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REVIEW

Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia

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Abstract: Several studies have demonstrated clinical benefits of sustained cholinesterase inhibition with rivastigmine in Alzheimer's disease (AD) and Parkinson's disease dementia (PDD). Unlike donepezil and galantamine that selectively inhibit acetylcholinesterase (AChE; EC 3.1.1.7), rivastigmine is a unique cholinesterase inhibitor with both AChE and butyrylcholinesterase (BuChE; EC 3.1.1.8) inhibitory activity. Rivastigmine is also available as transdermal patch that has been approved by the US Food and Drug Administration for the treatment of mild, moderate, and severe AD as well as mild-to-moderate PDD. In this review, we explore the role of BuChE inhibition in addition to AChE inhibition with rivastigmine in the outcomes of cognition, global function, behavioral symptoms, and activities of daily living. Additionally, we review the evidence supporting the use of dual AChE−BuChE inhibitory activity of rivastigmine as a therapeutic strategy in the treatment of neurological disorders, with a focus on the role of rivastigmine in subcortical dementias such as vascular dementia (VaD) and PDD. Toward this objective, we performed a literature search in PubMed and Ovid with limits to articles published in the English language before June 2016. The available evidence from the literature suggests that the dual inhibition of AChE and BuChE may afford additional therapeutic potential of rivastigmine in subcortical dementias (subcortical VaD and PDD) with benefits on cognition and behavioral symptoms. Rivastigmine was found to specifically benefit executive dysfunction frequently observed in subcortical dementias; however, large randomized clinical studies are warranted to support these observations.

Keywords: acetylcholinesterase, BuChE genotype, butyrylcholinesterase, Parkinson's disease dementia, rivastigmine, subcortical vascular dementia

Introduction

Cholinesterase inhibitors were developed based on the cholinergic hypothesis of Alzheimer's disease (AD), and in this condition, degeneration of cholinergic neurons in the brain leads to reduction in the levels of acetylcholine and cholinergic function, resulting in cognitive deficits.[1–3] Cholinesterase inhibitors reduce degradation of synaptic acetylcholine, improve brain acetylcholine levels in a dose-dependent manner, and thereby enhance cholinergic transmission in patients with Alzheimer's and other dementias.[4,5] Donepezil and galantamine are cholinesterase inhibitors with acetylcholinesterase (AChE; EC 3.1.1.7)-inhibiting activity, whereas rivastigmine inhibits both AChE and butyrylcholinesterase (BuChE; EC 3.1.1.8).[6] Evidence suggests that cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine

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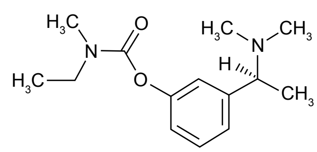
provide symptomatic pharmacological treatment, improving cognition and global function in patients with dementia.[7,8] Currently, the cholinesterase inhibitors approved by the US Food and Drug Administration (FDA) for the treatment of mild-to-moderate AD include donepezil,[9] rivastigmine,[10,11] and galantamine.[12] The US FDA also approved memantine, an *N*-methyl-D-aspartate receptor antagonist, for the treatment of moderate-to-severe AD.[13]

Rivastigmine is a pseudo-irreversible, carbamate-type, brain-selective, dual AChE–BuChE inhibitor (the structure and properties are shown in Table 1). The pharmacokinetic profile showed that compared with the oral formulation, rivastigmine transdermal patch provides smoother and continuous as well as controlled drug delivery over 24 h, thereby resulting in fewer side effects.[14–16] The transdermal patch formulation of rivastigmine has been approved in the US (FDA) for the treatment of mild, moderate, and severe AD and mild-to-moderate Parkinson's disease dementia (PDD),[11] and in the European Union, it is approved for the treatment of mild-to-moderately severe AD.[17] Both AD and PDD are associated with cortical cholinergic deficits[18] and therefore form the rationale for the use of pharmacological symptomatic treatment. The findings from an in vivo positron emission tomography (PET) imaging study showed greater cortical AChE deficit in patients with PDD than in those with AD.[18] Rivastigmine exerts symptomatic therapeutic effects through increasing acetylcholine levels in the brain, thereby making more acetylcholine available for synaptic transmission.[10,11,19] This increase in brain acetylcholine levels is believed to be responsible for the clinical improvements in AD and PDD.

