A critical review of cholinesterase inhibitors as a treatment modality in Alzheimer's disease

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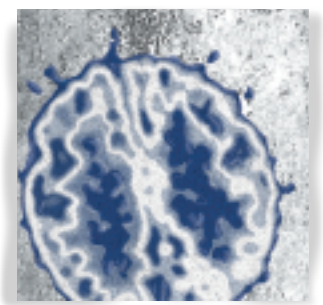

Early in the course of Alzheimer's disease (AD) treatment research, the cholinergic system was recognized as the most severely affected neurotransmitter system and therapeutic strategies were developed to restore cholinergic function in AD. While agents with various kinds of procholinergic action (eg, acetylcholine precursors, cholinesterase inhibitors [ChEIs], and muscarinic and nicotinic receptor agonists) have been evaluated for efficacy in AD, only the ChEIs have thus far demonstrated clinically significant cognitive effects. The ChEIs are the only agents to have consistently demonstrated efficacy in numerous multicenter, well-controlled trials in AD, and have been approved by many national regulatory authorities. Thus, ChEIs represent the first class of efficacious pharmacological approaches to AD treatment, and one that is likely to be used clinically in the indefinite future, since clinical applications of research into drugs with other mechanisms have not advanced as rapidly as many of us had hoped.

Early research into Alzheimer's disease launched the cholinergic hypothesis, based on the correlation between central cholinergic deficiency and clinical measures of cognitive decline. This was epitomized in therapeutic strategies employing a variety of procholinergic agents, of which only the inhibitors of cholinesterase (ChE), the enzyme that hydrolyzes acetylcholine in the synaptic cleft, have been proven clinically viable. Five such agents are reviewed: tacrine and donepezil, which act at the ionic subsite of acetylcholinesterase (AChE), and rivastigmine, galantamine, and metrifonate, which act at its catalytic esteratic subsite. Despite statistical evidence of efficacy from numerous well-controlled multicenter trials, important clinical utility issues remain outstanding: (i) number-needed-to-treat (NNT) analyses, quantifying the number of patients needing to be treated for one patient to show benefit, find values of 3 to 20; (ii) the pivotal trials themselves were conducted in nonrepresentative populations, largely comprised of physically healthy outpatients with mild-to-moderate Alzheimer's disease and a mean age of 72 years (thereby excluding over 90% of typical Alzheimer patients in State of California–funded clinics), treated for up to 6 months; and (iii) tolerability is underreported and characterized by a positive correlation between dose, effect, and cholinergic side effects—potentially serious adverse events include bradycardia, anorexia, weight loss and myasthenia with respiratory depression. Therapies thus require titration and constant monitoring. Nevertheless, acetylcholinesterase inhibitors (AChEIs) constitute the first class of effective agents and are likely to remain so in the continuing absence of viable alternatives.

Keywords: *Alzheimer's disease; treatment; acetylcholinesterase inhibitor; tacrine; donepezil; rivastigmine; galantamine; metrifonate*

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Pharmacological aspects

Selected abbreviations and acronyms

AD	*Alzheimer's disease*
ACh	*acetylcholine*
AChE	*acetylcholinesterase*
ADAS	*Alzheimer's Disease Assessment Scale*
ADASc	*Alzheimer's Disease Assessment Scale–Cognitive Subscale*
BChE	*butyrylcholinesterase*
ChAT	*choline acetyltransferase*
ChE	*cholinesterase*
ChEI	*cholinesterase inhibitor*
DDVP	*2,2-dimethyldichlorovinyl phosphate*
EMEA	*European Agency for the Evaluation of Medicinal Products*
MMSE	*Mini–Mental State Examination*
NDA	*New Drug Application*
NNT	*number needed to treat*

Cholinergic hypothesis

The well-established cholinergic defects in AD include: (i) decline of cholinergic basocortical projections; (ii) reduced activity of cerebral cortical choline acetyltransferase (ChAT), the key acetylcholine (ACh) synthesis enzyme; and (iii) cholinergic cell body loss in the nucleus basalis. The cholinergic hypothesis proposes that the cognitive deficits of AD are related to the observed decrease in central acetylcholinergic activity, and that increasing intrasynaptic ACh could enhance cognitive function and clinical well-being.[1] Additionally, there are correlations between cortical ChAT reduction or nucleus basalis cell reduction and cortical plaque density. Such cholinergic deficits correlate with cognitive decline as measured by the Blessed-Roth Dementia Rating Scale.[2] Thus, considerable therapeutic clinical research effort has focused on cholinergic strategies, the obvious rationale being that potentiation of central cholinergic function should improve the cognitive impairment associated with AD.

Cholinergic treatment approaches

Cholinergic treatment approaches include precursor loading, cholinesterase inhibition, direct cholinergic receptor stimulation, and indirect cholinergic stimulation.[1] Unfortunately, most of these cholinergic strategies have thus far proven either ineffective, effective but too toxic, or have not been completely developed. Among these, only ChEIs as a class have shown generally consistent symptomatic efficacy in short-term trials lasting from 3 to 6 months. These have been for the most part standardized, well-controlled multicenter studies, and have included agents such as tacrine, velnacrine, physostigmine, eptastigmine, donepezil, rivastigmine, metrifonate, galantamine, and others.

It is notable, also, that most of the ChEIs in development have been abandoned because of toxicity, and to some degree, efficacy issues. As a group, however, the few surviving agents are relatively well tolerated over the short term, and are associated with measurable cognitive benefit in a substantial proportion of patients with mild-to-moderate AD.

Rationale for, and mechanisms of, cholinesterase inhibition

As mentioned above, considerable evidence supports the concept of cholinergic insufficiency in AD, and the rationale for the use of ChEIs is their ability to boost ACh levels in synapses in tracts supporting cognitive function. When functioning normally, cholinergic neurons in the central nervous system (CNS) release ACh into the synaptic cleft, where it binds to postsynaptic or presynaptic receptors, either muscarinic or nicotinic, depending on the specific tract to which the cell belongs. ACh remains active until it is hydrolyzed to choline and acetate by acetylcholinesterase (AChE). By inhibiting AChE, and hence the hydrolysis of ACh in the synaptic cleft, ChEIs effectively increase the amount of ACh available for cholinergic receptors. This action, in theory, compensates at least partially for the effects of CNS cholinergic hypofunction in AD.

AChE contains two subsites, an ionic subsite and an esteratic subsite, that bind to ACh. The ionic subsite binds the quaternary amine group of ACh, then the ester group of ACh is cleaved by acylation at the catalytic esteratic site. Therefore, a potential ChEI medication can act at either of these two sites to prevent the normal interaction between ACh and AChE. Tacrine and donepezil act at the ionic subsite. Physostigmine, rivastigmine, and the metabolite of metrifonate (2,2-dimethyldichlorovinyl phosphate [DDVP]) act at the catalytic esteratic subsite.[3] (The same general mechanisms hold for butyrylcholin-

esterase [BChE], which is found in higher concentrations peripherally.) Specific inhibition of AChE can occur with relatively little inhibition of BChE when the side chains of the ChEIs interact with the peripheral anionic site of AChE. Donepezil has this property and is therefore selective for AChE.[4] Binding to the AChE sites may be either reversible or irreversible, and may be competitive or noncompetitive with ACh.

AChE in human tissue is present in several molecular forms: G4, a tetramer, is the most abundant AChE inhibitor in normal human brain, but its presence in the CNS decreases somewhat with aging and to an even greater extent in AD. It is located on the presynaptic membranes within the cholinergic synaptic cleft, so that when ACh binds to it, both hydrolysis and feedback inhibition of further ACh release occur. G1, a monomer, is found on postsynaptic membranes in the brain and participates in ACh degradation independently of its presynaptic release. Postsynaptic cholinergic receptor neurons and G1 monomeric AChE do not decrease significantly with AD or aging.[3] Rivastigmine is the only available ChEI that appears to be further subselective for the postsynaptic G1 monomer form of AChE.

