Drug Class Review: **Cholinesterase Inhibitors**

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel

Introduction

Alzheimer's Disease (AD) is the most common cause of dementia in North America. AD is a debilitating and expensive illness in the elderly population with a projected societal annual cost of care to the U.S. of at least $100 billion a year. The average lifetime cost per Alzheimer patient is $174,000. AD ranks third behind heart disease and cancer in expense and is the primary cause of nursing home admissions. The first clinical signs of AD are impairments of memory, language and visuospatial function, some of which can be explained by loss of cholinergic neurons in the basal forebrain. This loss contributes to the symptom development of AD. The main pharmacological approach to limiting cognitive and functional decline in AD is to increase synaptic levels of acetylcholine through use of cholinesterase inhibitors (CI). Currently available CI includes donepezil (Aricept®), galantamine (Reminyl®), rivastigmine (Exelon®) and tacrine (Cognex®).

Table 1: Cholinesterase inhibitors available in the U.S

Generic	Brand (Manufacturer)	Strengths & formulations	FDA approval date
Donepezil	Aricept- Eisai/Pfizer	5,10 mg tablets	November 25, 1996
Galantamine	Reminyl- Janssen	4,8,12 mg tablets Oral solution 4 mg/ml	February 28, 2001
Rivastigmine	Exelon- Novartis	1.5, 3, 4.5, 6 mg tablets Oral solution 2 mg/ml	April 25, 2000

Tacrine is not included in this review

FDA-Approved Indications and Off-Label Uses

Donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon®) are indicated for the treatment of mild to moderate dementia of AD. These agents have also been used in the treatment of Lewey body dementia, vascular dementia and mixed pattern dementia, as well as moderate to severe dementia of AD. Additionally, CI are employed in the treatment of behavioral disturbances commonly encountered in AD patients.

Methods

The agents included in this review include donepezil, galantamine and rivastigmine. Tacrine is excluded from the review due to the risk of hepatotoxicity associated with its use.

Computerized databases, including MEDLINE and Pub Med were searched for literature on the pharmacokinetics, pharmacodynamics, safety and efficacy of the CIs. Additionally, evidence based resources such as Cochrane and DARE were searched for these same criteria. Clinical trials, meta-analysis and pending publications were included in the review. Only articles published in English were considered. Data from poster presentations was reviewed for a portion of the long-term safety data and recently undertaken head to head trials.

Literature searches included a time frame from January 1990 to January 2003. Clinical trials were reviewed if the trial included at least 100 patients.

Pharmacology

The exact mechanism of action of donepezil, rivastigmine, and galantamine remains unknown, however, these agents are thought to work by increasing cholinergic function through the inhibition of cholinesterase (AChE), thereby increasing the available concentration of acetylcholine (ACh). Donepezil and rivastigmine are classified as reversible cholinesterase inhibitors, but rivastigmine has been termed a 'pseudo-irreversible' inhibitor due to its slow dissociation from acetylcholinesterase (AChE). In addition, only rivastigmine substantially inhibits butyrylcholinesterase (BChE), an enzyme with increased activity during the breakdown of acetylcholine in the brains of Alzheimer's patients. Galantamine has a duel mechanism of action. Like the others, it inhibits AChE, as well as modulating nicotinic receptors with allosteric binding to increase neurotransmitter release and enhance cholinergic function. Although these agents have shown the most promise, they do not ensure alteration of the underlying dementing process.

Table 2: Pharmacologic properties

Drug	Class	Selectivity
Donepezil	Piperidine	Acetylcholinesterase
Galantamine	Phenanthrene alkaloid	Acetylcholinesterase, allosteric nicotinic modulator
Rivastigmine	Carbamate	Acetylcholinesterase, butyrylcholinesterase

Pharmacokinetics

Table 3: Pharmacokinetic properties

Drug	Tmax (hr)	Serum half-life	Plasma protein binding	Food delays absorption	Metabolism
Donepezil	3-5 hrs	70-80 hrs	96%	No	CYP2D6, CYP3A4
Galantamine	30-60 min	5-7 hrs	10-20%	Yes	Non hepatic
Rivastigmine	0.5-2 hrs	2 hrs	405	Yes	CYP2D6, CYP3A4