Table 1 Structure and pharmacological features of rivastigmine[10,11]

Chemical name	(S)-3-[1-(dimethylamino) ethyl]phenyl ethylmethylcarbamate
Molecular formula	$C_{14}H_{22}N_2O_2$
Molecular weight	250.34
Structure	
Chemical class	Carbamate derivative
Pharmacologic class	Cholinesterase inhibitor
Cholinesterase inhibition	Slowly reversible
Formulations developed	Capsules, oral solution, and transdermal patch
Featured indication	Symptomatic treatment of dementia in AD and Parkinson's disease
Cholinesterase selectivity	Dual AChE–BuChE inhibitor
Absorption	Rapid and complete (oral); lag time of 0.5–1 h (patch)
Duration of AChE inhibition	8–10 h (oral); ~9 h (patch)
Plasma half-life	~1 h (oral); ~3.4 h (patch)
CSF peak concentrations	1.4–2.6 h
Apparent volume of distribution	1.8–2.7 L/kg
Protein binding	~40% bound to plasma proteins
Bioavailability	~36% for 3 mg dose
Metabolism	Cholinesterase-mediated hydrolysis to the decarbamylated metabolite
Elimination	Predominantly excreted via the renal route
Dosage and strength	1.5, 3, 4.5, or 6 mg (capsules); 2 mg/mL (oral solution); 4.6, 9.5, or 13.3 mg/24 h (patches)

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's disease; BuChE, butyrylcholinesterase; CSF, cerebrospinal fluid.

In this review, we discuss the advantage of BuChE inhibition in addition to AChE inhibition with rivastigmine on the outcomes of cognition, global function, behavioral symptoms, and activities of daily living (ADL). We also focus on the role of rivastigmine in subcortical vascular dementia (VaD) and PDD. Based on this context, we performed a literature search of English language articles on rivastigmine published in PubMed and Ovid before June 2016. Studies identified during the search were assessed for relevance based on the titles, abstracts, and/or the full text of the retrieved articles.

Rivastigmine: dual inhibitor AChE/BuChE

AChE and BuChE are two different cholinesterase enzymes located in the brain that are responsible for acetylcholine hydrolysis.[20,21] Of these, AChE is the primary cholinesterase mostly found at the nerve synaptic junctions and the areas that express intense activity in the adult human cerebral cortex,[22] whereas BuChE is mainly located in the glial cells of the brain[23] and plays an important role in cholinergic mediation.[24] As AD progresses, BuChE activity increases in the hippocampus and temporal cortex in contrast to the AChE activity, which decreases in these specific regions of the brain, thereby supporting the key role of BuChE in regulating brain acetylcholine levels.[25,26] Moreover, while BuChE activity increased with age in the AD brain, no correlation was observed in AChE activity with increasing age.[26] Studies have also shown that BuChE inhibition with rivastigmine correlated with improved cognition in patients with AD.[25,27,28] Initially, treatment efforts were focused on the inhibition of AChE; however, several studies have demonstrated the importance of both AChE and BuChE inhibition in the pathophysiology and pharmacological treatment of AD.[21] Further to the evidence of BuChE involvement in cholinergic regulation[20] and the suggested role of BuChE (K-variant allele) in the progression of AD,[29] dual inhibition may offer additional benefits,[30,31] especially over a long term.[32]

Rivastigmine has been shown to inhibit AChE in the brain in preclinical[33] and clinical[34] studies. Several large clinical studies[35–37] and meta-analyses[38–41] have demonstrated that rivastigmine improves cognitive function in AD. Studies in patients with AD have shown that rivastigmine exhibited dose-dependent efficacy,[42,43] and further investigations suggested that a higher dose of rivastigmine patch 13.3 mg/24 h (15 cm^2) conferred greater benefits on cognition, ADL, and global function than the 4.6 mg/24 h patch (5 cm^2) in patients with severe AD.[44,45] In the following sections, we provide evidence supporting the use of dual AChE−BuChE inhibitory activity of rivastigmine and summarize relevant findings in Table 2.