Theoretically, at least, the differential pharmacology of the available ChEIs might be expected to differentiate them with respect to clinical efficacy and adverse events. Whether or not this is so remains to be determined, and will be partially reviewed in the following sections.

Individual cholinesterase inhibitors

This section describes the individual ChEIs that either are available for prescribing, have extensive phase 2 and 3 results from clinical trials, or may soon be available for marketing.

Tacrine

Tacrine (Cognex™) is a noncompetitive reversible inhibitor of cholinesterase and one of the aminocridine class of compounds (along with velnacrine and NXX-066, which were not further developed). It binds near the catalytically active site of the AChE molecule to inhibit enzyme activity and prolong ACh activity on its receptor. Although this is considered to be its principal mode of action, at high concentrations it also blocks sodium and potassium channels,[5] has direct activity at muscarinic receptors,[6] as well as other actions.[6]

Tacrine is cleared by the liver through first-pass metabolism, and concentrations reach their maximum within 1 hour. At least three active metabolites are produced mainly by CYP 1A2 hydroxylation of the ring positions that subsequently undergo glucuronidation and elimination. There is a low but variable oral bioavailability (from 2% to 40% of an intravenous dose). Higher doses and multiple dosing can prolong its elimination half-life, and bioavailability is not proportional to dose.

Although over 30 clinical trials have been published, very few were of an adequate design and sample size to allow an overall assessment of efficacy and safety,[7] and only two were considered essential or pivotal by the Food and Drug Administration (FDA) for their approval of the drug.[8,9] There were other enrichment, crossover trials,[10-12] but only limited conclusions on efficacy and safety can be drawn from these, because their design limited placebo-controlled treatment to less than 6 weeks. A controlled release preparation of tacrine was tested in one trial, but the results were presented only in an abstract at a meeting.[13] Tacrine was approved for marketing by the FDA in 1993 and in several European countries soon after.

Donepezil

Donepezil (Aricept™) is a long-acting, piperidine-based, relatively selective and reversible AChEI. It is well absorbed, metabolized by the liver, and excreted. Following an initial positive phase 2 study,[14] two favorable phase 3 clinical trials were conducted in the US[15,16] that proved pivotal to the drug's approval by the FDA in late 1996. Subsequently, the drug has been approved in several European and South American countries, as well as in Japan. Only recently have additional randomized clinical trials been published, including an international study of 6 months' duration,[17] a Scandinavian study of 12 months,[18] and a study in institutionalized patients.[19]

Metrifonate

Metrifonate (O,O-dimethyl-(1-hydroxy-2,2,2-trichloroethyl)-phosphonate), an organophosphate compound synthesized in the 1950's, is widely used as an insecticide for fruit and field crops (brand name Trichlorfon®, Bayer Pharmaceuticals, Inc.), as an antiparasitic agent for domestic animals, and as a second line antischistosomiasis agent in humans (for a review, see Schneider and Giacobini, 1999; Extoxnet Pesticide Information Project,

(http://ace.ace.orst.edu/info/extoxnet®/pips/trichlor.htm). It was introduced for the treatment of schistosomiasis under the trade name Bilarcil® in the 1960s, and has been used extensively in developing countries around the world by millions of people. Although it is no longer the first-line medication for that indication, it remains a World Health Organization–approved drug.

It is unique among the ChEI class of medications in that it is a nonactive prodrug, which is nonenzymatically transformed into the active metabolite DDVP (Dichlorvos™), itself a marketed insecticide. Very low concentrations of DDVP, an irreversibly binding ChEI, steadily converted from metrifonate lead to levels that are sufficient to inhibit ChEs in vivo. Thus, metrifonate can be viewed as a drug delivery reservoir providing steady, titrated administration of DDVP. Phosphorylating agents such as DDVP react covalently and irreversibly with the cholinesterase enzyme to form an inactive phosphoryl enzyme. The controlled release of DDVP in the brain and its slow inhibition kinetics for ChE may contribute to a relatively mild acute cholinergic toxicity compared with other ChEIs (see below).

In 1998 and 1999, the results of four phase 3 clinical trials of metrifonate for AD were published and were generally supportive of its essential cognitive efficacy.[20-23] One 12-month trial, stopped prematurely, remains unpublished. Although metrifonate has been extensively tested in phase 3 trials, a New Drug Application (NDA) to the FDA was disapproved because of concerns about muscle weakness and respiratory depression occurring in a small proportion of patients treated with the higher efficacious doses. This circumstance has raised concern that other ChEIs may also have particular neurotoxicity or may have more serious chronic effects in some patients than the typical acute, and usually mild, gastrointestinal cholinergic effects described in clinical trials.

Rivastigmine

Rivastigmine (Exelon™) is a pseudoirreversible, selective AChE subtype inhibitor. Although it inhibits both AChE and BChE, it is relatively selective to AChE in the CNS, and within the CNS, to areas of the cortex and hippocampus, and to the G1 monomeric form of AChE. Moreover, rivastigmine is not metabolized by the hepatic microsome system. Rather, after binding to AChE, the carbamate portion of rivastigmine is slowly hydrolyzed, cleaved, conjugated to a sulfate, and excreted. Thus, it is unlikely to have significant *pharmacokinetic* interactions with other medications.

Following early phase 2 proof-of-concept trials (eg, ref 24; see *Table I*). Four phase 3 clinical trials were completed, all of similar design, and differing mainly in dosing methods. The results of two have been published.[25,26] Some results of the third have been included in secondary reports.[27-29] A fourth trial, allowing an adjustable dosage, remains unpublished.

Rivastigmine was approved by a centralized procedure in Europe including all 15 member states of the EU in May 1998, as well as by the FDA in April 2000. The new prescribing information document incorporates the most recent labeling revisions. US prescribing information can be found at the FDA's web site (http://fda.cder.gov), and at Novartis' web site (http:/www.novartis.com).

Galantamine

Galantamine (formerly galanthamine), an alkaloid extracted from Amaryllidaceae (*Galanthus woronowi,* the Caucasian snowdrop), but which is now synthesized, is a reversible, competitive inhibitor of AChE with relatively less BChE activity.[30-34] Since competitive inhibitors compete with ACh at AChE binding sites, their inhibition is, theoretically, dependent on the intrasynaptic ACh concentration in that they will be less likely to bind to sites in brain areas that have high ACh levels. Theoretically, competitive inhibitors will have more effect in areas with low levels of ACh and less effect in areas with higher ACh. Again, theoretically, this may provide a selective effect in the brain areas most deficient in intrasynaptic ACh. Conceivably, in areas where acetylcholine is high, a competitive agent may have little effect, and a noncompetitive acetylcholinesterase inhibitor may further increase acetylcholine levels and contribute to central cholinergic side effects. Two other characteristics of galantamine are its 10- to 50-fold greater selectivity for AChE than BChE,[33] and its allosteric modulation of nicotinic receptor sites, thus possibly enhancing cholinergic transmission.[34]

Galantamine has been approved in Austria and Sweden. A new drug application (NDA) has been filed, with possible FDA approval before September 2000.

Summary

The ChEIs differ from each other in their selectivity for AChE and BChE, mechanism of inhibition, reversibility,

and competition for binding. There are also differences in pharmacokinetics. An unresolved question is whether or not these differences result in differential clinical efficacy. Pharmacokinetic and pharmacodynamic differences will certainly be used in promoting these drugs to physicians.

