A Review of Butyrylcholinesterase as a Therapeutic Target in the Treatment of Alzheimer's Disease

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ABSTRACT

Objective: To examine the role of butyrylcholinesterase (BuChE) in cholinergic signaling and neurologic conditions, such as Alzheimer's disease (AD). The rationale for inhibiting cholinesterases in the management of AD, including clinical evidence supporting use of the dual acetylcholinesterase (AChE) and BuChE inhibitor rivastigmine, is discussed.

Data Sources: PubMed searches were performed using *butyrylcholinesterase* as a keyword. English-language articles referenced in PubMed as of September 2011 were included.

Study Selection and Data Synthesis: English-language articles related to BuChE considered to be of clinical relevance to physicians were included. English-language articles specifically related to AChE were not included, as the role of AChE in cholinergic signaling and the underlying pathology of AD is well documented. Reference lists of included publications were used to supplement the search.

Results: AChE and BuChE play a role in cholinergic signaling; BuChE can hydrolyze acetylcholine and compensate for AChE when levels are depleted. In the AD brain, AChE levels decrease, while BuChE levels are reportedly increased or unchanged, with changes becoming more pronounced during the disease course. Furthermore, BuChE genotype may influence AD risk and rate of disease progression. Strategies that increase acetylcholine levels (eg, cholinesterase inhibitors) demonstrate symptomatic efficacy in AD. Rivastigmine has proven cognitive efficacy in clinical trials, and data suggest that its action is mediated, in part, by inhibition of BuChE. Retrospective analyses of clinical trials provide evidence that BuChE genotype may also influence treatment response.

Conclusions: AChE-selective inhibitors and a dual AChE and BuChE inhibitor demonstrate symptomatic efficacy in AD. Mounting preclinical and clinical evidence for a role of BuChE in maintaining normal cholinergic function and the pathology of AD provides a rationale for further studies investigating use of rivastigmine in AD and the influence of BuChE genotype on observed efficacy.

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Cholinergic neurotransmitter systems are widely distributed in the human brain and play an important role in regulating many processes, including memory, learning, attention, and behavior.[1–3] Normal cholinergic function depends on the rapid hydrolysis of the neurotransmitter acetylcholine (ACh) by cholinesterases.[4] The human brain contains 2 major cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE).[5] AChE is reported to be the more abundant of the 2 cholinesterases in the brain.[5] However, there is increasing evidence that BuChE has an important role in cholinergic mediation.

In this review, we will consider the role of BuChE in normal cholinergic function and in pathological disease states, such as Alzheimer's disease (AD). The rationale for inhibiting cholinesterases in the symptomatic treatment of AD and mounting clinical evidence supporting the use of a dual inhibitor of both AChE and BuChE are discussed.

METHOD

Relevant articles were identified by performing searches of PubMed with *butyrylcholinesterase* as a search term. Searches were performed in September 2011. English-language articles related to BuChE considered to be of clinical relevance to physicians were included. Articles specifically related to AChE were not included, as the role of AChE in cholinergic signaling and the underlying pathology of AD is well documented. References within those articles included were used to supplement the search.

RESULTS

Mechanism of Action of AChE and BuChE in the Cholinergic Synapse and the Extrasynaptic Role of ACh-Hydrolyzing Enzymes

In the normal human brain, nerve impulses in the presynaptic neuron result in fusion of ACh-containing vesicles with the presynaptic membrane and the release of ACh into the synaptic cleft.[6] ACh diffuses across the synaptic cleft and interacts with cholinergic receptors on the postsynaptic neuron (Figure 1). AChE activity is important for terminating nerve impulses within the central nervous system (CNS) and maintaining pulsatile cholinergic stimulation. AChE is a serine hydrolase, which mediates the hydrolysis of ACh to choline and acetate (Figure 1).[6] Choline is then transported back to the presynaptic neuron and is used as a substrate for synthesis of ACh.[6] It is hypothesized that, in a manner analogous to the inactivation of glutamate in glutamatergic transmission, synaptically released ACh can also be hydrolyzed to choline and acetate by glial BuChE. Choline is then returned to the synaptic cleft for reuptake into cholinergic neurons (Figure 1).[5,7]

In addition to ACh activity at neuronal synaptic clefts, ACh activity is also detected in the extracellular fluid[8] and cerebrospinal fluid (CSF),[9] acting on nonexcitable cholinoceptive cells such as microglia,

Clinical Points

- Evidence for a role of butyrylcholinesterase (BuChE), including an effect of BuChE genotype, in the pathology of Alzheimer's disease is increasing.
- There are pharmacologic differences between the 3 main cholinesterase inhibitors approved for the symptomatic treatment of Alzheimer's disease, which may affect the clinical response; rivastigmine inhibits both acetylcholinesterase (AChE) and BuChE, while donepezil and galantamine are AChE-selective.
- An increased understanding of the relative importance of BuChE versus AChE over the disease course will help inform treatment decisions and optimize outcomes for each patient.

astrocytes, oligodendrocytes, and endothelial cells.[10] BuChE may be the primary extrasynaptic ACh-hydrolyzing enzyme.[11]