Preclinical studies of rivastigmine

Several preclinical studies have been conducted to investigate the effect of AChE and BuChE inhibition on the hydrolysis of brain acetylcholine. Preclinical studies[24,46] in AChE knockout mice have shown that BuChE was functional in the brain and had a role in the hydrolysis of acetylcholine, suggesting that inhibition of BuChE may enhance cholinergic transmission and is therefore desirable for cholinergic therapies. An in vitro study in male Wistar rats showed greater inhibitory potency (half maximal inhibitory concentration [IC_{50}]) of rivastigmine toward brain BuChE and AChE compared with donepezil under optimal assay conditions (BuChE: 31 vs 7,400 nM; AChE: 4.3 vs 6.7 nM).[47] The results from a preclinical study[48] using AChE knockout mice showed that infusion of rivastigmine increased hippocampal acetylcholine levels but not donepezil, suggesting that rivastigmine enhances acetylcholine levels by inhibiting BuChE. A 30-fold increase in the extracellular acetylcholine levels was observed in the hippocampus of untreated AChE knockout mice compared with the wild-type mice. The infusion of rivastigmine (1 and 10 μM) further doubled (30%–50%) acetylcholine levels in AChE knockout mice, whereas no effect was observed with donepezil (1 μM); however, following infusion of donepezil (1 μM) in wild-type mice, the hippocampal acetylcholine levels increased by more than 2-fold (150%).[48] A microdialysis study[49] was conducted to clarify the importance of BuChE in regulating brain cholinergic function in rat cerebral cortex. The results showed that rivastigmine (0.6 mg/kg intraperitoneally [i.p.]) inhibited AChE and BuChE by 40% and 25%, respectively, in the rat cerebral cortex, whereas administration of donepezil (1 mg/kg i.p.) was associated with a 27% inhibition of AChE, but no BuChE inhibition was observed. A preclinical study[50] in 5-week-old imprinting control region mice with cognitive dysfunction induced by amyloid-β peptide ($A\beta_{1-40}$) showed that repeated daily administration of a BuChE-selective inhibitor, *N*1-phenethyl-norcymserine (1 and 3 mg/kg); a dual AChE/BuChE inhibitor, rivastigmine (0.03, 0.1, and 0.3 mg/kg), or an AChE-selective inhibitor, donepezil (1 mg/kg), on days 0–3 significantly ameliorated cognitive dysfunction compared to the control mice ($P<0.001$ at all doses; rivastigmine 0.3 mg/kg: $P<0.05$). The finding from this study supports the role of BuChE inhibition as a therapeutic strategy in ameliorating cognitive dysfunction induced by AD pathology; further, the dual AChE/BuChE inhibition maximizes therapeutic efficacy.

Clinical studies of rivastigmine

The effect of rivastigmine in the treatment of patients with AD has been studied using medical imaging methods such as PET and magnetic resonance imaging (MRI). The findings from a double-blind, placebo-controlled study[51] using ^{18}F-fluorodeoxyglucose-PET demonstrated that treatment with rivastigmine (3, 6, or 9 mg/day) over 6 months in patients with mild-to-moderate probable AD significantly increased brain hippocampal metabolism by 32.5% in rivastigmine responders ($P<0.03$) compared with nonsignificant decrease in rivastigmine nonresponders and those treated with placebo (6.4% and 4.1%, respectively). Rivastigmine prevented clinical progression of symptoms and showed marked metabolic increase in memory-related cortices and the prefrontal system in rivastigmine responders.[51] A pilot study[52] in patients with mild AD using functional MRI showed that a single 3 mg dose of rivastigmine increased bilateral activation in the fusiform gyrus during the face-encoding task and in the prefrontal cortex during a simple working memory task. Results from the *N*-[^{11}C]methylpiperidyl-4-acetate-PET study[53] showed that in patients with probable AD (n=11), rivastigmine at a dose of 9 mg/day (for 3–5 months) reduced AChE activity by 29%–37% in various cortical regions (frontal, temporal, and parietal cortices), with greater AChE inhibition in the frontal cortex ($P=0.003$) than the temporal cortex ($P=0.05$), whereas donepezil 10 mg/day reduced the brain AChE activity by 38.5% in the frontal cortex ($P=0.0006$), by 28.7% in the temporal cortex ($P=0.02$), and by 28.1% in the parietal cortex ($P=0.05$). The findings from this study showed that AChE inhibitors (rivastigmine and donepezil) induce greater AChE inhibition in the frontal cortex in the AD brain.