Clinical evidence

This section describes the evidence for the clinical efficacy of the ChEIs described above, based on published or available phase 3 and 4 trials. The significant trials are summarized by drug, below, and in *Table I,* with respect to methodological parameters and outcome.
It is important to consider that most of these trials were designed with the main objective of obtaining marketing approval from the FDA or the European Agency for the Evaluation of Medicinal Products (EMEA). As such, the protocols were fairly similar to each other, generally selecting outpatients with mild-to-moderate AD, usually with Mini–Mental State Examination (MMSE) scores between 10 and 26, inclusively (galantamine trials used a narrower range). Patients in these trials were generally physically healthy, usually treated for 6 months or less, and had a mean age of 72 years, a decade lower than the median age of AD patients in the US.[35]

Tacrine

Two multicenter trials have demonstrated tacrine's significant effect on the Alzheimer's Disease Assessment Scale (ADAS) Cognitive Subscale (ADASc) assessment and on measures of daily function. In one 12-week trial,[8] patients receiving 80 mg of tacrine improved significantly on the ADAS and clinical global rating compared with the groups that received smaller doses or placebo. In another 30-week study,[9] 663 patients were randomized to treatments with three different dosages or placebo. Statistically significant treatment effects for the 120-mg and 160-mg daily dosage groups were found on the ADAS and a clinician interview–based impression of change.
Tacrine's FDA-approved dosing regimen is an artifact of the forced titration study design of the 30-week multicenter trial. The recommended starting dose is 10 mg qid, to be maintained for 6 weeks, while serum transaminase levels are monitored every other week. Provided the drug is tolerated and transaminase levels do not increase to above three times the upper limit of normal, the dose is then increased to 20 mg qid. After 6 weeks, dosage should be increased to 30 mg qid, again with biweekly monitoring, and then, if tolerated, to 40 mg qid for the next 6 weeks. Generally, the drug is effective at doses of tacrine above 120 mg daily.

Donepezil

Except for two early trials of 12 weeks' duration,[15,16] trials generally last 24 or 52 weeks. Results of both pivotal studies showed statistically significant benefit in both cognition and clinician-rated improvement. When the studies are taken together, there is a clear trend toward a greater effect of 10 mg/d versus 5 mg/d. Medication is initiated at 5 mg/d and then increased to 10 mg/d after 2 or 4 weeks. Fewer cholinergic adverse events occur when the dose is increased after 4 weeks, compared with 1 week.
More recently, a study of nursing home patients[19] chosen for their severity and at least mild behavioral symptomatology did not show statistically significant cognitive effects or behavioral effects for donepezil. (For much of the trial some patients had improved on the MMSE, but this was not found at the end of 24 weeks.)

Metrifonate

Early metrifonate trials in AD used weekly doses; later trials used once-daily doses in order to reduce fluctuations between peak and trough inhibition levels and to achieve a more stable level of AChE inhibition.[36] The phase 3 trials generally used a loading-dose strategy for the first 1 to 3 weeks of treatment, followed by individualization of dosage based on body weight, with the exception of one trial that used a fixed 50-mg/d dosage throughout.[22] Metrifonate clinical trials are summarized in *Table I*.

Rivastigmine

The four main trials were of 26 weeks' duration and randomized, double-blind, placebo-controlled, and parallel-group. Details of each with respect to sample-size and dosage regimen are provided in *Table I.* In the trials, patients were randomized to placebo or to 3, 6, or 9 mg/d fixed doses of rivastigmine (B351, unpublished data), to a 2 to 12 mg/d adjustable dosage range (B304, unpublished data), or to two dose ranges of rivastigmine, 1 to 4 mg/d or 6 to 12 mg/d.[25,26]
In the two dose-ranging trials, doses were titrated weekly during the first 7 weeks to one of two preassigned dosage

Citation	Duration (wk)	No. of patients	Age (y)	Female (%)	Outcomes	Dose (mg/d)
Tacrine						
Davis et al,[10] 1993	6	215	70.4	53	ADASc, CGIC, MMSE, PDS	40, 80
Farlow et al,[8] 1992	12	468	72	52	ADASc, CGIC, MMSE, PDS	40, 80
Knapp et al,[9] 1994	26	663	71.9	52	ADASc, CGIC, MMSE, PDS, GDS, ADASnc	80, 120, 160
Donepezil						
Rogers et al,[15] 1998	12	468	73.7	63.5	ADASc, CIBIC+, MMSE, QoL, CDR-SBs	5,10
Rogers et al,[16] 1998	24	473	73.4	61.9	ADASc, CIBIC+, MMSE, QoL, CDR-SBs	5,10
Burns et al,[17] 1999	24	818	72	57.6	ADASc, CIBIC+, MMSE, CDR-SB, IDDD	5,10
Winblad et al,[18] 1999	52	286	72.5	64.3	GBS Scale, MMSE, PDS, GDS	5,10
Tariot et al,[19] 1999	24	208	85.6	82.5	MMSE, CDR, NPI	5,10
Metrifonate						
Cummings et al,[20] 1998	12	480	73.5	59	ADASc, CGIC, MMSE, ADLs	10-20 vs 15-25 vs 30-60
Morris et al,[21] 1998	26	408	73.6	60.5	ADASc, CGIC, MMSE, NPI, ADL (DAD), GDS	30-60
Raskind et al,[22] 1999	26	264	74.6	64.1	ADASc, CGIC, MMSE, NPI, ADL (DAD), GDS	50
DuBois et al,[23] 1999	26	605	72.1	63.7	ADASc, CGIC, MMSE, NPI, ADL (DAD), GDS	40/50 vs 60/80
Rivastigmine						
Forette et al,[24] 1999	18	114	71.2	NR	ADASc, CIBIC+ NOSGER	6-12 (bid vs tid)
Corey-Bloom et al,[25] 1998	26	699	74.5	61	ADASc, NYU-CIBIC+, MMSE, ADL (PDS), GDS	1-4, 6-12
Rosler et al,[26] 1999	26	725	72	59	ADASc, NYU-CIBIC+, MMSE, ADL (PDS), GDS	1-4, 6-12
B351 (unpublished)	26	702	74	56	ADASc, NYU-CIBIC+, MMSE, ADL (PDS), GDS	3, 6, 9
B303 (unpublished)						
Galantamine						
Raskind et al, [42] 2000	26	636	75	62	ADASc, CIBIC+ ADL, (DAD)	24, 32
Tariot et al,[43] 2000	20	978	77	64	ADASc, CIBIC+, ADCS-ADL, NPI	8, 16, 24

Table I. Description of key phase 3 and 4 cholinesterase inhibitor placebo-controlled, randomized clinical trials. All trials included only patients with probable Alzheimer's disease (NINCDS-ADRDA criteria) or Dementia of Alzheimer's type (*DSM-IV* criteria), and generally with baseline MMSE scores between 10 and 26 inclusive, with exceptions noted in *Table II*.

ADASc	Global (difference)	Global (response %)	MMSE	ADL	Other
2.4				NS	
				signif	
2.4 (ITT)				signif	
				--	3-wk open-label withdrawal period
2.9 (10 mg) 2.5 (5 mg)	0.44 0.36	25% vs 26% vs 11%	0.4	--	6-wk open-label withdrawal period
2.9 (10 mg) 1.5 (5 mg)	0.4* 0.3* (*estimated)	25% vs 21% vs 14%	NR	signif	ADL complex tasks signif
--	--	--	2.0 signif	signif	GDS, 0.3 (signif), approx MMSE is approx
--	--	--	NS	--	NPI (NS) CDR (signif)
2.94 (highest dose)	0.35 (high dose) 0.29 (mid dose)	NR	1.37	NS	
2.86	0.28	NR	0.43 (NS)	NS	NPI (2.75) hallucination item GDS (0.10) NS
1.7	0.20	NR	1.85	signif DAD Scale	NPI (3.42) agitation and aberrant motor behavior items signif GDS (0.04) NS
3.24 (higher dose) 1.30 (lower dose)	0.35 (high) 0.21 (low)	NR	1.19	signif DAD Scale	NPI (1.44 pts) NS, hallucination, apathy, and aberrant motor behavior items signif or nearly GDS (0.21) signif
4.84 (at bid dosing)	NR	57% (bid) vs 16% PLC			
3.78 (2.69 - 4.87)	0.29 (0.07 - 0.51)	24% vs 16% PLC improved		3.38 on PDS	GDS (0.19) signif OC: 21% of higher-dose patients vs 44% of PLC patients declined by 4 pts or more on the ADASc
2.28	0.44	40% (high) vs 22% PLC	0.88	2.73 on PDS	GDS (0.21) signif Responders, all signif: 27% vs 18% improved by ≥4 pts on DASc, high dose vs PLC
3.8 (32 mg/d)	NR	70% (32 mg/d) 55% (PLC)	NR		
3.1 (24 mg/d) 3.1 (16 mg/d)	NR	64% (24 mg/d) 66% (16 mg/d) 49% (PLC) (improved or no change vs worsening)	NR	signif	NPI 2.0 (signif) ADASc ≥4 37% vs 35.6% vs 19.6%

Outcome effect sizes are drug-placebo differences and are based on the highest dose used in the trial and generally on the more conservative (modified) intent-to-treat analyses. All effects listed are statistically significant at the $P<0.05$ level, two-tailed. Outcomes are not comparable among studies, especially on clinicians "global" ratings, and should be used as a guide only, since actual differences depend on statistical model and type of analysis, and are not performed consistently from study to study. Abbreviations, see next page.