Dosing and Administration

Donepezil is effective at doses of 5 or 10 mg/day and is given as a once daily dose. Initial dose is 5mg and titration to 10mg is recommended only after 4-6 weeks at the 5mg dose. In clinical trials the 10mg dose of donepezil was not significantly more effective than the 5 mg dose, however trends in clinical trials suggest that the 10 mg dose may provide added benefit for some individual patients. It can be given without regard to food. Although the package insert recommends dosing at bedtime, the favored administration time is with lunch or in the early afternoon. This regimen lessens the occurrence of nightmares and vivid dreams.

Galantamine is effective at doses of 16-32mg/day given in two doses, preferably with morning and evening meals. The initial starting dose is 4 mg twice a day (8mg/day). After a 4-week minimum, the dose should be increased to 8 mg twice daily (16 mg/day). A further increase to 12 mg twice a day may be attempted after an additional 4-week period. Patients with moderate renal or hepatic impairment (Child-Pugh score 7-8) should not exceed 16mg/day. Galantamine is not recommended in patients with severe renal or hepatic impairment (CrCl<9; Child-Pugh score 10-15). The concentration of galantamine oral solution is 4mg/ml. The oral solution can be mixed with 3 to 4 ounces of any non-alcoholic drink such as mineral water, cola, coffee, tea, milk and orange juice. However, galantamine oral

solution should not be mixed with a beverage and then stored for later use. There is no compatibility data available for galantamine oral solution with specific foods.

Rivastigmine is effective at doses of 6-12mg/day given in two doses (3, 4.5 or 6 mg twice a day). The recommended starting dose is 1.5mg twice daily with subsequent increases of 1.5mg BID every 4 weeks. This longer titration has been shown to decrease the gastrointestinal symptoms seen with more rapid titration, thereby increasing tolerance of the agent. In preliminary reports by Shua-Haim and another by Edwards, the incidence of gastrointestinal adverse effects can be reduced to 3.8% from a package insert incidence of 47% and a discontinuation rate of 7%. The maximum dosage is 12 mg/day.

With all three agents there have been reports involving abrupt loss of effect with drug discontinuation. The CI maybe restarted at this point but it should be kept in mind that the original level of effect may not be resumed. If a patient was discontinued for greater than 3 days, titration should be used to reinstitute therapy.

Table 4: Dosing and administration

	Donepezil	Galantamine	Rivastigmine
Initial Dose	5mg QD	4 mg BID	1.5 mg BID
Recommended Titration	4 weeks	4 weeks	4 weeks
Minimum Therapeutic dose	5 mg QD	8-12 mg BID	3-6 mg BID
Food Considerations	None- give with lunch	Give with food	Give with food
Dose adjustments in special populations	None	Moderate renal and hepatic impairment- not to exceed 16 mg/day	None

Efficacy

Efficacy Measures[17-23]

1. Alzheimer's Disease Assessment Scale (ADAS-Cog) – The ADAS-Cog is the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS). The ADAS has demonstrated validity and reliability in overall dysfunction and the cognitive and non-cognitive subscale of the test. It is an 11-item scale with scores ranging from 0 (no impairment) to 70 (very severe impairment). The average score of patients with mild to moderately severe AD is 15-25. On average, untreated patients with moderate AD decline 7 to 11 points per year while mild or severe patients may only decline 0 to 5 points per year. This difference in scale sensitivity to stage of disease is important to recognize when comparing different treatments in different populations. An improvement of 4 or more points is considered to be clinically meaningful.
2. Mini-Mental State Examination (MMSE) – The MMSE is a short test that quantifies cognitive impairment. Scores range from 0 to 30 with 0 implying severe impairment and 30 being the best possible score. Scores of 10 to 26 encompass moderate to mild stage dementia, respectively. Brooks et.al.[14] and Salmon et.al.[15] have reported the annual decline in untreated patients to be 2.8 points per year.
3. AD Cooperative Study-Activities of Daily Living Inventory (ADCS/ADL)- Is a rating scale which involves a 23 item assessment of ADL that is scored from 0(greatest impairment) to 52(no impairment). The ADCS/ADL-Sev version is adapted for nursing home use and in patients with severe impairment (MMSE< 10). This scale is scored form 0 to 78.