Distribution of AChE and BuChE in the CNS

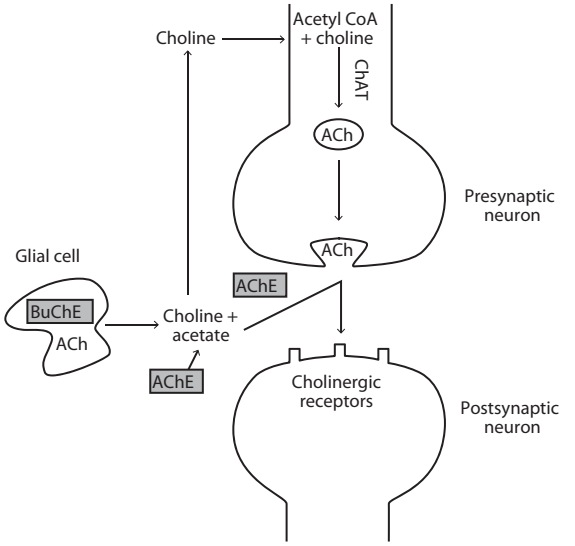
Immunohistochemical and in situ hybridization studies have investigated the distribution of choline acetyltransferase, a specific marker of cholinergic neurons, in the peripheral nervous system and CNS.[12] Using these methods, cholinergic neurons have been detected in the striatum, basal forebrain, cerebral cortex, mesopontine tegmental nuclei, cranial motor nuclei, and spinal motor neurons.[12]

AChE is consistently associated with both cholinergic and cholinoceptive neurons. BuChE immunoreactivity has been detected in all brain regions using an enzyme-linked immunosorbent assay.[13] AChE is expressed at particularly high levels in the hippocampus formation[5,14] and the motor, premotor, and neocortical areas of the human cerebral cortex.[15] BuChE is also expressed in the hippocampus and temporal neocortex, but at lower levels than AChE.[5] Mesulam et al[5] reported that hippocampal and neocortical AChE is localized in the axons and pyramidal neurons, while BuChE is associated with glial cells. However, Darvesh et al[16] reported that, in the hippocampal formation, AChE is present in both neurons and neuropil, while BuChE is only detected in neurons, and suggested that these enzymes may colocalize. In the amygdala, the number of BuChE-positive neurons is reported to exceed the number of AChE-positive neurons, with BuChE residing predominantly in the neurons and their dendritic processes and AChE residing in the neuropil.[16] The distinct distribution of AChE and BuChE within the brain suggests that these enzymes may both play important biological roles.

Elucidating the Roles of AChE and BuChE in Cholinergic Signaling

Studies in AChE-knockout mice have investigated the role of AChE and BuChE in cholinergic signaling. Mice nullizygous for AChE show no AChE activity and normal BuChE activity but still appear to have structurally intact cholinergic pathways.[17–19] Mesulam et al[19] reported that both AChE-knockout and wild-type mice show BuChE activity in all parts of the brain that receive cholinergic innervations and demonstrated that BuChE could hydrolyze the acetylcholine surrogate acetylthiocholine. Hartmann et al[20] reported a dose-dependent increase in ACh levels in wild-type mice, but not in AChE-knockout mice, treated with an AChE-selective inhibitor. In contrast, infusion of a BuChE-selective inhibitor resulted in elevation of ACh levels in AChE-knockout mice but had no effect on wild-type mice.[20] Evidence for a role of BuChE in cholinergic signaling in humans comes from a study that demonstrated that BuChE can hydrolyze acetylthiocholine in human brain tissue treated with the AChE inhibitor BW-284C51.[5] Together, these studies in AChE-knockout mice and human brain tissue have shown that BuChE can hydrolyze ACh and can compensate for AChE when levels are depleted.

Figure 1. Hydrolysis of ACh by AChE and BuChE



Abbreviations: ACh = acetylcholine, AChE = acetylcholinesterase, BuChE = butyrylcholinesterase, ChAT = choline acetyltransferase, CoA = coenzyme A.

In addition to having a role in the hydrolysis of ACh, BuChE is also known to have nonenzymatic functions. It has been suggested that AChE may accelerate amyloid deposition in the Alzheimer's brain[21] and that BuChE can associate with amyloid-β (Aβ) protein and may delay the onset and rate of neurotoxic Aβ fibril formation in vitro. [22] AChE and BuChE may also be involved in inflammatory pathways.[23]

Changes in AChE and BuChE Activity in Alzheimer's Disease, Dementia With Lewy Bodies, and Parkinson's Disease Dementia: The Cholinergic Hypothesis

AD is characterized by marked cholinergic dysfunction.[24] More specifically, degeneration of cholinergic neurons; loss of cholinergic transmission; depletion of ACh, especially in moderate-to-severe disease stages; and changes in AChE and BuChE activity are commonly observed in the cerebral cortex and hippocampus of patients with AD.[24,25] These factors are thought to contribute to disease progression,[24,26]

with degeneration of cholinergic circuits associated with the progressive impairment in memory and cognitive function that is typically observed.