Abbreviations for Table I: ADASc, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADASnc, Alzheimer's Disease Assessment Scale–Noncognitive Subscale; ADL, activities of daily living; CDR-SBs, Sum of the Boxes of the Clinical Dementia Rating; CGIC, Clinical Global Impression of Change; CIBIC+, Clinician's Interview-Based Impression of Change scale with caregiver input; DAD, Disability Assessment for Depression; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders,* 4th ed; GBS Scale, Gottfries–Bräne–Steen Scale; GDS, Global Deterioration Scale; IDDD, Interview for Deterioration in Daily living activities in Dementia; ITT, intention to treat; MMSE, Mini–Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NOSGER, Nurses Observation Scale Geriatric; NPI, Neuropsychiatric Inventory; NS, not significant; NR, nonresponders; NYU, New York University; OC, observed cases; PLC, placebo; PDS, Progressive Deterioration Scale; pts, points; QoL, quality of life; signif, significant.

ranges, 1 to 4 mg/d or 6 to 12 mg/d, and dose decreases were not permitted, possibly contributing to lesser tolerability during these stages of treatment. During the flexible-dose phase (weeks 8-26), doses could be further increased or decreased within the low- or high-dose range, with the aim of administering the highest well-tolerated dose.

Galantamine

Early clinical trials have been published reporting galantamine's effects in approximately 220 subjects with AD.[33,37-41]

They include a 3-month double-blind phase II dose-finding trial conducted in Europe (Shire GAL-93-01), comparing approximately 18, 24, and 36 mg daily doses of galantamine with placebo, divided into three times per day (tid) dosing. Effects on cognitive performance and side effects appeared dose-related. Cognitive performance (as measured by the ADASc) was statistically superior at all doses compared with the placebo group. At 36 mg (12 mg tid) galantamine there was both greater efficacy and a high dropout rate (50%) due largely to cholinergic side effects, while both cognitive efficacy and side effects were less at 18 mg/day.

One multicenter, placebo-controlled study involved 167 AD patients first entered into a 3-week single-blind, dose-titration "enrichment" phase, similar to early trials with tacrine. The 141 drug responders were randomized either to continue galantamine therapy, or to receive placebo for the following 10-week double-blind phase. Those who had remained on galantamine had improved by 1.66 ADASc points, while those switched to placebo had deteriorated by 1.40 points.[41]

Four phase 3 trials (GAL-USA-1, GAL-INT-1, GAL-INT-2, and GAL-USA-10) were completed. The first two, GAL-USA-1 and GAL-INT-1, used a fixed-dose treatment design. Subjects were titrated to doses of placebo, 12, or 16 mg bid galantamine, then followed for 6 months.[42] The third trial, GAL-INT-2, used a flexible dose-titration design and was 3 months in duration; and the fourth, GAL-USA-10[43] used three dosing regimens (8 mg/d, 16 mg/d, and 24 mg/d) and lasted 20 weeks.

The results of the first trial indicated that treatment with either 24 or 32 mg/d galantamine improved cognition. There were no significant differences in efficacy between the two galantamine treatment groups.

Summary of clinical evidence

Taken as a whole, the trials show consistent cognitive efficacy as measured by a standard cognitive battery for AD clinical trials, the ADASc. Changes in clinicians' global ratings and in activities of daily living also could be observed in many trials, but not as frequently. Statistically significant outcomes are in part dependent on whether or not all patients randomized are analyzed or just those patients who complete clinical trials.

Adverse events

Whereas efficacy outcomes such as the ADASc and clinical global ratings are usually reported consistently from study to study and drug to drug, adverse events are reported in highly variable ways. For example, some studies report only adverse events occurring greater than 5% of the time, or 5% of the time and twice the rate of placebo. Others report mean changes in weight or in heart rate, but not critical values such as the percentage of patients losing 7% or more of their weight, or those who develop clinically significant bradycardia. Thus, relatively uncommon, but clinically and economically important adverse effects can be underreported. Notwithstanding these variations, certain adverse events are common to all ChEIs and can be clearly observed among the clinical trials.

Significant cholinergic side effects occur in about 15% or fewer of patients receiving higher doses. Most adverse events are cholinergically mediated, and are characteristically mild in severity and short-lived, lasting less than a few days. Often they are related to titration of medication. Patients tend to rapidly become tolerant to the adverse events when they occur.

Because of the actions of ChEIs, these drugs need to be used cautiously in patients with significant asthma, significant chronic obstructive pulmonary disease, cardiac conduction defects, or clinically significant bradycardia. The long-acting effects of ChEIs and their effects on other esterases suggest that if surgery is needed, regional or local anesthesia should be used, if possible. With respect to general anesthesia, since some ChEIs decrease BChE activity, it is important to use short-acting muscle relaxants not metabolized via BChE. Furthermore, higher doses of muscle relaxants may be required because of the increased intrasynaptic ACh.

Tacrine

Elevated transaminases were the main reason for withdrawals in the two largest studies.[8,9] For patients without prior exposure to tacrine, the odds of withdrawal during the study on tacrine relative to placebo were 3.63 (95% confidence interval [CI] 2.80, 4.71, $P<0.001$).[7] The number requiring treatment to be discontinued because of liver enzyme increases is much lower in practice than in clinical trials, since 87% of those rechallenged were able to tolerate and continue tacrine.[44]

Common symptomatic adverse effects are dose-related and include (Parke Davis Prescribing Information)[10]: nausea and/or vomiting in 28% of patients (20% in excess of the rate in the placebo group), diarrhea in 16% (11% in excess of placebo), anorexia in 9% (6% in excess of placebo), myalgia in 9% (4% in excess of placebo). Other side effects that led to withdrawal from clinical trials of tacrine included dizziness (12%), confusion (>5%), insomnia (>5%), ataxia (>5%), agitation (4%), and hallucinations (2%). Tacrine is not tolerated in about 10% to 20% of patients because of such peripheral cholinergic effects as nausea, vomiting, diarrhea, dyspepsia, or appetite loss.

An adverse event affecting the internal validity of the tacrine clinical trials was the direct and reversible hepatotoxicity associated with tacrine. Transaminases were elevated above three times the upper limit of normal in approximately 30% of patients. This occurred generally within 6 to 12 weeks of starting medication and was reversible. However, as per protocol, most patients who had elevated transaminases had to be withdrawn from the clinical trials, and thus there were fewer patients who completed the trials than with other ChEIs. Nearly 90% of patients who had elevated transaminases and were then rechallenged were able to tolerate and continue medication.[44]

Effective doses of tacrine were 120 or 160 mg per day, given as 30 or 40 mg qid, necessitating a gradual titration from an initial daily dose of 40 mg over 12 weeks, and weekly or biweekly monitoring of transaminases for hepatotoxicity was required. Thus, tacrine is not a convenient drug to prescribe or take, regardless of its efficacy. Also, the variations in the clinical trial designs made it difficult to fully explore the prevalence of other side effects.

