAS-Cog and five additional tests including verbal fluency)[a,b] ADAS-Cog[a]	Positive effects of RVon VaDAs, ADAS-Cog. Mean change ± SE from baseline to week 24, on VaDAs ITT: placebo 0.6 ± 0.48; RV − 0.7 ± 0.47 ($p = 0.028$); on ADAS-Cog: placebo 0.4 ± 0.38; RV − 0.7 ± 0.38 ($p = 0.029$)	AEs were mostly mild to moderate. Serious AEs occurred in 15.2% of the RV group and 11.0% of the placebo group The most common AEs were nausea (26.4 vs 3.8% of RV and placebo groups, respectively), vomiting (22 vs 2.3%), diarrhea (9.1 vs 4.4%), and dizziness (8 vs 4.9%)
Narasimhalu et al. [283]	Randomized, double-blind, placebo-controlled, 24-week study	$n = 50$ patients with ischemic stroke with cognitive impairment (no dementia) Female: 66%; mean age: 69 years RV 1.5–9 mg/day ($n = 25$); placebo ($n = 25$)	ADAS-Cog[a] Cognitive Battery including animal and food verbal fluency	No effect of RV on ADAS-Cog ($p = 0.21$) A positive effect of RVcompared with placebo in animal verbal fluency. Mean change from baseline to week 24: placebo 0.03; RV1.7 ($p = 0.02$)	The incidence of clinically significant AEs was similar in the RV and placebo groups (36 vs 40% of patients in the RV and placebo groups, respectively). One death and five patients with severe AEs in each group were reported. Two patients in the RV and three in the placebo group discontinued treatment because of clinically significant AEs. The most frequent AEs were: nausea (4 vs 0%), vomiting (12 vs 0%), diarrhea (4 vs 0%), headache (4 vs 8%), giddiness /dizziness (8 vs 0%), gastrointestinal upset (4 vs 4%), sleeping difficulties (4 vs 0%), breathlessness (4 vs 4%), and chest pain (8 vs 0%)
Galantamine					
Erkinjuntti et al. [285]	Randomized, multi-center, double-blind, placebo-controlled, 6-month study	$N = 592$ patients with probable VaD or Alzheimer's disease combined with cerebrovascular disease Female: 47%; mean age: 75 years GAL 24 mg/day ($n = 396$); placebo ($n = 196$)	ADAS-Cog/11 (11-item versions)[a,b] Also, ADAS-Cog/13 (includes two additional items: comprehension and concentration/distractibility)	Positive effects of GAL compared with placebo on ADAS-Cog/11 and ADAS-Cog/13 Mean change ± SE from baseline to month 6 ITT, on ADAS-Cog/11: placebo 1.0 ± 0.5; GAL − 1.7 ± 0·4 ($p < 0.001$); on ADAS-Cog/13: placebo 0.9 ± 0.6; GAL − 2.4 ± 0.4 ($p < 0.001$)	The proportion of patients with any AEs was higher in the GAL group than in the placebo group (83.3 vs 67.9%). Most AEs were mild to moderate and transitory. More GAL patients than placebo patients discontinued treatment (19.7 vs 8.2%). Nine patients (2.3%) in the GAL group and seven (3.6%) in the placebo group died. The most frequent AEs were nausea (23.5 vs 7.1% of GAL and placebo groups, respectively), vomiting (12.9 vs 5.6%), and injury (3.8 vs 15.1%)

Table 2 (continued)

Study identification	Study design	Sample characteristics and dose	Neuropsychological tests including language assessment items	Outcomes	AEs (Alzheimer's disease)
Auchus et al. [286]	Randomized, double-blind, placebo-controlled, parallel-group, multinational, 26-week study	$n = 786$ patients with probable VaD Female: 36%; mean age: 72.3 years ± 8.9 SD GAL 8–24 mg/day ($n = 396$); placebo ($n = 390$)	ADAS-Cog/11 (11-item versions)[a,b] Also, ADAS-Cog/13 (includes two additional items: distractibility and delayed word recall test) and ADAS-Cog/10 (includes 10 non-memory items from ADAS-Cog)	Greater improvement with GAL compared with placebo on ADAS-Cog/11, ADAS-Cog/13, and ADAS-Cog/10. Mean change ± SD from baseline to week 26 ITT LOCF, on ADAS-Cog/11: placebo − 0.3 ± 6.32; GAL − 1.8 ± 5.94 ($p = 0.001$); on ADAS-Cog/13: placebo − 0.4 ± 7.3; GAL − 2.3 ± 6.9 ($p = 0.001$); on ADAS-Cog/10: placebo − 0.1 ± 4.6; GAL − 0.9 ± 4.2 ($p = 0.01$)	The proportion of patients with at least one AE was 76% in the GAL group and 71% in the placebo group. Most AEs were mild to moderate. Serious AEs occurred in 20% of GAL patients and 18% of placebo patients. 13% of GAL patients and 6% of placebo patients discontinued treatment because of AEs The most frequent AEs were: nausea (13 vs 4% of the galantamine and placebo groups, respectively), diarrhea (9 vs 6%), vomiting (8 vs 2%), fall (7 vs 9%), dizziness (14 vs 7%), anorexia (6 vs 1%), injury (6 vs 6%), and urinary tract infection (6 vs 7%)