AChE is thought to be the predominant cholinesterase in healthy human brains. However, decreased AChE activity and increased or unchanged BuChE activity have been observed in certain brain regions in AD.[24,27] In patients with AD, BuChE activity is reported to be significantly higher in men than in women.[28] In the AD brain, BuChE activity is associated with amyloid plaques and neurofibrillary tangles,[29–32] with BuChE covering up to 6 times more of the plaque area compared with age-matched controls.[33]

Patients with Parkinson's disease and Parkinson's disease dementia show reduced AChE activity in the frontal cortex compared with healthy controls.[34] Higher levels of AChE and BuChE are observed in patients with Parkinson's disease dementia compared with Parkinson's disease.[34] In the CSF, AChE and BuChE levels were significantly higher in patients with Parkinson's disease dementia compared with those with Parkinson's disease but were similar between patients with Parkinson's disease and controls.[35] A further study reported that the CSF ratio of AChE:BuChE was lower in patients with Parkinson's disease dementia compared with those with Parkinson's disease, but AChE and BuChE activity was comparable.[36] BuChE activity in the CSF has been shown to vary according to the severity or duration of dementia associated with Parkinson's disease or the disability stage of the disease.[36] No differences in BuChE activity were detected in the CSF and serum in demented patients with dementia with Lewy bodies, nondemented patients with dementia with Lewy bodies, and controls.[37]

Changes in Expression of AChE and BuChE During the Course of Alzheimer's Disease

In addition to changes in activity, changes in AChE and BuChE protein expression are reported to occur throughout the disease course. Both AChE and BuChE are known to exist in 6 polymeric forms divided into 2 classes, asymmetric and globular, based on the presence and absence of a collagen-like tail.[38] The globular forms of AChE and BuChE may be further subdivided into G1, G2, and G4 forms.[39] The G4 form is the most predominant form expressed in the CNS and is responsible for degradation of ACh at the cholinergic synapse.[38] The G1 form is found in smaller amounts in the brain.[38] As AD progresses, there is an increase in the G1 form of both AChE and BuChE and a decrease in the G4 form of AChE, particularly in the hippocampus and amygdala.[39,40] Ogane et al[41] reported a decrease in the membrane-bound G4 form of AChE by 71%, 45%, and 47% in the frontal cortex, parietal cortex, and caudate putamen, respectively, and a decrease in the G1, G2, and G4 aqueous soluble forms of AChE in the caudate putamen (unchanged in the frontal and parietal cortex) in patients with AD compared with controls. Increased levels of glial-derived BuChE and decreases in synaptic AChE result in a relative increase in the ratio of BuChE to AChE in cortical regions from approximately 0.6 to 11.[42]

High levels of BuChE in gray matter have been correlated with annual cognitive decline in a prospective, autopsy-confirmed population with dementia with Lewy bodies.[43] However, high CSF BuChE activity may be associated with greater levels of cognitive function in patients with AD.[28] It has been hypothesized that low levels of BuChE in the CSF may correlate with high levels of BuChE/AChE/Aβ/apolipoprotein E (APOE) complexes (BAβAC) in the vicinity of, or trapped within, plaques, along with cerebral amyloid angiopathy, increased neurotoxicity, and greater central neurodegeneration.[10]

The observed changes in BuChE activity and expression throughout the course of AD, and the relationship between BuChE levels and cognitive function, emphasize the potential value of BuChE in addition to AChE as a therapeutic target in patients with AD.

Influence of BuChE Genotype on Enzymatic Activity and the Rate of Disease Progression

BuChE-K is the most common polymorphism of BuChE and is found in up to one-third of Asians and Caucasians.[44] The BuChE-K genotype arises from a DNA point mutation[45] and is associated with approximately 30% lower BuChE activity than wild-type alleles.[45] BuChE-K shows reduced ability to inhibit Aβ fibril formation.[46] A higher load of cholinesterase-positive neuritic plaques has been reported in the cerebral cortex of BuChE-K carriers with late-onset AD.[47] Postmortem analysis of 30 patients with autopsy-diagnosed dementia (AD or dementia with Lewy bodies) reported significantly less phosphorylated tau protein but no significant differences in Aβ protein in patients with ≥ 1 BuChE-K allele compared with wild-type alleles.[48]

Reports on the impact of BuChE genotype on the risk of developing AD are conflicting. It has been reported that BuChE-K is overrepresented among patients with AD and that carriers of BuChE-K show an increased risk of developing AD.[49–52] A further study demonstrated that BuChE-K is associated with an increased risk of AD, but only in BuChE-K homozygotes ≥ 70 years of age.[53] However, it has also been reported that BuChE-K is expressed at a lower frequency in patients with AD compared with healthy controls.[54] Several studies have reported no significant difference in the frequency of BuChE-K alleles between patients with and without AD.[55–61] A higher allelic frequency of BuChE-K has also been reported in patients with dementia with Lewy bodies relative to Parkinson's disease dementia.[62]

Despite several studies reporting an association between BuChE-K and the risk of developing AD, it has been suggested that BuChE-K may actually protect against disease progression. A community-based study of 339 patients with severe AD found that the presence of a BuChE-K allele was associated with a slower average rate of cognitive decline (Mini-Mental State Examination [MMSE] score).[63] Differing profiles in cognitive test performance have also been reported in a study comparing healthy volunteers with silent or wild-type BuChE alleles, providing further evidence of a role for BuChE in cognitive function.[64]