Table 2 Summary of the studies on AChE–BuChE inhibition by rivastigmine

Authors	Study design	Animals		Main findings
Ogura et al[47]	In vitro	Male Wistar rats		Rivastigmine showed greater inhibitory potency (IC_{50}) toward brain BuChE and AChE than donepezil under optimal assay conditions
Naik et al[48]	In vivo microdialysis	Adult male and female AChE–/– and AChE+/+ mice		Rivastigmine unlike donepezil increased hippocampal acetylcholine levels in AChE knockout mice (AChE–/–), suggesting that rivastigmine enhances extracellular acetylcholine levels by inhibiting BuChE
Cerbai et al[49]	In vivo microdialysis and HPLC	Male Wistar rats		BuChE in addition to AChE co-regulates acetylcholine activity in rat cerebral cortex
Furukawa-Hibi et al[50]	In vivo	Male, 5-week-old ICR mice and control mice		Inhibiting BuChE is a therapeutic strategy for ameliorating cognitive dysfunction in AD, and dual AChE/BuChE inhibition maximizes therapeutic efficacy
Authors	**Study design**	**Indication**	**Number of patients**	**Main findings**
Clinical studies				
Potkin et al[51]	26 weeks, DB, PC study and FDG-PET	Mild-to-moderate probable AD	n=27 Rivastigmine 3 mg/day: 5; rivastigmine 6 mg/day: 7; rivastigmine 9 mg/day: 8; placebo: 7	Metabolism increased in brain hippocampus and prefrontal cortex in rivastigmine responders
Rombouts et al[52]	fMRI study	Mild AD	n=7 Rivastigmine 3 mg single dose	Rivastigmine increased bilateral activation in the fusiform gyrus and prefrontal cortex
Kaasinen et al[53]	$[^{11}C]$MP4A PET study	Probable AD	n=11 Donepezil 10 mg/day: 6; rivastigmine 9 mg/day: 5	Rivastigmine 9 mg/day induced AChE inhibition in frontal, temporal, and parietal cortices, with greater AChE inhibition in the frontal cortex than the temporal cortex
Kennedy et al[34]	Single-dose study	Healthy volunteer	n=8 Rivastigmine 3 mg, placebo	Decrease in the CSF AChE and BuChE activity was observed following a 3 mg single oral rivastigmine dose
Cutler et al[54]	OL, multiple-dose study	Probable AD	n=18 Rivastigmine 1, 2, 3, 4, 5, or 6 mg bid (three patients per group)	Rivastigmine 6 mg bid oral dose showed a maximum mean inhibition
Giacobini et al[28]	OL study	Probable AD	n=18 Rivastigmine 1, 2, 3, 4, 5, or 6 mg bid (three patients per group)	Cognitive improvement with rivastigmine in AD is associated with BuChE inhibition in addition to inhibiting AChE in the CSF
Darreh-Shori et al[27]	12-month, OL study	Mild AD	n=11 Rivastigmine dose increments of 1.5 mg bid every 2 weeks	Rivastigmine inhibits both AChE and BuChE and the sustained cholinesterase inhibition correlates with cognitive abilities of patients with AD after treatment
Eskander et al[55]	Ex vivo study	AD	Eight brains from AD patients	Rivastigmine also inhibits cholinesterases (AChE and BuChE) bound to cortical plaques and tangles in AD in dose-dependent manner
Nordberg et al[56]	13-week, randomized, OL comparative study	Mild-to-moderate AD	n=63 Rivastigmine: 22, donepezil: 20, galantamine: 21	Rivastigmine reduces both AChE and BuChE activities, but donepezil and galantamine do not inhibit BuChE activity
Parnetti et al[57]	Patients enrolled in clinical trials with AChE inhibitors were recruited from three European centers	Probable AD	n=144 Donepezil 5 or 10 mg/day: 104; galantamine 12 or 16 mg/day: 15; rivastigmine 6, 9, or 12 mg/day: 16; placebo: 9	Rivastigmine decreased CSF AChE and BuChE activity, whereas donepezil or galantamine treatment increased CSF AChE activity but did not influence CSF BuChE activity

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's disease; bid, twice daily; BuChE, butyrylcholinesterase; CSF, cerebrospinal fluid; DB, double-blind; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; fMRI, functional magnetic resonance imaging; HPLC, high-performance liquid chromatography; IC_{50}, half maximal inhibitory concentration; ICR, imprinting control region; OL, open-label; PC, placebo-controlled; $[^{11}C]$MP4A PET, *N*-$[^{11}C]$methylpiperidyl-4-acetate-positron emission tomography.

Several clinical studies have also demonstrated the role of rivastigmine in dual AChE–BuChE inhibition. A clinical study[34] in healthy young male volunteers showed that a single 3 mg oral dose of rivastigmine produced a maximum cerebrospinal fluid (CSF) AChE inhibition of 38.9% and CSF BuChE inhibition of 9.7% at 2.4 h. Furthermore, an open-label, multiple-dose study[54] in patients with probable AD showed the therapeutic potential of rivastigmine, with the 6 mg twice daily (bid) group showing a maximum mean inhibition of 61.7% of AChE activity at 5.6 h post-dose.

Results from a single-center, open-label study[28] supported the role of BuChE and its inhibition with rivastigmine in the regulation of cognitive functions in patients with probable AD. A significant correlation was observed between the change in the Computerized Neuropsychological Test Battery summary score and the CSF AChE (r=–0.56, $P<0.05$) and CSF BuChE (r=–0.65, $P<0.01$) inhibition activity. The important role of BuChE in cognitive processing was further supported by the result of this study because improvement in speed-, attention-, and memory-related performance was significantly correlated with the inhibition of BuChE activity but not with AChE activity in the CSF. A 12-month, open-label study[27] in patients with mild AD showed sustained AChE–BuChE inhibition of rivastigmine in the CSF (3 months: AChE: r=0.87, P=0.0002; BuChE; r=0.95, $P<0.0001$; 12 months: AChE: r=–0.67, P=0.02; BuChE: r=–0.86, P=0.0003). The findings showed that at 12 months, the AChE and BuChE activities in the CSF were lower compared with baseline values by 36% and 45%, respectively. In addition, a positive cognitive effect, particularly in memory and attention, was noted for up to 6 months of treatment.