ADAS-Cog Alzheimer's Disease Assessment Scale-Cognitive Subscale, *AE* adverse event, *DP* donepezil, *GAL* galantamine, *ITT* intent-to-treat population, *ITT LOCF* intention to treat-last observation carried forward, *LOCF* last observation carried forward, *LS* least-squares, *ns* non-significant, *RV* rivastigmine, *SD* standard deviation, *SE* standard error, *VaD* vascular dementia, *VaDAs* Vascular Dementia Assessment Scale, *WFp* word fluency phonological, *WFs* word fluency semantic

[a]Negative change indicates improvement

[b]Indicates that the battery/measure was used as a primary outcome measure

[c]Domain-specific analysis of ADAS-Cog was not reported in these studies. Information on the Clinician's Interview-Based Impression of Change-Plus version that includes subjective language/speech functioning based on patients and informants' interviews in six trials [262, 275, 276, 280–282] has not been included

Two galantamine trials yielded positive outcomes in different versions of the ADAS-Cog in probable vascular dementia [285, 286]. In one network meta-analysis, Battle and coworkers [287] reviewed potential differences in the efficacy and safety of donepezil, rivastigmine, and galantamine in eight placebo-controlled randomized controlled trials (4373 participants) in VCI, including possible or probable vascular dementia or cognitive impairment following stroke. This meta-analysis included 2193 patients treated with donepezil [266, 279, 280], 800 with rivastigmine [283, 284, 288] at usual doses (donepezil: 5 and 10 mg/day, rivastigmine: 3–12 mg/day) and higher doses of galantamine (16–24 mg/day) were given to 1380 patients [285, 286]. Shi et al. [289] also reviewed the trials of AChEIs combined with memantine. The primary outcome measures for cognition were the Vascular AD Assessment Scale-Cognitive Subscale, a scale that also assesses executive function [290] not included in the ADAS-Cog [207]. However, the primary outcomes measures in two reviewed trials [283, 288] were different. The Mini-Mental State Examination [291] and the Frontal Assessment Battery [292] were tested in one trial [288], whereas the Ten-Point Clock Drawing [293] and Color Trails 1 and 2 [294] were used in the other [283]. In addition, concerns about the utility of the different versions of the ADAS-Cog [207] in preclinical and mild cognitive impairment phases of AD and VCI have been raised [295]. Although the ADAS-Cog [207] evaluates memory, language, and praxis domains, item-specific analyses were not performed in the reviewed trials of VCI, which precludes reaching valid conclusions on the role of AChEIs in language impairments in the different types of VCI.

5.1 Post-Stroke Aphasia

Aphasia, defined as the impairment of language functions caused by left-hemisphere damage [84, 296], is considered an important cause of disability and reduced quality of life in stroke victims [297, 298]. In addition, aphasia is one of the most frequent neurological symptoms associated with large territorial or strategically placed infarcts in patients with VCI and dementia [299].

Speech and language therapy interventions are the mainstay options for treating PSA [296, 300, 301]. Several important advances in developing precision rehabilitation approaches for PSA have been met during the past few years [4, 300, 302–307]. First, the central issue of establishing the minimum frequency, intensity, and dosage of speech and language therapy to promote a beneficial response has been addressed [304, 305, 307]. Second, a consensus statement provided evidence-based recommendations for evaluating outcome measures, including key domains beyond language and communication deficits, such as emotional well-being and quality of life [308]. Third, the current understanding of neurobiological mechanisms responsible for PSA recovery is enriched by information provided by biomarkers, pharmacotherapy, and non-invasive brain stimulation [4, 302].