4. Global Deterioration Scale (GDS) -a 7-point global status rating scale used to stage patients based on magnitude of impairment based on cognitive and functional capacity. A score of 1-2 is considered normal with dementia severity worsening with increasing score. It may be more sensitive to mild and severe impairment.
5. Clinical Dementia Rating (CDR) - a global status rating used to assign a performance impairment rating based on six cognitive function categories including memory, orientation, judgment, problem solving, community affairs, home and hobbies, and self-care. It distinguishes mild (CDR 1.0), moderate (CDR 2.0) and severe (CDR 3.0) dementia. The term can also be seen described as CDR-SB ("sum of boxes" used to calculate score). The CDR has utility in describing the middle stages of AD. The scale is appropriate for assessing long-term clinical outcomes and has demonstrated validity. Reliability has been demonstrated with the CDR.
6. Sever Impairment Battery (SIB)-This is a 40 item test developed to assess cognitive function in severe dementia. The primary subscale assesses memory, orientation, language, attention, construction and visual-spatial ability. The scores range from 0(total impairment) to 100(no impairment). For untreated patients with a MMSE of 5-9 decline is approximately 3 per month and for untreated patients with a MMSE of 10-15 decline is roughly 2 per month.
7. Clinician's Interview Based Assessment of Change-Plus (CIBIC-Plus) – CIBIC-Plus is a global change rating scale. It is more appropriate for measuring clinical outcomes associated with treatment of 6 months or less duration than a global status rating. The patient and caregiver are interviewed separately. A seven-point scale is used for scoring the clinician's impression of change from baseline at each visit. One (1) represents marked improvement, 2=moderate improvement, 3= mild improvement, 4 = no change, 5=mild worsening, 6=moderate worsening and 7 is marked worsening.
8. Neuropsychiatric Inventory (NPI) - This scale is used to assess 12 aspects of behavior change including delusions, hallucinations, mood, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, anxiety, aberrant motor activity, nighttime behavior, and appetite and eating behavior. It is based on a clinician interview of the caregiver. Scores are derived by multiplying the frequency by the severity for each of the 10 items and range from 10 to 120 with 120 implying most frequent, severe behaviors. There is a nursing home version of the scale (NPI-NH).
9. Progressive Deterioration Scale (PDS) – The PDS was designed to assess functional changes in patients with AD as they progress through different stages of disease. The scale is based on the GDS staging of disease. It is a 29-item scale that the caregiver completes and it assesses orientation, memory, time, finances, hobbies, and performance of tasks, social interactions, and self-care. Scores range from 0 to 100 with mean scores of 48 for mild, 34 for moderate, and 15 for severe impairment. The PDS is validated and reliable in correlating degree of functioning to stage of disease. Extrapolation of results from individual areas has not been validated in terms of assessing change (i.e. change in memory).

Alzheimer's Disease

There is evidence in several randomized controlled trials to support the observation that CI therapies (vs placebo) significantly slow progression of cognitive and functional decline in patients with mild to moderate AD who are living with a caregiver in the community. All treatments exhibited statistically significant advantages compared to placebo in cognitive, global, and staging assessments. The average treatment difference when compared to placebo on the ADAS-Cog for all agents based on Level I evidence was between 2 and 4.1 points. There have been no randomized trials, which demonstrate superiority amongst the agents. A single randomized trial found that donepezil significantly slows cognitive and functional decline in patients with moderate to severe AD who are living with a caregiver in the community. There have been no trials documenting the effects of CI use in nursing home patients with mild to moderate disease. There is some evidence to support associated benefit from long-term use of CI in delaying nursing home placement and extending efficacy, but causality remains unsubstantiated. Behavior changes may also be reduced in association with treatment but the trials assessing behavior have severe limitations of small number of subjects, short duration, and information available primarily in abstract or poster form. Studies use a variety of efficacy measures to assess the progression of Alzheimer's disease, however between the different agents,

ADAS-Cog is the only measurement that is consistently reported as a primary endpoint. **Table 5** reviews the major efficacy trials in AD from both functional and cognitive endpoints.