According to the results from an ex vivo study,[55] in patients with a clinical history of AD, rivastigmine could inhibit AChE activity in neurons and axons in a dose-dependent manner at concentrations of 10^{-6}–10^{-4} M, whereas rivastigmine inhibited BuChE activity in the cerebral cortical neurons at a concentration of 10^{-5} M. The results from this study suggest that rivastigmine is a more potent inhibitor of BuChE. Moreover, a 13-week, randomized, open-label study[56] in patients with mild-to-moderate AD showed that rivastigmine significantly decreased activity of both AChE and BuChE in the CSF by 42.6% ($P<0.001$ vs baseline; AChE protein levels decreased by 21.8%) and 45.4% ($P<0.001$ vs baseline; BuChE protein levels decreased by 9.3%), respectively, whereas donepezil and galantamine did not significantly decrease BuChE activity, and these enzymes were associated with increased levels of cholinesterases in the CSF. Similarly, results from a clinical study[57] in patients with probable AD showed that rivastigmine treatment decreased CSF AChE and BuChE activity and was statistically significant in only rivastigmine 12 mg/day group ($P<0.01$) as there were fewer patients in the 6 and 9 mg/day groups; however, treatment with donepezil ($P<0.0001$) and galantamine ($P<0.001$) showed significant increase in CSF AChE activity, but no change in BuChE activity was observed. The change in CSF AChE activity with donepezil treatment was dose related (mean percentage change with 5 and 10 mg/day: +88% and +116%, respectively), and the percentage change in CSF AChE activity was significantly different between the two doses ($P<0.01$), whereas the change in CSF AChE activity with galantamine was not dose related (8 and 12 mg/day: +53% and +52%, respectively).

BuChE genotype

The most common BuChE variant is the K-variant that develops due to a point mutation in the DNA that results in alanine-to-threonine substitution at the 539 amino acid position (Ala539 → Thr). This polymorphism is associated with a 30% reduction of serum BuChE activity due to lower expression of the enzyme.[58,59] Several studies have been conducted to determine the association between the K allele of BuChE and the risk of developing AD, and the association of BuChE-K variant and risk of developing AD still remains unclear.[58] Results from a study suggested a protective role of the BuChE-K allele in disease progression.[29] Further, a retrospective analysis[60] of patients with AD (n=994) investigated the influence of age on response to cholinesterase inhibitor therapy. An analysis of response according to the BuChE genotype suggested that the differential effect might be related to the ability of rivastigmine to inhibit BuChE in addition to AChE.[60] Furthermore, another retrospective analysis[32] showed differential responses to cholinesterase inhibitors in patients with AD (aged <75 years) (n=994) who were grouped according to their BuChE genotype. The results demonstrated significantly greater responses to rivastigmine compared with donepezil on the Severe Impairment Battery, Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale, Global Deterioration Scale, and Neuropsychiatric Inventory (NPI) in BuChE wild-type carriers but not in carriers of BuChE-K. A retrospective exploratory analysis[61] of a randomized, placebo-controlled study (Investigation in Delay to Diagnosis of Alzheimer's disease with Exelon [InDDEx];[62] n=1,018) of patients with amnestic mild cognitive impairment showed that rivastigmine compared with placebo reduced progression to AD (12.9% vs 30%; hazard ratio: 0.369; χ^2 test, P=0.0745) and functional decline on ADCS-ADL (−6.08 vs −10.9, respectively; P=0.046) in women with the BuChE wild-type genotype, and rivastigmine reduced cognitive decline in men with the BuChE-K allele compared with those receiving placebo (–2.23 vs –4.71, respectively; P=0.037). The results from a community-based study of patients with severe AD[29] showed that individuals (with baseline Mini-Mental State Examination [MMSE] scores ≤8 points) carrying the BuChE-K allele had slower rate of cognitive decline. A multicenter outpatient study[63] (n=152) on the prevalence of wild-type BuChE genotype showed that most of the patients (n=146 [96.1%]) with AD were wild-type BuChE carriers, and those with AD with wild-type BuChE were associated with greater cognitive decline, unlike patients with the BuChE-K allele that is associated with lower BuChE enzyme expression, thereby leading to less rapid cognitive decline. Moreover, various studies[58,64–67] have shown the protective role of the BuChE K-variant alleles in reducing the risk of AD in apolipoprotein E ε4 (APOE ε4) noncarriers and delaying the onset and progression of AD.