Benefits provided by speech and language therapy can be enhanced by adding pharmacotherapy [40]. Implementing this combined intervention in PSA is gaining credence because the adjunction of a cholinergic agent to aphasia therapy not only augments benefits but can also speed up recovery [12, 309]. Information on the pharmacotherapy of PSA with cholinergic agents comes from randomized placebo controlled trials (two studies) [139, 310], case–control studies (two studies) [311, 312], open-label studies (two studies) [12, 312, 313], case-series [309], and single cases [7, 86, 276, 314, 315]. Table 3 shows pharmacological trials targeting the cholinergic system in PSA. Available data on the cholinergic treatment of PSA with AChEIs reveal a total of 156 treated patients (111 with donepezil, 5 and 10 mg/day; and 45 with galantamine, 8 and 16 mg/day). Ninety-six patients were treated in the chronic period and 60 in the acute phase. A single patient with severe PSA was treated with rivastigmine without benefits [316]. All but one study [310] reported significant improvements in aphasia severity with gains in spontaneous speech, repetition, naming, and auditory comprehension. Communication in activities of daily living showed significant improvements in the four trials where this function was tested [7, 12, 86, 139]. The study showing a negative effect of donepezil found that the drug worsened comprehension compared with the placebo [310]. As the sample in that trial comprised 20 participants with moderate ($n = 13$) and severe ($n = 7$) Wernicke's aphasia ($n = 11$) and global ($n = 9$) chronic PSA [310], the negative results could probably be reliant on aphasia severity [4]. In support of this argument, an evaluation of a responder analysis in two trials [139, 313] showed that most patients with moderate and severe aphasias did not respond to donepezil [317]. Adverse events in the reviewed trials were mild and rarely required a dose reduction but not drug withdrawal. Compared with the relatively high frequency in AD, the mildness of PSA adverse events could be attributed to the later population's younger age and short duration of trials.

Based on the positive outcomes of drug trials with donepezil and galantamine, the interest in the pharmacological treatment of PSA is growing [4, 43, 298, 318–323]. Therefore, the initiative of treating language and communication deficits in PSA with AChEIs received more attention in the past two decades than the option of modulating the cholinergic system with drugs to attenuate language deficits in AD, PPA-AD, and VCI. It is possible that the investigation of other potential therapeutic targets for these conditions overshadowed further analysis of cholinergic deficits [324]. Moreover, the modest benefits obtained with AChEIs in AD [325, 326] and VCI [278] and the absence of benefits in CADASIL [281] may have also contributed to reducing

Table 3 Trials of cholinergic pharmacotherapy in post-stroke aphasia

Authors/year	Study design and sample size	Aphasia evolution (mean ± SD)	Age of patients (mean ± SD), years	Drug, duration/dose	Other treatments	Language tests	Outcomes	Adverse events
Berthier et al. [313] Berthier [296]	16-week, open-label pilot study with 6 months post-washout under DP $n = 11$	Chronic stage 4.4 ± 3.5 years	56 ± 13.2	Weeks 0–4: DP 5 mg/day Weeks 5–16: DP 10 mg/day Weeks 17–20: washout	Distributed SLT, 2 h/week	WAB-AQ[a], PALPA subtests	Significant improvement in the WAB-AQ from baseline to endpoints at weeks 4 ($p < 0.01$) and 16[a] ($p < 0.01$) Significant improvement of PALPA subtests tapping nonword pairs discrimination ($p < 0.01$), word repetition ($p < 0.01$), naming ($p < 0.05$), and oral sentence-picture match ($p < 0.01$) from baseline to endpoint at week 4; and on subtests tapping nonword repetition ($p < 0.01$) and oral sentence-picture match ($p < 0.01$) from baseline to endpoint at week 16 No differences in task performance (WAB-AQ and PALPA) between DP 5 mg/day and DP 10 mg/day. Performance in WAB-AQ remained above baseline scores after DP withdrawal Benefits were maintained in WAB-AQ after a 6-month extension phase of DP alone	Mild irritability and increased sexual drive ($n = 2$) in the open-label pilot phase[a] and no adverse events in the post-washout 6 months under DP.