Donepezil

The most common gastrointestinal side effects of donepezil include nausea, vomiting, diarrhea, and anorexia. Additionally, some patients developed muscle cramps, headache, dizziness, syncope, or flushing. Hematological side effects include anemia, thrombocytopenia and eosinophilia. Cardiac effects included bradyarrhythmia, and syncope. CNS effects included headache, dizziness, insomnia, weakness, drowsiness, fatigue, and agitation. Weight loss occurred at twice the rate of placebo in the nursing home study, but was not reported in the other trials. Cholinergically-related adverse effects show a dose response. Adverse effects led to withdrawal from the 24-week study in 16% of patients in the 10-mg group, 6% of patients in the 5-mg group, and 5% in the placebo group.[16] Adverse effects occurred at a higher rate when the titration from 5 mg to 10 mg was made in 1 week compared with 6 weeks.

Metrifonate

As evidenced by the proportion of patients completing trials *(Table II)* metrifonate was generally well tolerated over periods of 6 months or less; the tolerability over longer periods is not known. Metrifonate is similarly or better tolerated than other ChEIs in that the vast majority of metrifonate-treated patients enrolled in phase 3 studies complete these clinical trials, and cholinergic adverse events were reported as frequently or less, compared with patients in other ChEI trials. Significant side effects occur in no more than 11% or so of patients receiving higher doses.

The most commonly reported adverse events include diarrhea, nausea, abdominal pain, leg cramps, and rhini-

Design and participants	Adverse events
• **Donepezil**	
Rogers et al,[15] 1998 12-wk, double-blind, placebo-controlled; 468 outpatients, MMSE between 10 and 26, randomized to placebo, 5 mg/d, or 10 mg/d	Nausea (22% vs 8%), diarrhea (13% vs 3%), vomiting (6% vs 5%), insomnia (18% vs 5%), fatigue (8% vs 5%), muscle cramps (8% vs 4%), among those AEs reported in donepezil over 5% of the time
Rogers et al,[16] 1998 24-wk, double-blind, placebo-controlled, randomized to placebo, 5 mg/d, or 10 mg/d; 473 outpatients, MMSE between 10 and 26; 80%, 85%, and 68% completed, respectively	Fatigue (8% vs 2%), diarrhea (17% vs 7%), nausea (17% vs 4%), vomiting (10% vs 2%), anorexia (7% vs 2%), muscle cramps (8% vs 1%), dizziness (8% vs 4%), and rhinitis (6% vs 2%),among those AEs reported in donepezil over 5% of the time. Among serious AEs reported, there were 4 accidental fractures and one episode of syncope in the 10-mg/d group compared with none in the 5-mg or placebo group
Tariot et al,[19] 1999 24-wk, double-blind, placebo-controlled, randomized to 10 mg/d or placebo; nursing home sites, 208 patients with possible or probable AD or AD with cerebrovascular disease; 82% of donepezil and 74% of placebo-treated patients completed	Asthenia (14% vs 9%), abdominal pain (10% vs 5%), myasthenia (6% vs 3%), anorexia (9% vs 5%), and weight loss (19% vs 10%) occurred just under twice as often as with the placebo. Weight loss was particularly marked in patients > 85 y and averaged 3 kg in the 19% with weight loss reported as an AE in this study (compared with 10% placebo)
Burns et al,[17] 1998 24-wk, double-blind, placebo-controlled study; 818 outpatients randomized to placebo, 5 mg/d, or 10 mg/d; 80%, 78%, and 74% completed, respectively	Nausea (24% vs 7%), diarrhea (16% vs 4%), vomiting (16% vs 4%), anorexia (8% vs 4%), dizziness (9% vs 5%), and insomnia (8% vs 4%), among those AEs reported in donepezil over 5% of the time. Vital signs and weight loss, syncope, and accidental fractures were not reported
Winblad et al,[18] 1999 52-wk, double-blind, placebo-controlled randomized to 10 mg/d or placebo; 286 outpatients; 67% of each group completed the trial	Asthenia (7.7% vs 3.5%), vertigo (7.7% vs 2.1%), syncope (6.3% vs 2.8%), and bone fractures (5.6% vs 3.5%) donepezil-treated group vs placebo. Vital signs and weight change were not reported
• **Metrifonate**	
Cummings et al,[20] 1998 Placebo-controlled, parallel-group, oral loading doses daily for 2 wk followed by one of 3 maintenance doses for the next 10 wk; 480 patients randomized to one of 3 dosing ranges or placebo after a loading dose regimen; maintenance dose ranges: 10-20 mg/d, 15-25 mg/d, and 30-60 mg/d; 96% of placebo and 89% of highest dose completed	Abdominal pain (12% vs 3%), diarrhea (19% vs 8%), flatulence (6% vs 1%), nausea (16% vs 9%), leg cramps (8% vs 1%). Dose-related decreases in heart rate, 1.6 to 7.4 bpm, 3 patients discontinued because of bradycardia
Morris et al,[21] 1998 Placebo-controlled, double-blind, parallel-group, oral loading doses daily for 2 wk followed by maintenance doses for next 24 wk; 408 patients, MMSE 10-26; randomized to drug or placebo; maintenance doses: 30 to 60 mg/d; 79% and 88% completed in drug and placebo, respectively	Diarrhea (18% vs 8%), leg cramps (9% vs <1%), rhinitis (7% vs 1%). Decrease in heart rate of 4.5 bpm compared with placebo
Raskind et al,[22] 1999 Placebo-controlled, double-blind, parallel-group, fixed dose for 26 wk; 264 patients MMSE 10-26, randomized to 50 mg of drug or placebo; 82% and 84% completed drug and placebo, respectively	Abdominal pain, leg cramps, agitation, and rhinitis (each 8% or 10% compared with 2% each for placebo. Decrease in heart rate of 6.1 bpm compared with placebo *Metrifonate studies: continued next page* ➜

Table II. Summary of safety data in key phase 3 and 4 cholinesterase inhibitor placebo-controlled, randomized clinical trials. All trials included only patients with probable Alzheimer's disease (NINCDS-ADRDA criteria) or Dementia of Alzheimer's type (DSM-IV criteria), although patients may have had evidence of cerebrovascular disease as well. Figures are abstracted from references or reports but are approximate because of changing sample size and variations in the