Although APOE ε4 is the main genetic risk factor for AD, it has been understudied in the literature.[68] The results from a systematic review[69] showed that the Northern Europe had the highest regional prevalence estimates for APOE e4 carriers in AD populations (e4/–: 61.3% [95% CI 55.9–66.7]; e4/4: 14.1% [95% CI 12.2–16.0]), whereas Asia (e4/–: 41.9% [95% CI 38.5–45.3]; e4/4: 7.7% [95% CI 5.8–9.6]) or Southern Europe/Mediterranean (e4/–: 40.5% [95% CI: 36.8–44.1]; e4/4 prevalence: 4.6% [95% CI: 2.7–6.4]) had the lowest regional prevalence estimates. The findings from a meta-analysis[70] in Chinese population showed statistically significant positive association between the APOE ε4 allele carriers and AD (odds ratio [OR] =3.93, 95% CI 3.37–4.58, $P<0.00001$); moreover, carriers of homozygotes APOE ε4/ε4 and heterozygous APOE ε4/ε3 alleles have statistically significant association with AD (OR =11.76, 95% CI 6.38–21.47, and OR =3.08, 95% CI 2.57–3.69, respectively; $P<0.00001$). A retrospective analysis[71] in mild-to-moderately severe AD patients showed inconsistency with carriers of APOE ε4 and drug response. In this study, rivastigmine 6–12 mg/day improved ADAS-cog by 1.67 points in APOE ε4 carriers (n=246) and declined ADAS-cog by 0.48 points in the APOE ε4 noncarriers (n=121). Moreover, an open-label, nonrandomized, multicenter study[72] in patients with mild-to-moderately severe AD (n=214) showed no difference in response to rivastigmine (1.5–6 mg bid) for APOE ε4 carriers and noncarriers on cognition, indicating that at least one APOE ε4 allele does not determine difference in the response to rivastigmine.

BuChE progressively replaces AChE in acetylcholine hydrolysis in patients with advanced stages of AD, and particularly in the BuChE wild-type carriers, the rate of hydrolysis is higher compared with the BuChE K-variant. Rivastigmine has an added advantage of inhibiting BuChE in addition to AChE, thereby showing advantages over other AChE inhibitors, and particularly in individuals with BuChE wild-type genotype.

Rivastigmine in subcortical VaD

VaD is associated with cholinergic deficit, and cholinesterase inhibitors may be beneficial in the treatment of VaD.[73] The commonest type of VaD is subcortical VaD, which develops due to interruption or reduction in the blood flow in subcortical region of brain.[74] A range of behavioral and cognitive changes, particularly executive dysfunction (main characteristic of subcortical dementia), accompany subcortical VaD and are attributed to disruption of the frontal subcortical circuits.[75] Rivastigmine has shown beneficial effects of improvement in global function, ADL, behavioral symptoms, and/or cognition in patients with AD and PDD.[76] Data from the open-label studies[77] have shown similar benefits of improved cognition and behavioral symptoms in patients with subcortical VaD. The results from a 12-month, follow-up study[78] showed that rivastigmine (3–6 mg/day) improved cognition (ten-point clock [TPC] drawing test) ($P<0.05$) and reduced both caregiver stress (relative stress scale [RSS]) ($P<0.05$) and behavioral discharge ($P=0.09$) in patients with subcortical VaD. Moreover, an open-label follow-up study[79] in patients with subcortical VaD (n=16) showed significant improvements with rivastigmine (3–6 mg/day) at 22 months in the TPC drawing test scores of 2.1 points over baseline ($P<0.01$) and 3 points over aspirin (100 mg/day) ($P<0.001$); NPI scores by 3.3 points over baseline ($P<0.05$) and 4.2 points over aspirin (100 mg/day) ($P<0.01$); and reduced caregiver stress by 8.5 points on the RSS over baseline ($P<0.05$) and a mean treatment effect of 11.8 points ($P<0.01$). A 12-month, randomized, controlled, open-label study[80] (n=208) suggested that rivastigmine (3–6 mg/day) is useful in probable subcortical VaD. The results showed significant improvement in the total scores of the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale compared with baseline and in those treated with aspirin (100 mg/day) at month 12 ($P<0.001$). Further analysis of the individual items on the BEHAVE-AD showed that rivastigmine treatment provided benefits on all items of the scale, except for delusions (not significant). Rivastigmine was also shown to specifically address the impairment in executive function commonly observed in subcortical VaD. The specific improvement in executive function provided by rivastigmine was also supported by results from a 22-month, open-label study[81] in patients with subcortical VaD (n=16). There was significant improvement on the total BEHAVE-AD score in patients receiving rivastigmine (3–6 mg/day) compared to those on aspirin (100 mg/day) ($P=0.001$), the other treatment arm. Analysis of the individual items on the BEHAVE-AD indicated that rivastigmine therapy was associated with improvements on all items of the scale, except for diurnal rhythm disturbance. Moreover, the sub-analysis of individual NPI items indicated significant benefits in terms of anxiety, hallucinations, and wandering in patients treated with rivastigmine compared to those treated with aspirin (P=0.001, P=0.005, and P=0.014, respectively). Rivastigmine (3–6 mg/day) was also shown to be superior to aspirin (100 mg/day) plus nimodipine (60 mg/day) in cognition and functional and behavioral outcome measures in a 16-month open-label study[82] in subcortical VaD (n=64). In particular, benefits in executive function and attention that are the core cognitive features of subcortical VaD were observed in the rivastigmine group compared to the aspirin plus nimodipine group. An overall improvement was observed in the behavioral symptoms with rivastigmine as assessed using BEHAVE-AD. In patients treated with rivastigmine, the total BEHAVE-AD scores at 16 months significantly improved compared with baseline and with that of the aspirin plus nimodipine group ($P<0.001$); conversely, a significant deterioration in BEHAVE-AD scores compared with baseline ($P<0.05$) was observed in patients treated with aspirin plus nimodipine. Long-term treatment with rivastigmine in a prospective study[83] (n=245) consistently showed improvement of behavioral symptoms (BEHAVE-AD) on both total score and individual items in patients with subcortical VaD ($P<0.0001$); only delusion was found to not have significant improvement in this study. However, a 26-week, randomized, placebo-controlled study[84] of rivastigmine (6 mg/day) in patients from China with subcortical VaD (n=40) showed no apparent cognitive benefit (on MMSE and Frontal Assessment Battery) over 6 months, whereas the mean total NPI score (standard deviation [SD]) decreased from 15.0 (14.6) to 11.4 (9.4) with rivastigmine treatment, indicating a positive treatment effect of ~4 points in behavioral symptoms (on the NPI). However, large randomized clinical studies with longer duration are warranted to investigate treatment benefits of rivastigmine in subcortical VaD.