Table 3 (continued)

Authors/year	Study design and sample size	Aphasia evolution (mean ± SD)	Age of patients (mean ± SD), years	Drug, duration/dose	Other treatments	Language tests	Outcomes	Adverse events
Berthier et al. [139]	20-weeks, double-blind, randomized, placebo-controlled, parallel-group study $n = 26$ Two groups: DP group: $n = 13$ Placebo group: $n = 13$	Chronic stage 36.0 ± 30.5 months	DP group: 48.1 ± 10.6 Placebo group: 48.3 ± 9.2	Weeks 0–4: DP 5 mg/day Weeks 5–16: DP 10 mg/day Weeks 17–20: washout	Distributed SLT, 2 h/week	WAB-AQ[a] CAL[a] PALPA subtests	Severity of aphasia (WAB-AQ) improved more in the DP group than in the placebo group at endpoint [week 16] ($p = 0.037$) Performance in the picture naming subtest of the PALPA improved more in the DP than in the placebo group at the endpoint [week 16] ($p = 0.025$) Performance in the CAL improved more in the DP than in the placebo group when comparing 5 mg/day with 10 mg/day	More adverse events in the DP group (61%) than in the placebo group (23%). Irritability (30%), insomnia, and tiredness (15%) were observed only during DP titration. Recurrence of poststroke seizures (15%) under DP without relapsing after a dose reduction. Adverse events in the placebo group included headache ($n = 1$), abnormal dreams ($n = 1$), and anorexia ($n = 1$)
Chen et al. [312]	12-weeks, case–control pilot study $n = 60$ Two groups: DP group and control group	Acute stage	–	Weeks 0–12: DP 5 mg/day	Not reported	WAB-AQ[a]	The improvement in the WAB-AQ was greater in the DP group (34.14 ± 17.70) than that in the control group [20.69 ± 17.26] ($p = 0.004$). All verbal WAB subtests significantly improved in the DP group ($p = 0.05$)	Not reported

Table 3 (continued)

Authors/year	Study design and sample size	Aphasia evolution (mean ± SD)	Age of patients (mean ± SD), years	Drug, duration/dose	Other treatments	Language tests	Outcomes	Adverse events
Woodhead et al. [310]	25-weeks, randomized, double-blind, placebo-controlled cross-over design $n = 20$	Chronic stage	62.4 (range: 43–90)	25 weeks (5 phases): drug only (DP 5 mg/day); drug (DP 10 mg/day) and phonological training; placebo only; placebo and phonological training The presentation order of placebo and drug phases differed between the two randomized groups	Auditory-phonological training (10 h/week for 5 weeks)	CAT[a]	Phonological training significantly improved auditory comprehension in patients with severe aphasia ($p < 0.05$) DP worsened speech comprehension compared with placebo ($p < 0.005$), but a trend towards better picture naming was found with the active drug compared with the placebo ($p = 0.075$)	No significant differences in the number of adverse events between DP (32) and placebo (28) ($p > 0.2$). The most frequent adverse events were insomnia, headaches, dizziness, and muscle cramps
Berthier et al. [12]	10-week open-label study $n = 10$	Chronic stage 30.1 ± 21 months	51.6 ± 5.8	Weeks 0–8: DP 5 mg/day and DP 10 mg/day Weeks 9–10: DP 10 mg/day and plus ILAT	ILAT (3 h/day; total: 30 h in 2 weeks)	WAB-AQ[a]	Significant improvements in overall aphasia severity (WAB-AQ) from baseline to both endpoints (DP alone: $p < 0.001$; DP and ILAT: $p < 0.001$)	Mild irritability, sleep problems, and occasional headaches in three patients occurred, not forcing a reduction in dose or withdrawal of drug treatment at any time

Table 3 (continued)

Authors/year	Study design and sample size	Aphasia evolution (mean ± SD)	Age of patients (mean ± SD), years	Drug, duration/ dose	Other treatments	Language tests	Outcomes	Adverse events
Hong et al. [311]	16-week, open-label case- controlled study $n = 45$ Two groups: GAL group ($n = 23$); control group ($n = 22$)	Chronic stage 2.2 ± 1.5 years	60.4 (range: 22–74)	Weeks 0–4: GAL 8 mg/day Weeks 5–16: GAL 16 mg/day	Not reported	WAB-AQ and its language subtests[a]	Significant improvements in the WAB-AQ in the GAL group ($p = 0.007$) from baseline to endpoint (week 16). Significant improvements in the GAL group in most of the WAB subtest: spontaneous speech ($p = 0.027$), comprehension ($p = 0.018$), and naming ($p = 0.013$) No changes observed in the control group on WAB-AQ ($p = 0.308$) Educational background, scores in MMSE, and subcortical involvement predicted a good response to GAL	Not reported

Trials shown in the Table treated included ≥10 patients. Only approved drugs are included in the Table. Information on single cases and case series have been described in text when appropriate (Sect. 5.1)

CAL Communicative Activity Log, *CAT* Comprehensive Aphasia Test, *DP* donepezil, *GAL* galantamine, *ILAT* Intensive Language-Action Therapy, *MMSE* Mini-Mental State Examination, *PALPA* Psycholinguistic Assessments of Language Processing in Aphasia, *SD* standard deviation, *WAB-AQ* Aphasia Quotient of the Western Aphasia Battery

[a]Primary outcomes measures

incentives for further research on investigating the role of AChEIs in cognitive-specific domains (language and communication) in AD, PPA, and VCI. However, a reformulation of the cholinergic hypothesis in the pathogenesis of AD and the development of more alternatives of cholinergic therapies are underway [14, 17, 85, 161].