Table 1. Summary of Some of the Available AChE-Selective, BuChE-Selective, and Dual AChE and BuChE Inhibitors[11,42,78]

AChE-Selective Inhibitor	BuChE-Selective Inhibitor	Dual Inhibitor
BW284c51	Bambuterol	Eptastigmine
Donepezil	Bisnorcymserine	(–)-Heptyl-physostigmine
Diisopropylfluorophosphate	Cymserine	Metrifonate
Echothiophate	Ethopropazine	Physostigmine
Edrophonium	(–)-4'-Isopropylphenyl carbamate of thiaphysovenol	Rivastigmine
Galantamine		Tacrine
Huperzine A	Iso-OMPA	
Neostigmine	MF-8622	
Phenserine	Phenylethylcymserine	
	(–)-Physovenine	
	(–)-Thiaphysovenine	

Abbreviations: AChE = acetylcholinesterase, BuChE = butyrylcholinesterase.

Influence of BuChE and APOE Epsilon 4 Genotype on Risk of Developing Alzheimer's Disease

APOE epsilon 4 (APOE ε4) is a commonly reported genetic risk factor for AD.[65] High levels of APOE protein have been associated with low cerebral glucose metabolism, high cerebral Aβ load, and phosphorylated tau in the CSF, while BuChE levels were found to have the opposite relationship.[10] A further study reported an association between high levels of APOE protein and low levels of BuChE.[66] CSF BuChE activity is reported to be 40% to 60% higher in APOE ε4–negative patients than in those with 1 or 2 APOE ε4 alleles.[28]

Data suggest a complex interplay between BuChE and APOE ε4 genotype and the risk of developing AD. In carriers of APOE ε4, wild-type BuChE has been reported to be associated with an increased risk of developing AD.[67] Hiltunen et al[68] reported a lower frequency of BuChE-K in AD patients under the age of 75 years who were also carriers of APOE ε4 compared with nondemented controls. Other studies have reported an association between BuChE-K and APOE ε4 and the risk of developing late-onset AD.[50,51,69,70] Sodeyama et al[55] reported a significant association of BuChE-K with the neuropathological changes of AD in carriers of APOE ε4, but not in noncarriers, over the age of 75 years. Another study showed that, in the presence of APOE ε4, carriers of BuChE-K showed a dose-dependent reduction in CSF BuChE activity compared with noncarriers.[71] However, in the absence of APOE ε4, BuChE activity was essentially indistinguishable between carriers of BuChE-K and noncarriers.[71] A further study reported that, in non–APOE ε4 carriers, BuChE-K may protect against AD but only in women.[72]

The rate of AD progression may be influenced by both APOE ε4 and BuChE genotype. A post hoc exploratory analysis of a 3- to 4-year, randomized, placebo-controlled trial of rivastigmine in patients with mild cognitive impairment showed that the rate of progression to AD and loss of hippocampal volume were highest in carriers of both APOE ε4 and BuChE-K and lowest in carriers of BuChE-K without APOE ε4.[73] In support of these findings, Darreh-Shori et al[71] observed that in a study of patients with AD, MMSE scores were lowest in carriers of both BuChE-K and APOE ε4 and highest in carriers of BuChE-K who were APOE ε4 negative. However, a number of other studies have reported no association between BuChE-K, APOE ε4 alleles, and AD.[49,53,57–61,74–76]

The frequency of BuChE-K and APOE ε4 alleles in patients with dementia with Lewy bodies and Parkinson's disease dementia has also been investigated. A higher frequency of BuChE-K and APOE ε4 was observed in patients with dementia with Lewy bodies compared with Parkinson's disease dementia.[62] Furthermore, more rapid cognitive decline was observed in patients with Parkinson's disease dementia who were carriers of both BuChE-K and APOE ε4 compared with other genotypes.[62] Singleton et al[77] reported no increase in BuChE-K allele frequency between patients with dementia with Lewy bodies or Parkinson's disease dementia; however, an increased number of BuChE-K homozygotes was observed among patients with dementia with Lewy bodies and Parkinson's disease dementia compared with controls.[77]

APOE ε4 genotype has been shown to modulate BuChE phenotype, particularly in carriers of wild-type BuChE in which CSF levels of BuChE protein were approximately 30% lower in APOE ε4 carriers versus noncarriers.[71] It has been hypothesized that APOE ε4 facilitates accumulation of BAβAC, that wild-type BuChE is the predominant form of BuChE protein in these complexes, and that the observed reduction in BuChE expression is a negative feedback mechanism to reduce ACh hydrolysis.[71] On this basis, patients with AD and wild-type BuChE alleles may be predicted to show the greatest clinical response to BuChE inhibition.

Rationale for Inhibiting AChE and BuChE in Patients With Alzheimer's Disease

By inhibiting cholinesterases, cholinesterase inhibitors (ChEIs) provide a dose-dependent increase in ACh levels, enhancing cholinergic transmission in the brain of patients with AD and providing relief from symptoms of cholinergic deficits.