Dubois B et al,[23] 1999 Placebo-controlled, parallel-group, dose-ranging (2 ranges and placebo), oral loading doses daily for 2 wk followed by maintenance doses for the next 24 wk; 605 patients; MMSE 10-26; randomized to 40 or 50 mg/d, to 60 or 80 mg/d, or to placebo; depending on weight. 87%, 85%, and 85% completed treatment, respectively	Diarrhea, nausea, 11% at highest dose, 2 to 2½ times more common than placebo; leg cramps, 3%-6%, >3 to 6 times more frequent. Decrease in hemoglobin of 0.9 to 1.0 g/dL. Decrease in heart rate 8-9 bpm vs 3 bpm with placebo; bradycardia (heart rate <50) in 7% in high-dose group vs 2% in placebo group
• Rivastigmine	
Forette et al,[24] 1999 (Study B104) Placebo-controlled, double-blind, randomized, parallel-group, 2 doses and placebo for 18 wk, including 10-wk titration phase; 114 patients, MMSE 10-26, randomized to bid dosing (n=45), or tid (n=45), or placebo, with dosing in 6-12 mg/d range	
Corey-Bloom et al,[25] 1998 (Study B352) Placebo-controlled, double-blind, parallel-group, dose-ranging to 2 doses and placebo for 26 wk; 699 patients; MMSE 10-26; randomized to lower dose (1-4 mg/d), higher dose (6-12 mg/d), or to placebo. There was an upward dose titration for the first 7 wk, followed by a flexible dose phase to wk 26; 85%, 65%, and 84% completed the trial	In titration phase, higher dose vs placebo: nausea 48% vs 11%), vomiting (27% vs 3%), anorexia (20% vs 3%), flatulence (5% vs 1%), sweating (6% vs 2%), asthenia (10% vs 2%), somnolence (9% vs 2%), fatigue (10% vs 4%), dizziness (24% vs 13%). Maintenance phase: nausea (20% vs 3%), vomiting (16% vs 2%), dyspepsia (5% vs 1%), dizziness (14% vs 4%); 21%, 6%, and 2% of higher dose, lower dose, and placebo patients decreased weight by >7% of baseline
Rosler et al,[26] 1999 (Study B303) Placebo-controlled, double-blind, parallel-group, dose-ranging to 2 doses and placebo for 26 wk; 725 patients; MMSE 10-26; randomized to lower dose (1-4 mg/d), higher dose (6-12 mg/d), or placebo; doses were increased within the dosage ranges over the first 12 wk, and then maintained within two dosage ranges, 1-4 mg/d and 6-12 mg/d, for the next 14 wk; 86%, 67%, and 87% completed the trial	Except for nausea (17% vs 10%), there were no significant differences between low dose and placebo; higher dose vs placebo: nausea (50% vs 10%), vomiting (34% vs 6%), anorexia (14% vs 2%), abdominal pain (12% vs 3%), diarrhea (17% vs 9%), malaise (10% vs 2%), fatigue (10% vs 3%), dizziness (20% vs 7%), headache (19% vs 8%);24%, 9%, and 7% of higher dose, lower dose, and placebo patients lost >7% of body weight
B351 (not published) Placebo-controlled, double-blind, parallel-group, titration to one of 3 fixed doses over the first 12 weeks, then to 26 wk; 702 patients, MMSE 10-26, randomized to 3 mg, 6 mg, 9 mg/d, or placebo	Note: results presented incompletely in summary publications (Schneider et al,[27] 1998; Birks et al,[28] 2000)
B 304 (not published) Placebo-controlled, double-blind, parallel-group, adjustable dosing between 2 and 12 mg per day	
• Galantamine	
Raskind et al,[42] 2000 Placebo-controlled, double-blind, parallel-group, dose-ranging over 26 wk, with titration by 8mg/d every 1 wk to target doses of 24 mg/d or 32 mg/d; 636 patients randomized; 68%, 58%, and 81% completed the trial	Nausea (37.3 vs 43.6% vs 13.1%, 24 mg/d to 32 mg/d vs placebo), vomiting (20.8% to 25.6% vs 7.5%), diarrhea (12.3% to 19.4% vs 9.9%), anorexia (13.7% to 20.4% vs 5.6%), weight loss (12.3% to 10.9% vs 4.6 %), abdominal pain (6.6% to 10.9% vs 4.2%), dizziness (13.7% to 18.5% vs 11.3%), tremor (5.2% to 3.3% vs 0.5%). Much of the nausea and vomiting were related to the rate of titration of dose
Tariot et al,[43] 2000 Placebo-controlled, double-blind, parallel-group, dose-ranging over 20 wk, with titration by 8 mg/d every 4 wk to target doses of 8 mg/d, 16 mg/d, or 24 mg/d galantamine; 978 patients randomized; 76%, 78%, 78%, and 84% completed the trial	Nausea (16.5% vs 13.3% vs 4.5%, 24 mg/d, 16 mg/d, and placebo, respectively), vomiting (9.9% vs 6.1% vs 3.6%), anorexia (8.8% vs 6.5% vs 3.1%), diarrhea (5.5% vs 12.2% vs 5.9%). Significant dose-related weight loss of greater than 7% of body weight in 11% vs 6% vs 3.5% (24 mg/d, 16 mg/d, and placebo, respectively)

analyses. Dropouts are for all reasons to avoid bias, not just those attributed to side effects. Adverse events listed are usually only those occurring significantly more often (or sometimes 5% more often) than placebo. Abbreviations, see next page.

Abbreviations for Table II: AD, Alzheimer's disease; AEs, adverse events; bpm, beats per minute; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders,* 4th ed; MMSE, Mini–Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

tis. Leg cramps occur in 7% to 10% of patients, and 3 to 10 times more frequently than with placebo. The most obvious reason for this is tonic stimulation of myoneural nicotinic receptors. Increased incidence of leg or muscle cramping has been reported with other ChEIs as well. The statistically significant decrease in heart rate of about 5 to 9 beats per minute (bpm) at higher doses of medication is likely due to vagotonic effects observed with some ChEIs, and might be of clinical concern. The extent of clinically significant bradycardia (eg, heart rate <50 bpm) was reported in only one trial, and was 7% and 32 times more frequent than with placebo.

Of significant concern, however, is that approximately 20 patients out of 3000 in the metrifonate clinical studies developed "asthenia, myasthenia, and malaise," and "4 patients with muscular weakness received respiratory support. " (Letter from Bayer Pharmaceuticals, September 18, 1998.) This observation, occurring at the higher efficacious doses of metrifonate, led to the FDA disapproving the NDA and to development being discontinued.

Rivastigmine

As with other ChEIs, side effects were primarily gastrointestinal and occurred in the high-dose (6-12 mg/d) group. Side effects occurred primarily during dose escalation and led to withdrawal in one study in 23% of the high-dose group, 7% of the low-dose group, and 7% of the placebo group. Of note, inclusion criteria for these clinical trials allowed for patients with a broader range of medical comorbidities to be entered into these studies than into those with donepezil or tacrine, perhaps improving somewhat the potential generalizability of the findings.

Adverse effects that occurred with rivastigmine treatment are exemplified by findings in one study.[25] Side effects that occurred in the 6- to 12-mg/day group at a level significantly greater than placebo during the titration phase were sweating, fatigue, asthenia, weight loss, malaise, dizziness (24% vs 13% placebo), somnolence (9% vs 2% placebo), nausea (48% vs 11% placebo), vomiting (27% vs 11% placebo), anorexia (20% vs 3% placebo), and flatulence. In the maintenance phase, dizziness (14% vs 4% placebo), nausea (20% vs 3% placebo), vomiting (16% vs 2% placebo), dyspepsia (5% vs 1% placebo), sinusitis (4% vs 1% placebo) occurred statistically more in the 6- to 12-mg/day group than in the placebo group. Reference to the FDA-approved prescribing information (April 2000) notes the higher than expected incidence of gastrointestinal disturbances printed in bold type (http://www.fda.edu.gov & http://www.novartis.com). The FDA approval letter requests that the sponsor of the medication perform further analyses to better characterize these effects.

Galantamine

Gastrointestinal side effects were among the most frequent adverse events in both groups and more common at the higher doses. As with some other ChEIs, the rate of discontinuation in the 5-month clinical trial[43] was about the same for galantamine-treated patients as for those receiving placebo (10% vs 7%). The main adverse events were: nausea (16.5%, 13.3%, and 4.5%), vomiting (9.9%, 6.1%, and 3.6%), anorexia (8.8%, 6.5%, and 3.1%), and diarrhea (5.5%, 12.2%, and 5.9%), in the 24-mg/d, 16-mg/d, and placebo groups, respectively. Furthermore, there was a significant dose-related weight loss of greater than 7% of body weight in 11%, 6%, and 3.5% of patients in the groups defined above.

Particular adverse events of concern

Myasthenia or fatigue

Myasthenia and respiratory depression were of particular concern with metrifonate, leading to its therapeutic demise. Although these might be unique to the irreversible binding of metrifonate at the myoneural junction, it could occur with other ChEIs as well. The number of instances was small, since myasthenia and respiratory depression occurred in only about 20 patients out of about 3000, yet large enough to have a significant public health impact.

Bradycardia

Cholinergic compounds have vagal tonic effects that may significantly lower heart rate, and could possibly

cause or exacerbate bradyarrhythmias, thus leading to syncope and falls. There is clear evidence that metrifonate has this effect. Unfortunately, the clinical trial reports of other ChEIs do not adequately report heart rate changes, so this is difficult to assess. Yet, even a very low rate of syncope or falls can have marked consequences with respect to overall safety, effectiveness, and outcomes.