6 Conclusions

Influential neuroscientific studies have linked language functions with the activity of several neurotransmitters, including Ach [2, 3, 5, 6, 40, 42, 54, 321]. As a result, current models of language processing and advances in its neurobiology are contributing to appraising the modulatory role of ACh in human language functions [1, 5, 7, 43, 327]. Therefore, it is crucial to understand how the cholinergic system and language interact. That may entail identifying the brain regions that receive cholinergic innervation and are involved in language and cognitive control, as well as determining how these regions can be modulated with pharmacotherapy to improve language domains affected by cholinergic dysfunction.

Even though subtle language and communication deficits in AD and VCI may emerge before the onset of clinical symptoms, the putative role of cholinergic depletion on language deficits has received limited attention. Most pivotal trials evaluating the safety and efficacy of cholinergic agents in AD and VCI did not focus on the cognitive evaluation of language domains. They used coarse-grained testing tools, thus overlooking the preclinical identification of altered language integrity. As early detection of language deficits is essential in neurodegenerative and vascular brain diseases to prevent further deterioration [16, 17], it is imperative to take advantage of emerging developments in cholinergic biomarkers, such as multimodal neuroimaging, to enhance precision in diagnosis and implement individualized treatment. This information could help decide whether to use cholinergic pharmacotherapy in doubtful cases and assess the treatment effect in patients with demonstrated reduced cholinergic activity in the very early stages of language dissolution.

Available cholinergic agents targeting global cognition, behavior, and activities of daily living have been tried over the years for the symptomatic treatment of AD [328] and VCI [11] and are being investigated for PSA [4, 321]. Based on recent evidence, researchers advocate that AChEIs have not reached their therapeutic ceiling. They recommend further studies to examine whether they remain a cornerstone treatment for AD, particularly when combined with disease-modifying therapies [17]. Future studies should address the drawbacks of the reviewed cholinergic trials on AD and VCI, which used coarse-grained testing batteries and relied mostly on the total sum scores of ADAS-Cog to estimate language functioning. This approach precludes the assessment of the role of AChEIs on specific language subdomains. In addition, the ADAS-Cog fails to capture essential changes in language and memory during the pre-dementia and mild cognitive impairment phases of AD and VCI [295], thus undermining the detection of beneficial changes induced by pharmacological treatments in these early stages. Finally, as all of the clinical trials reviewed were conducted before developing novel neuroimaging biomarkers, additional trials are necessary to explore further the potential of cholinergic treatments for AD and VCI.

The data analysis revealed a slower decline or improvement in language performance among patients with neurodegenerative and vascular brain diseases treated with AChEIs. However, the limited positive results found in language domains call for well-designed intervention trials that comprehensively evaluate language and verbal communication (e.g., fine-grained language testing and automatic detection of speech errors) and consider language a co-primary endpoint [20]. Further, given that the benefits of AChEIs in AD and VCI trials have been modest [329], possibly owing to the absence of concomitant cognitive training, future studies should explore the joint application of AChEIs and language rehabilitation, which has been suggested to be more effective than the "drug-only" approach in previous research [90, 239]. The theoretical justification for using combined drug-behavioral interventions in future trials of AD and VCI is the well-known capacity of ACh and behavioral interventions to maximize experience-dependent plasticity [90]. This combined intervention has augmented and expedited benefits in language skills in previous pharmacological trials of PSA [12, 330, 331]. Furthermore, trials using AChEIs in patients with PPA and positive biomarkers of cholinergic depletion, such as the logopenic variant and PPA-AD, are strongly needed. That would help identify the role of AChEIs in language functions in these populations, which has yet to be fully explored.

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Author contributions All authors contributed to the article and have read and approved the submitted version. GD, MJT-P, DL-B, and MLB substantially contributed to the conception and design of the article, as well as the interpretation of the relevant literature. All authors contributed to drafting several versions of the manuscript and revised it critically for important intellectual content. MLB formulated the idea for the publication and critically revised the final manuscript.

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