A number of ChEIs have been developed with varying potency against AChE and BuChE, many of which are close analogs of the same pharmacophore. The selectivity (AChE-selective, BuChE-selective, or dual inhibitor) of some of the available ChEIs, based on their inhibitory potency against human erythrocyte AChE and plasma BuChE, is presented in Table 1. Several of these compounds are BuChE-selective, while others (eg, rivastigmine and tacrine) show inhibitory potency against both AChE and BuChE (Table 1).

Effects of AChE- and BuChE-Selective Inhibitors: Preclinical Data

A number of preclinical studies have investigated the effect of AChE- and BuChE-selective inhibitors on the hydrolysis of ACh within the brain. AChE inhibitors

may have varying potency against the different molecular forms of AChE. In the rat brain, heptylphysostigmine and diisopropylfluorophosphate showed selectivity for the G1 over the G4 form of AChE in aqueous-soluble extracts, while neostigmine was selective for G1 in both aqueous- and detergent-soluble extracts.[79] Physostigmine, echothiophate, BW284c51, tacrine, and metrifonate were shown to inhibit both forms with similar potency.[79] In human brain tissue, it was shown that heptylphysostigmine preferentially inhibits G1 over G4 and edrophonium inhibits G4 more potently than G1, while physostigmine inhibits both equally.[41] Given that G1 is relatively unchanged in AD, while membrane-bound G4 decreases, inhibitors that preferentially inhibit the G1 form of AChE may have therapeutic applications.

Transcortical administration of donepezil, an AChE-selective inhibitor, was shown to increase extracellular ACh levels.[80] Freely moving rats treated with the AChE inhibitor phenserine showed a greater than 3-fold increase in brain ACh levels.[81] In 3-month-old rats with 3-(±)-(2-carboxypiperzin-4-yl)-propyl-1-phosphonic acid (CPP)–induced learning deficits, phenserine was shown to reduce the number of mistakes made in a 14-unit T maze compared with rats treated with CPP only.[82]

Giacobini et al[11,83] reported a 15-fold increase in the extracellular concentration of ACh in rat brains perfused intracortically with MF-8622, a selective BuChE inhibitor. BuChE-selective inhibitors have also demonstrated efficacy on cognition in animal studies. Greig et al[84] demonstrated that, when administered to aged rats, N1, N8-bisnorcymserine, and N1-phenethylcymserine inhibited BuChE activity, were nontoxic, and improved performance in a 14-unit T maze compared with untreated controls. The observed low cholinergic toxicity of cymserine analogs observed in the rat model is of particular interest, as centrally mediated cholinergic effects are a common barrier to treatment with high doses of ChEIs in humans.

Overview of ChEIs

ChEIs are a first-line therapy for the management of AD. Three main ChEIs are approved for the symptomatic treatment of mild-to-moderate AD: rivastigmine, galantamine, and donepezil.[85–87] All 3 drugs are available as oral capsules, but rivastigmine is the only ChEI to also be approved in a transdermal patch formulation for both AD and Parkinson's disease dementia in a number of countries worldwide.

Rivastigmine, galantamine, and donepezil are from distinct chemical classes (carbamate, phenanthrene alkaloid, and piperidine, respectively)[85,86,88] and differ substantially in their pharmacologic and pharmacokinetic properties. Donepezil and galantamine are rapidly reversible inhibitors of AChE.[89] Rivastigmine is a slowly reversible (pseudoirreversible) inhibitor and shows inhibitory activity against both AChE and BuChE. Under optimal assay conditions, rivastigmine has been shown to have a greater inhibitory potency (IC_{50}) toward AChE than donepezil (4.3 nM versus 6.7 nM).[90]

Preclinical Data With Rivastigmine, Donepezil, and Galantamine

Cerbai et al[91] reported that intraperitoneal administration of donepezil (1 mg/kg) was associated with 27% inhibition of AChE and no inhibition of BuChE, while rivastigmine (0.6 mg/kg) inhibited AChE by 40% and BuChE by 25% in the rat cerebral cortex. Infusion of rivastigmine, but not donepezil, has been shown to increase ACh levels in the hippocampus of AChE-knockout mice, suggesting that, in the absence of AChE, rivastigmine can enhance extracellular ACh levels by inhibiting BuChE,[92] and reinforcing observations that BuChE can compensate for AChE when AChE levels are depleted.

Furukawa-Hibi et al[93] compared the effects of N1-phenethylcymserine, rivastigmine, and donepezil in 5-week-old imprinting control region mice with cognitive dysfunction induced by intracerebroventricular injection of Aβ peptide. Repeated daily administration of N1-phenethylcymserine, rivastigmine, and donepezil ameliorated Aβ-induced cognitive dysfunction on days 0–3 after Aβ challenge, suggesting that BuChE as well as AChE may be a therapeutic target for managing cognitive dysfunction.[93]