Rivastigmine in PDD

Studies have shown that rivastigmine provides significant benefits on cognition, particularly in executive function and attention, ADL, and neuropsychiatric symptoms, especially hallucinations and delusions, in patients with PDD. In an open-label study[85] in patients with PDD (n=28), rivastigmine improved the cognitive function. At week 26, the cognition as assessed by ADAS-cog (total score) and the motor function as assessed by Unified Parkinson's Disease Rating Scale (UPDRS; total score) improved significantly from baseline by 7.3 points ($P<0.002$) and 3.2 points ($P<0.06$), respectively. The specific items that significantly improved in the ADAS-cog at week 26 were recognition (P=0.02), word finding (P=0.05), remembering instructions (P=0.005), and concentration (P=0.003). Further, the MMSE subscore of attention improved significantly by 1.1 points at week 26 ($P<0.002$); however, rivastigmine did not cause worsening of motor function (a subscore of UPDRS) during the study. Rivastigmine targets the cognitive domain that is frequently impaired in PDD. A randomized, double-blind, placebo-controlled, multicenter study[86] in patients with PDD (n=487) showed significant improvements with rivastigmine over placebo on the power of attention at week 24 ($P<0.01$), continuity of attention at both week 16 (P=0.001) and week 24 (P=0.0001), cognitive reaction time at week 24 ($P<0.0001$), and reaction time variability at both week 16 ($P<0.05$) and week 24 ($P<0.001$). The findings from this study showed that rivastigmine treatment was associated with significant benefits in all aspects of attention (sustained attention, focused attention, consistence of responding, and central processing speed). A randomized, double-blind, placebo-controlled study[87] in PD patients with cognitive impairment (ie, mild cognitive impairment and PDD) (n=176) showed that rivastigmine delayed the deterioration of cognitive function and lowered the incidence of falls. In the rivastigmine group, the Montreal Cognitive Assessment scores were significantly higher compared with the placebo group (P=0.002) at 12 months; and the average number of falls per person and the incidence of falls of patients were significantly lower in the rivastigmine group compared with the placebo group ($P<0.01$) at 12 months. A retrospective ADAS-cog factor analysis study[88] including data from patients with PDD (n=969) showed significant improvements on both "memory" ($P<0.0001$) and "language" (P=0.0033) with rivastigmine (6–12 mg/day) treatment compared with placebo at week 24/26. Results from a multicenter, double-blind, placebo-controlled, parallel-group study[89] in patients with PDD (n=541) showed that rivastigmine was associated with significant improvements over placebo on executive function tests and had an impact on flexibility of thinking, problem solving, and planning skills. With regard to letter fluency, rivastigmine was associated with improvements in correct responses, set loss errors, and responses made ($P<0.05$) at week 24; more correct substitutions on the symbol digit modalities test (P=0.02) and significantly higher card sorting recognition errors (P=0.03) were recorded. Several neuropsychiatric disorders are associated with dysfunction in the frontal–subcortical circuit at cortical and/or subcortical levels,[90,91] and the findings from this study[89] support the hypothesis that rivastigmine may affect the frontal subcortical circuits contributing to improvements in executive function.