Anorexia

An increased incidence of anorexia appears to be a consistent finding across clinical trials and appears to be dose-related. The reported absolute incidence varies across trials from approximately 8% to 25% at the highest dose of ChEIs, and from 3% to 10% in comparable placebo patients. Anorexia was 4 to 8 times more likely with donepezil (depending on the dose) in patients treated with donepezil than with placebo. Unfortunately, the severity and circumstances of the anorexia have not been adequately defined.

Weight loss

Similarly, there is a substantially increased rate of significant weight loss with higher doses of ChEIs compared with placebo patients. The proportion of patients losing greater than 7% of their baseline weight varies from approximately 10% to 24% in the higher doses and from 2% to 10% of the placebo-treated patients in those trials with donepezil, rivastigmine, and galantamine that report the statistic. The absolute risk differences ranged from 7.5% to19 %. Not all trials reported weight-change data, however, or these were reported as mean differences in weight, a relatively uninformative statistic in that it does not describe clinically significant changes in individual subjects.

Summary and issues

This review has described the overall efficacy and summarized safety data from most of the pivotal clinical trials of the four ChEIs available on some of the world markets (metrifonate being available as an antihelminthic). Higher doses were consistently more effective than lower doses. Doses of 5 mg of donepezil, 80 mg/d of tacrine, 40 mg/d of metrifonate, 4 mg/d of rivastigmine, or 8 mg/d of galantamine tend not to be efficacious. The essential paradox with ChEIs is that the higher the dose over a longer period of time, the greater the effect and the greater the side effects. It is important to determine whether both efficacy and side effects occur in the same patients or different patients. Thus, in the context of the amply demonstrated statistical efficacy many outstanding issues involving safety and effectiveness remain. Some of these are discussed below.

Relative effectiveness

There are at least three aspects to comparing effectiveness. The first is the magnitude of effect on the primary outcomes of these trials, usually the ADASc and a global rating. To some extent, this can be done by comparing the mean drug-placebo differences and their confidence intervals. However, the main limitation of this kind of comparison is that studies were done under different circumstances, at different times, were analyzed differently, and reported differently. In the latter case, often there is not enough information provided to calculate confidence intervals. The second limitation is that different types of analyses are reported with different populations not equivalently accounting for dropouts. The third is that, by focusing only on efficacy, no consideration is given to overall treatment *efficiency* or the proportion of all patients who truly benefit. In effect, high dropout rates or adverse events are not discounted from overall efficacy. Lastly, these are highly selected populations of AD patients not necessarily representative of community-dwelling patients, and treatments generally only lasted 6 months (see below). Relative effectiveness needs to be tested in head-to-head comparisons.

Safety

In publications, adverse events are underreported. As a generality, the higher doses in clinical trials were the more effective and the more associated with adverse effects. Summaries of the total number of events in each treatment group may be given, but they are not broken down by time to event, whether the event led to discontinuation, or to a significant event such as a fall or a hip fracture. Only the more frequent events tend to be reported, for example, in many publications, only those events occurring over 5% of the time and twice that of (or statistically significantly greater than) placebo. Such limited reporting tends to hide infrequent events occurring with

high specificity and at high-risk rates such as hip fracture, falls, syncope, bradycardia, severe anorexia, or weight loss. At best, adverse event reporting gives a poor estimate of the events likely to occur. The outcomes with metrifonate illustrate this well: adverse events were unremarkable and appeared even mild when any individual trial was examined. Yet, when the FDA examined all patients together, it was obvious that myasthenia and respiratory distress occurred at the higher and efficacious doses to such an extent that the drug could not be approved.

Clinical utility

Despite this extensive portfolio of clinical trials and the overall impression of clear and measurable cognitive efficacy, the actual clinical usefulness of ChEIs as a class and of individual ChEIs has yet to be fully documented over the long term. Are patients and physicians experiencing clear clinical benefits? Even after all these many clinical trials, the true clinical relevance of the statistically significantly clear efficacy of ChEIs remains to be determined.

Patients selected using these criteria have previously been shown to represent less than 10% of the typical Alzheimer patients in State of California–funded clinics.[45] They are most certainly not representative of AD patients as a whole or of those many patients with concomitant medical illnesses or behavorial problems. In addition, there is little experimental evidence on the effects of ChEIs over 6 months. Observational data including AD patients who have been treated for longer periods of time are of limited use, since they largely include the patients who tolerated or benefited from medication and those who have slower rates of decline, and hence are a biased sample (discussed elsewhere).

In an effort to better understand utility, some authors have reconceptualized dichotomous outcomes (eg, the proportion of patients who improved their ADASc scores by 4 or more, or the proportion of patients who do not worsen their ADASc scores by 4 or more compared with placebo) as a "number needed to treat"(NNT) statistic (eg, see reference 46). This statistic, the inverse of the absolute risk difference, proposes to quantify the number of patients needing to be treated in order for 1 patient to show benefit. Generally, among these analyses, the NNT might range between 3 and 20, albeit with wide confidence intervals. Unfortunately, the NNT statistics do not address how physicians, patients, caregivers, and health authorities value clinical outcomes such as differences on cognitive scores or global ratings, and certainly do not address whether improvement over the course of 6 months is sufficient or meaningful therapy in a relentlessly progressive illness with a chronic course over several years.

Another effort to assist clinical relevance is contained in the rivastigmine EMEA prescribing information. There, the EMEA looked specifically at a subgroup of patients who both improved on the ADASc by 4 points or more and did not worsen on both global ratings and activities of daily living. By restricting the outcomes to people who benefited in three domains of functioning, the EMEA hoped to get a more specific estimate of the actual numbers of patients who benefited cognitively, clinically, and functionally. In this analysis, the proportion of responders was 10% vs 6% for higher-dose rivastigmine (6-12 mg/d) compared with placebo.

Clinical utility is a balance between efficacy, safety, and tolerance. To date, no effectiveness trials have been conducted, nor have there been trials directly comparing one ChEI with another in typical, ordinary AD patient populations. These kinds of trials are urgently needed.

Duration of efficacy and long-term efficacy

The randomized clinical trials are nearly all of 6 months' duration. One donepezil trial suggested that it took 3 months after discontinuation for patients to return to the placebo group's level of function, while another trial showed that donepezil was effective for 12 months (although many patients did not complete). Thus, the empirical evidence is that ChEIs—and donepezil in particular—may stabilize or improve cognitive symptoms for 6 to 12 months compared with a contemporaneous placebo-treated group. Claims regarding long-term treatment and efficacy come from largely uncontrolled and always observational studies of patients who have survived the 6-month acute treatment trial. Early small-scale and small sample-size studies suggested that long-term use of physostigmine was associated with a reduced rate of decline, even in patients who failed to show improvement acutely.[47-50] Results were reported[51] from a nonrandomized, open-label study of donepezil conducted after a double-blind, placebo-controlled trial of donepezil in patients with mild-to-moderate AD. Patients followed longitudinally for up to 98 weeks

showed a decline in scores on the ADASc that was interpreted to be slower than the decline observed in a previously obtained, untreated cohort of US military veterans a decade earlier (ie, "historical controls").
Similar data have been reported at meetings from cohorts treated long term with rivastigmine (Novartis, data on file) and with galantamine.[42] Interestingly, the rivastigmine data set regarding long-term therapy indicates that patients who started treatment with rivastigmine later than a cohort that received therapy somewhat earlier (as a result of both groups having first participated in a randomized, placebo-controlled, parallel-group trial) showed cognitive improvement of the same order of magnitude as one would expect in any cohort, but also demonstrated a persistently reduced level of performance, though not significantly so, in comparison with the cohort treated several months longer (Novartis, data on file).
Finally, after the completion of one tacrine clinical trial,[9] a large percentage continued to receive tacrine openly and these patients were followed over time. Patients receiving higher doses of tacrine, 120 mg or 160 mg per day over a 2-year period or more, had a reduced likelihood of entering a long-term care facility compared with those who received 80 mg or less of tacrine, doses that would be considered subtherapeutic.[52] One possible implication of such data is that early and adequate treatment with a ChEI might achieve benefits that diminish over time, but nonetheless represent meaningful, and perhaps long-lasting, gains in function in contrast to treatment later in the course of illness. Unfortunately, these nonsignificant observational data have been used by pharmaceutical companies to argue that a delay in treating with a ChEI will lead to permanent harm. A more parsimonious explanation, however, is that these are biased observations based on the effect of survivors. Many of these observations were obtained retrospectively, were biased in favor of patients who tolerated and benefited from medication during the double-blind, placebo-controlled trials, generally depended on historical comparisons, and must be interpreted cautiously.