A study that utilized rivastigmine to inhibit cholinesterases in cortical plaques and tangles from persons with AD reported dose-dependent inhibition of AChE at concentrations of 10^{-6} to 10^{-4} M and complete inhibition of BuChE at 10^{-5} M.[94] These data suggest that rivastigmine inhibits AChE and BuChE bound in plaques and tangles,[94] as well as free AChE and BuChE. Furthermore, in vitro data have indicated that when cholinesterases are exposed to Aβ for several hours, AChE is inactivated by Aβ, while BuChE remains highly active.[95] This finding highlights the potential importance of dual inhibition of AChE and BuChE to counteract BuChE-derived depletion of ACh in areas in which the concentration of Aβ is expected to be high. It has been suggested that rivastigmine may inhibit hyperfunctional BAβACs, as it is predicted that these complexes may be found at high concentrations in the vicinity of Aβ deposits in the brains of patients with AD. [10,94]

Clinical Data Supporting the Use of ChEIs in Alzheimer's Disease

Inhibition of AChE and BuChE in the CSF with ChEIs. In healthy volunteers, a single 3-mg dose of rivastigmine was shown to significantly inhibit AChE activity in the CSF.[96] Rivastigmine treatment has also been associated with decreased AChE activity,[97–101] reduced or unchanged BuChE activity,[97–99,101] and decreased AChE and BuChE protein levels[99] in the CSF of patients with AD. A 12-month study of rivastigmine in 11 patients with mild AD reported reductions in the activity of AChE and BuChE in both the CSF and plasma, suggesting that rivastigmine provides sustained long-term inhibition of cholinesterases.[102] Giacobini et al[103] reported the results of an open-label study that investigated how activity of AChE and BuChE in the CSF correlates with cognition in patients with mild-to-moderate AD receiving rivastigmine for at least 3 days. CSF levels of AChE and plasma levels of BuChE were inhibited by rivastigmine

in a dose-dependent manner, and there was a significant correlation between AChE and BuChE activity and the Computerized Neuropsychological Test Battery summary score.[103] Galantamine treatment has been shown to inhibit synaptic AChE variants in the CSF and the brain (measured using 1-[^{11}C] methylpiperidin-4-yl propionate and positron emission tomography) and was associated with positive effects on the patients' cognitive performance.[104]

Pharmacologic differences between the 3 commonly used ChEIs may have long-term clinical implications. Rivastigmine and donepezil have been shown to reduce AChE activity in the frontal, temporal, and parietal cortex in patients with AD.[105,106] However, donepezil treatment has also been associated with increased AChE activity,[97,99,101] increased BuChE activity,[99] and increases in AChE and BuChE protein levels.[99] Similarly, increased AChE activity has also been reported following treatment with galantamine.[98,101]

Significant increases in the number of cortical nicotinic ACh receptors in the brain of patients with AD have been observed following treatment with rivastigmine for 3 months, although the effect was not maintained at 12 months.[107] Galantamine treatment has also been associated with sustained inhibition of AChE for up to 12 months and changes in ^{11}C nicotine binding, which correlated positively with results on a cognitive test of attention.[108] A further study demonstrated that 12 months of treatment with galantamine was associated with significant increases in regional cerebral blood flow in cortical areas, which correlated with AChE activity, nicotinic receptor activity, and cognition.[109]

Rivastigmine treatment has also been associated with preservation of cerebral glucose metabolism in cortical brain regions of patients with AD compared with untreated controls and a significant dose-related increase in cerebral glucose metabolism in the right frontal association region.[110] A positive correlation between changes in cerebral glucose metabolism and cognitive performance was observed in patients receiving 10.5–12 mg/d of oral rivastigmine.[110]

Efficacy of ChEIs in patients with Alzheimer's disease. Despite obvious pharmacologic differences, rivastigmine, galantamine, and donepezil have all demonstrated symptomatic efficacy on the ability to perform activities of daily living (ADL), behavioral symptoms, cognition, and global function in clinical trials of patients with AD.[111–114]

Head-to-head data comparing efficacy of rivastigmine with an AChE-selective inhibitor are limited. EXCEED (EXelon Comparison of Efficacy vErsus Donepezil) was a large, international, randomized, controlled trial that evaluated the long-term efficacy, safety, and tolerability of 3–12 mg/d of rivastigmine in capsule form and 5–10 mg/d of donepezil in 994 patients with moderate to moderately severe AD.[115] Both treatment groups were comparable on measures of cognition and behavior. However, rivastigmine demonstrated superior efficacy to donepezil on the Alzheimer's Disease Cooperative Study–ADL scale (ADCS-ADL; $P = .007$) and the Global Deterioration Scale ($P = .049$) in the intent-to-treat, last-observation-carried-forward population.[115]