Visual hallucinations frequently complicate the clinical course of PDD. They predict more rapid decline in the clinical course of the illness. A specific benefit was found with rivastigmine treatment in patients with PDD who manifest with visual hallucinations. A double-blind placebo-controlled study[92] in patients with PDD (n=541) showed significantly greater rivastigmine–placebo treatment difference at week 24 on the ADAS-cog in visual hallucinators (4.27 points; P=0.002) than nonhallucinators (2.09 points; P=0.015) at week 24. The rivastigmine–placebo treatment difference on the Alzheimer's Disease Cooperative Society-Clinician's Global Impression of Change (ADCS-CGIC) was 0.5 among the visual hallucinators (P=0.030) and 0.3 among the nonhallucinators (P=0.111). This supported a greater benefit of rivastigmine in visual hallucinators. A 48-week active treatment extension study showed sustained benefits of rivastigmine over baseline in patients with PDD with no new safety concerns.[93] The results from a 6-month, prospective, longitudinal, open-label, observational, single-center study in South Korea[94] in patients with PDD (n=23) showed that rivastigmine is useful in controlling several neuropsychiatric symptoms and is beneficial for caregiver distress in patients with PDD. Over 6 months, the NPI total score significantly improved with rivastigmine treatment by −5.4 points (P=0.049), with improvements in the domains of hallucination (P=0.048), depression and dysphoria (P=0.001), and appetite (P=0.024); moreover, total caregiver distress scores decreased significantly (P=0.020).

Approval of rivastigmine for the treatment of mild-to-moderate PDD[10] was based on EXPRESS (n=541), a large, 24-week, double-blind, randomized, placebo-controlled study.[95] The study showed significant improvements with rivastigmine in ADAS-cog scores compared with placebo at week 16 (P=0.002) and week 24 ($P<0.001$) (mean −2.1 points improvement from baseline with rivastigmine vs a 0.7 point decline from baseline with placebo at week 24). There were clinically meaningful improvements (moderate or marked) observed in the ADCS-CGIC scores in patients treated with rivastigmine compared with those treated with placebo (19.8% vs 14.5%, respectively) at week 24. Compared with placebo, rivastigmine also demonstrated significant benefits on ADCS-ADL (P=0.02), NPI-10 (P=0.02), MMSE (P=0.03), cognitive drug research power of attention tests (P=0.009), Delis–Kaplan executive function system verbal fluency test ($P<0.001$), and the TPC drawing test (P=0.02) at week 24. In the retrospective analysis of the EXPRESS study,[96] ADAS-cog items were further examined to determine the impact of rivastigmine on various cognitive domains. Patients receiving rivastigmine (3–12 mg/day) improved significantly on all three key symptom domains (memory [$P<0.001$], language [P=0.003] and praxis [P=0.003]) compared with placebo at week 24; moreover, significant treatment differences with rivastigmine (3–12 mg/day) were observed on the following cognitive items: word recall, following commands, ideational praxis, remembering test instructions, and comprehension of spoken language ($P<0.05$).

The long-term safety data from a 76-week, prospective, open-label, randomized study[97] in patients with mild-to-moderate PDD (n=583) showed that treatment with rivastigmine capsule (12 mg/day) or patch (9.5 mg/24 h patch) was well tolerated. The commonest adverse events (AEs) with rivastigmine capsules and patch were nausea (40.5% and 8.3%, respectively), tremor (24.5% and 9.7%, respectively), fall (17.0% and 20.1%, respectively), vomiting (15.3% and 2.8%, respectively), and application site erythema (0% and 13.9%, respectively). The motor symptoms of PD were not found to worsen with treatment as the rate of progression was in the expected range due to the natural progression of the disease. The results from a 24-week, randomized, double-blind, placebo-controlled study[98] on rivastigmine showed that more patients receiving rivastigmine (10.2%) compared with those receiving placebo (3.9%) reported tremor, although this did not reflect in the total UPDRS part III score and there was no significant difference between rivastigmine and placebo (P=0.83) (mean baseline UPDRS part III motor scores [SD]: 34.0 [14.6] [rivastigmine] and 32.2 [13.2] [placebo]). The incidence of worsening Parkinsonism, bradykinesia, and rigidity were all <5% in both treatment groups. The positive impact of rivastigmine on the ability of patients to perform various ADLs was observed in a post hoc analysis of a prospective, multicenter, randomized, double-blind, placebo-controlled study.[99] At week 24, compared with placebo, rivastigmine was associated with significantly better outcomes in both basic ADLs (−0.5±6.19 vs −1.7±5.46; P=0.025; effect size 22.1%) and high-level function ADLs (0.1±4.95 vs −1.0±4.49; P=0.017; effect size 22.9%).

Conclusion

Dual inhibition of AChE and BuChE by rivastigmine may be considered as a potential therapeutic advantage for subcortical dementias (PDD and subcortical VaD) to benefit in cognition, global function, and behavioral symptoms. Rivastigmine was found to specifically benefit executive dysfunction that is frequently observed in subcortical dementias; however, large randomized clinical studies are warranted to support these observations.

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