Effect on behavior

The evidence that ChEIs may improve behavior is based on case series and secondary analyses of efficacy trials (eg, see refs 21, 53, 54). Patients enrolled into ChEI trials are selected largely on the basis of their ability to cooperate. They are not generally agitated, psychotic, or depressed, and have low baseline scores on these parameters. The metrifonate trials, for example, used behavioral rating scales, and, in general, found small, but statistically significant, drug–placebo differences. Different subscales from study to study were observed to be significant, so that there was little consistency. For example, in two trials, there was a significant effect on the hallucination or aberrant motor behavior items, and, in one trial, on agitation or apathy on the NPI (Neuropsychiatric Inventory), a structured interview of the caregiver's assesment of behavorial problems. The overall scores were very low, as were the differences. Clinical significance remains to be determined. The effectiveness of ChEIs on behavior, however, may be in delaying the onset of troublesome behaviors, perhaps by maintaining cognitive function,[43,54] or perhaps through enhancing attentional processes and activation. ChEIs have not been formally tested in patients with a priori clearly defined behavioral problems.

Neuroprotection

The importance of disease-modifying treatment has been well described. [55,56] In essence, delaying the onset of appearance of disease by 5 years would result in a 50% reduction in both the incidence and prevalence of AD,[57]and families would consider drugs that slow the clinical course of AD to be valuable.[58] To the extent that cholinergic therapies may have effects beyond the short-term symptomatic improvement in cognition or function, their potential for delaying onset or modifying clinical progression is discussed below.
Basic and preclinical data suggest possible novel mechanisms by which ChEIs may actually modify illness progression. For instance, relationships have been reported between amyloid precursor protein and the cholinergic system. Activation of the M_1 muscarinic receptor can stimulate secretion of amyloid precursor proteins via the α-secretase pathway, with attendant reduction in beta-amyloid (Aβ) release.[59,60] Similar results have been reported with a variety of cholinergic agonists and some, but not all, ChEIs.[59,61-63] Taken together, the studies suggest that ChEIs (and some other cholinergic agents) can prevent the formation of amyloid and promote normal processing of amyloid precursor proteins.[64] Further, muscarinic receptor activation and signal transduction via G-proteins have been shown to be disrupted by Aβ proteins.[65]

Conclusions

ChEIs are the best-proven efficacious treatments for some aspects of AD. Other therapeutic approaches are not as well tested or as clearly efficacious, and newer potential therapeutic agents are still at an early stage of clinical development. Therefore, ChEIs are likely to be with us and used for at least the next few years. However, therapeutic results are usually modest, affecting only a minority of patients, but these patients are helped significantly. The duration of effect and long-term safety are not known. It often takes time for clinicians to appreciate the full magnitude of clinically meaningful effects of new drugs. ❑

Revisión crítica de los inhibidores de la colinesterasa : una modalidad de tratamiento en la Enfermedad de Alzheimer

La investigación inicial en la Enfermedad de Alzheimer se orientó hacia la hipótesis colinérgica, basándose en la correlación entre el déficit colinérgico y las mediciones clínicas de los deterioros cognitivos. Esto se tradujo en a estrategias terapéuticas que utilizaban una variedad de agentes procolinérgicos, de los cuales persisten sólo los inhibidores de la colinesterasa (enzima que hidroliza la acetilcolina en el espacio sináptico). En este artículo se revisan cinco de estos inhibidores: la tacrina y el donepecilo que actúan en los subsitios iónicos de la acetilcolinesterasa, y la rivastigmina, la galantamina y el metrifonate, los que actúan en el subsitio esterático catalítico. A pesar de las evidencias estadísticas que demuestran de la eficacia de estos fármacos en numerosos estudios multicéntricos bien controlados, hay importantes temas de utilidad clínica que permanecen sin clarificarse : 1) el análisis del número de casos que requieren ser tratados, para lo cual es necesario cuantificar el número de pacientes que deben ser sometidos al tratamiento para que uno de ellos se beneficie, lo que se logra con valores entre 3 y 20 sujetos, 2) los principales estudios se realizaron en poblaciones no representativas e incluyeron pacientes ambulatorios -físicamente sanos-, con Enfermedad de Alzheimer leve a moderada, con una edad promedio de 72 años y que fueron tratados hasta por 6 meses (de este modo se excluyeron cerca del 90% de los pacientes con Enfermedad de Alzheimer típica que esteban en diversas clínicas del estado de California) y 3) la tolerancia a los fármacos con alta probabilidad está subinformada y se caracteriza por una correlación positiva entre dosis, efecto y síntomas laterales colinérgicos (los efectos adversos más importantes incluyen bradicardia, anorexia, baja de peso y miastenia con depresión respiratoria. Estos tratamientos requieren de un ajuste paulatino de las dosis y de un monitoreo con tante. A pesar de todo, los inhibidores de la acetilcolinesterasa constituyen la primera clase de agentes efectivos y posiblemente se mantendrán en uso, de no aparecer nuevas alternativas terapéuticas viables.

Revue critique des inhibiteurs de la cholinesterase dans le traitement de la maladie d'Alzheimer

La mise en évidence par les travaux de recherche sur la maladie d'Alzheimer d'une corrélation entre la déficience cholinergique centrale et les mesures cliniques du déclin cognitif a permis très tôt de formuler l'hypothèse dite de la voie cholinergique. Celle-ci s'est traduite par l'élaboration de stratégies thérapeutiques basée sur divers types d'agents procholinergiques dont seuls sont encore utilisés à ce jour les inhibiteurs de la cholinestérase, l'enzyme hydrolysant l'acétylcholine dans la fente synaptique. Cinq produits appartenant à cette classe sont examinés ici : la tacrine et le donépézil, qui agissent au niveau du site secondaire ionique de l'acetylcholinestérase, ainsi que la rivastigmine, la galantamine et le métrifonate, qui agissent au niveau du site secondaire catalytique estérasique. Bien que l'efficacité de ces produits ait été confirmée sur le plan statistique par de nombreuses études multicentriques bien contrôlées, d'importantes questions relatives à leur utilité clinique restent en suspens: (1) les études visant à déterminer le nombre de sujets à traiter (NST) pour obtenir une amélioration chez 1 patient trouvent des valeurs variant entre 3 et 20; (2) les études ayant servi de base aux analyses ont été menées sur des populations non représentatives, composées en grande partie de patients physiquement sains, consultants externes, atteints de maladie d'Alzheimer légère à modérée et dont la moyenne d'âge était de 72 ans (étaient ainsi exclus jusqu'à 90 % de patients des cliniques financées par l'Etat de Californie atteints de maladie d'Alzheimer avérée) et dont le traitement avait au plus duré 6 mois; (3) sur le plan de la tolérance, enfin, alors que les études mettent en évidence une corrélation positive entre la dose, l'efficacité et les effets secondaires de type cholinergique, les disparités méthodologiques entraînent une sous-estimation des effets indésirables, dont les plus importants comprennent la bradycardie, l'anorexie, la perte de poids et la myasthénie avec dépression respiratoire. Ces thérapeutiques nécessitent donc la détermination soigneuse du dosage optimal ainsi qu'une surveillance constante. Il n'en demeure pas moins que les inhibiteurs de l'acétylcholinestérase représentent la première classe de molécules efficaces et le resteront probablement tant que nous ne disposerons pas d'alternatives sérieuses pour traiter la maladie d'Alzheimer.

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