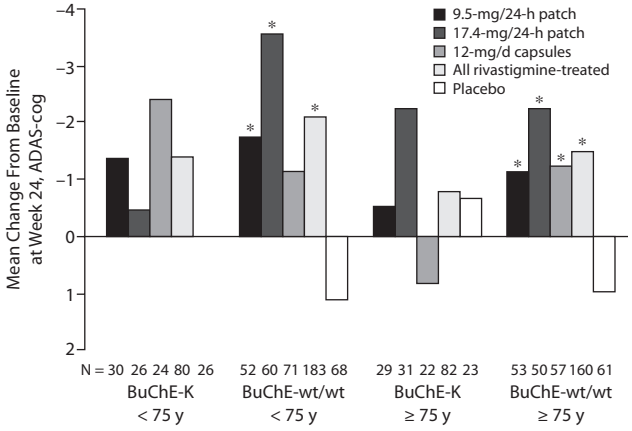
A 6-month, open-label study of rivastigmine in 382 patients with AD who had previously failed to benefit from treatment with donepezil (due to lack of efficacy, tolerability, or both) showed that 56.2% of patients were responders to rivastigmine.[116] Furthermore, a prospective, 3-month observational study investigated the efficacy of rivastigmine in patients with mild-to-moderate AD who showed deterioration when receiving treatment with an AChE-selective inhibitor.[117] Switching to rivastigmine from donepezil or galantamine was associated with a response on the Clinical Global Impressions of Change in 67.7% and 66.7% of patients, respectively.[117] Mean MMSE scores were also shown to improve after switching, while ADL, instrumental ADL, and Zarit scores remained stable.[117] This study also reported a 30.5% reduction in the number of patients receiving concomitant antipsychotics and discontinuation of benzodiazepines in all but 1 patient following switching from an AChE-selective inhibitor to rivastigmine.[117] These data provide a rationale for switching in cases of poor efficacy and tolerability. However, given the current understanding that the potential importance of BuChE as a therapeutic target increases throughout the disease course, the comparative clinical response of AChE-selective and dual AChE and BuChE inhibitors requires more detailed evaluation, particularly in patients at more advanced disease stages.

Efficacy of BuChE-selective inhibitors in patients with Alzheimer's disease. Darvesh et al[118] reported deterioration in cognitive function in a patient with AD following reduction of ethopropazine, a BuChE-selective inhibitor, and subsequent improvements following reinstatement of treatment. To date, no large-scale, randomized controlled trials of a BuChE-selective inhibitor in patients with AD have been performed. Studies in patients with mild-to-moderate AD, the patient population in the majority of ChEI trials, would be unlikely to highlight treatment advantages of BuChE inhibition.[119] BuChE-selective inhibitors may be more effective than AChE-selective inhibitors in patients with severe AD, although this remains to be tested clinically.

Effect of BuChE genotype on response to ChEIs. O'Brien et al[120] reported that patients with dementia with reduced-activity BuChE phenotypes show slower rates of cognitive decline and preserved attentional performance compared with patients with wild-type BuChE alleles, supporting the hypothesis that BuChE may be involved in disease progression. Patients with wild-type BuChE alleles, but not those with reduced function alleles, showed improved attention when receiving ChEI therapy.[120] The potential involvement of BuChE in attention is supported by the observed distribution of BuChE in the human amygdala and hippocampal formation.[16]

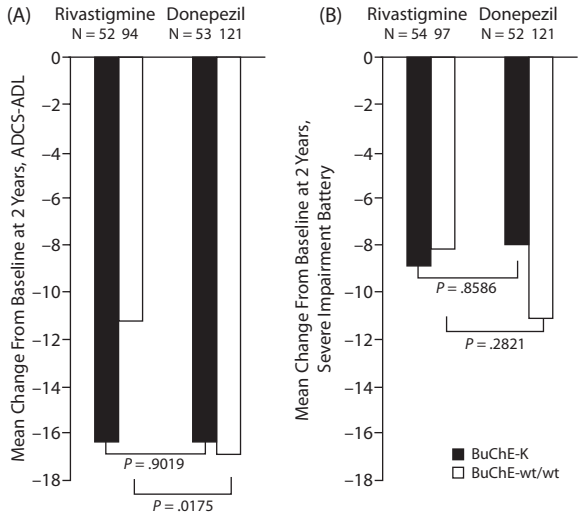
Trials of rivastigmine provide a wealth of data pertaining to the use of dual ChEIs in the symptomatic treatment of mild-to-moderate AD. The Alzheimer's Disease with ENA 713 (ADENA) program comprised four 26-week, randomized, double-blind trials of rivastigmine capsules in patients with mild-to-moderate AD.[121–124] Stratification of patients in the

Figure 2. Mean Change From Baseline on the ADAS-cog at Week 24 of the IDEAL Study by Age and BuChE Genotype[a,b]



[a]Adapted with permission from Lane and He.[126]
[b]Negative change indicates improvement.
*$P < .05$ versus placebo. *P* values are based on an analysis of covariance model adjusted for age, gender, race, years of education, and baseline score.
Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale, BuChE = butyrylcholinesterase, IDEAL = Investigation of transDermal Exelon in ALzheimer's disease study, wt = wild type.

Figure 3. Mean Change From Baseline on (A) the ADCS-ADL and (B) the Severe Impairment Battery at 2 Years in the EXCEED Study by BuChE Genotype[a,b,c]



[a]Data obtained from Novartis (data on file).
[b]*P* values are based on an analysis of covariance model adjusted for age, gender, and baseline score and compare rivastigmine and donepezil.
[c]Negative change indicates deterioration.
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living scale, BuChE = butyrylcholinesterase, EXCEED = EXelon Comparison of Efficacy vErsus Donepezil study, wt = wild type.

ADENA database by BuChE genotype found that patients with wild-type BuChE alleles showed a significant response to rivastigmine compared with placebo on the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog; 2.29 versus 7.24, respectively; $P < .0001$) and Progressive Deterioration Scale (3.20 versus 9.59, respectively, $P = .006$). In contrast, no significant differences were observed in the response to rivastigmine in carriers of BuChE-K alleles (Novartis, data on file).

Retrospective analyses of the Investigation of transDermal Exelon in ALzheimer's disease (IDEAL) study, a 24-week, randomized, double-blind trial of rivastigmine 9.5-mg/24-h patch, 17.4-mg/24-h patch, and 12-mg/d capsules[125] have also investigated the effect of BuChE genotype and age on the response to rivastigmine. When stratified by BuChE genotype, significant differences ($P < .05$) were observed in the mean change from baseline on the ADAS-cog and the ADCS-ADL in rivastigmine-treated patients compared with placebo in patients with wild-type BuChE alleles but not carriers of BuChE-K (Novartis, data on file). Further stratification by age demonstrated significant changes from baseline on the ADAS-cog in rivastigmine patch–treated patients with wild-type BuChE alleles under the age of 75 years and in all rivastigmine-treated groups in patients with wild-type BuChE alleles over the age of 75 years.[126] No significant effects of treatment were observed in patients with BuChE-K alleles, irrespective of age (Figure 2).[126] Patients under the age of 75 years treated with 17.4-mg/24-h rivastigmine patch showed significant changes from baseline at week 24 on the ADCS-ADL.[126] However, in patients over the age of 75 years, significant effects of treatment (17.4-mg/24-h patch and 12-mg/d capsule groups) were only observed in BuChE wild-type carriers and not in carriers of BuChE-K (Novartis, data on file and Lane and He[126]). However, it should be noted that these analyses were retrospective, were based on small numbers of patients, and were only intended to be hypothesis-forming and thus must be interpreted with caution.

In a secondary subgroup analysis of data from the EXCEED study,[115] significant differences in favor of rivastigmine compared with donepezil were observed on the Severe Impairment Battery ($P = .033$) and the ADCS-ADL ($P = .004$) in patients with wild-type BuChE and APOE ε4 genotype.

Retrospective analyses of data obtained in the EXCEED study demonstrated that patients with wild-type BuChE alleles, but not BuChE-K, showed greater response to rivastigmine than donepezil on the ADCS-ADL after 2 years of treatment (Novartis, data on file; Figure 3A). There was a trend toward greater deterioration on the Severe Impairment Battery in patients with wild-type BuChE randomized to receive donepezil compared with rivastigmine, although this did not reach significance. No significant differences in treatment response on the Severe Impairment Battery were observed in patients with BuChE-K alleles (Novartis, data on file; Figure 3B). Further retrospective analysis of data obtained in EXCEED demonstrated superiority of rivastigmine to donepezil on the ADCS-ADL and Neuropsychiatric Inventory in younger patients (< 75 years), while no significant treatment differences in favor of rivastigmine were seen in older patients.[127] Treatment differences on the ADCS-ADL were particularly marked in patients with 2 wild-type BuChE alleles. Therefore, a further retrospective analysis examined the effect of BuChE

genotype on the response to rivastigmine and donepezil in patients below 75 years of age.[128] Younger patients with 2 wild-type BuChE alleles showed a significantly greater response to rivastigmine compared with donepezil on the ADCS-ADL and the Severe Impairment Battery. In contrast, no significant treatment differences were observed in BuChE-K carriers.[128] The apparent greater efficacy of rivastigmine compared with donepezil in patients with wild-type BuChE alleles may reflect rivastigmine's ability to inhibit both BuChE and AChE.

Overall, data from IDEAL, ADENA, and EXCEED suggest that BuChE genotype may influence outcomes and provide rationale for dual inhibition of BuChE and AChE in the management of AD. Given the nature of AD, individualized approaches to treatment may optimize therapeutic outcomes. As discussed above, genotyping for BuChE has already been used in clinical studies and has potential to be used in clinical practice; however, cost implications and time constraints limit its current clinical utility.

CONCLUSIONS

BuChE-positive neurons are found in areas of the brain involved in working memory, attention, executive function, and behavior. Mounting preclinical and clinical evidence suggests that BuChE may be important in maintaining normal cholinergic function and in neurologic conditions including AD, dementia with Lewy bodies, and Parkinson's disease dementia and that this role may become more pronounced during the disease course. AChE-selective inhibitors and rivastigmine, a dual inhibitor of both AChE and BuChE, demonstrate efficacy in AD. Available data on the effect of BuChE genotype are limited and are largely based on prospective or retrospective analysis of clinical trial databases. These analyses were generally based on small patient numbers, and the studies were not powered to detect differences in efficacy between treatment groups stratified according to genotype. However, further investigation in more severe disease stages and advantages of dual inhibitors in specific patient populations is warranted.

An increased understanding of AD pathology, including the role of BuChE, will enable physicians to make best use of the available therapeutic options for their patients.

Drug names: donepezil (Aricept and others), edrophonium (Enlon, Tensilon, and others), galantamine (Razadyne), rivastigmine (Exelon and others), tacrine (Cognex).

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