Lewey Body Dementia and dementia associated with Parkinson's Disease[39-42]

Open-label studies have suggested that cholinesterase inhibitor drugs may exert positive effects upon all aspects of the neuropsychiatric syndrome in Parkinson's Disease (PDD) and Lewey Body Dementia (DLB) but particularly apathy, anxiety, impaired attention, hallucinations, delusions, sleep disturbance, and cognitive test performance. Initial double blind, placebo-controlled studies in PDD and DLB have so far confirmed these encouraging results. Patients with dementia with Lewy bodies who suffer from behavioral disturbance or psychiatric problems may benefit from rivastigmine if they tolerate it, but the evidence is weak.[64]

Vascular Dementia[43, 44]

Between 20 and 35% of all dementias are vascular in origin, their etiology is due to cerebrovascular disease and the risk factors are known (e.g. hypertension, diabetes, smoking, or hyperlipidemia). Primary and secondary preventions are the basis of therapeutics. Symptomatic treatment is emerging, notably in the field of cognitive disorders. In that respect, monoamine oxidase inhibitors, and more recently acetylcholinesterase inhibitors, are in the process of being recognized as first-line treatments of established vascular dementia. There is no standard treatment for VaDs, and still little is known on the primary prevention (brain at risk for CVD) and secondary prevention (CVD brain at risk for VCI/VaD). There is no standard symptomatic treatment for VaD. Recently symptomatic cholinergic treatment has shown promise in AD with VaD, as well as probable VaD.

Meta-analyses & Systematic Reviews

There have been Cochrane Reviews conducted for all three CI.[61, 62, 63] For donepezil 16 trials were included for a total of 4365 patients. These trials encompassed 12,24 and 52 week durations. There was a statistically significant improvement on the ADAS-Cog for both 5 and 10 mg/day doses. Benefits were also demonstrated in ADLs, behavior and global clinical state. For galantamine, seven trials were included with six of these being Phase II or III industry sponsored trials. The trials encompassed 12 weeks to 6 months of duration. Dosages of galantamine showing the best effects were 16-32 mg. In this dosage range, significant changes were seen in ADAS-cog at 3months. Seven trials including 3370 patients were included in the review of rivastigmine. Doses of 6-12 mg were associated with a significant improvement in ADAS-cog and PDS.

These three Cochrane reviews support the use of CIs in dementia due to AD. All three reviews documented significant changes in measures of cognitive function in comparison to placebo.

A meta analysis of CIs was conducted by Lanctot, et al.[65] They reviewed 16 trials meeting their inclusion criteria, for a total of 5159 patients were treated with a CI and 2795 received a placebo. The numbers needed to treat (NNT) for 1 additional patient to benefit were 7 (95% CI 6-9) for stabilization or better, 12 (95% CI 9-16) for minimal improvement or better and 42 (95% CI 26-114) for marked improvement; the number needed to treat for 1 additional patient to experience an adverse event was 12 (95% CI 10-18). The conclusion of the analysis was that treatment with CIs may results in a modest therapeutic effect. However, treatment with a CI correlates with significantly higher rates of adverse events and discontinuation of treatment. The numbers needed to treat to benefit 1 additional patient are small.

Livingston and Katona[66] substantiated the NNT demonstrated in the review by Lanctot. The preceding authors conducted a review of 5 trials with 1415 participants. They concluded that 3-7 patients would need to be treated with appropriate dosages of the CI in order to prevent deterioration in one patient.

Table 5: Efficacy Trials of Cholinesterase Inhibitors

Trial	Type	N	Duration	Mean Baseline MMSE	Treatment	Results and significance (Difference from baseline)	
						ADAS-Cog	CIBIC Plus
Rogers, 1998[A 24]	RDB, MC, PC	473	30 weeks	18.9-19.2	Donepezil 5 and 10 mg	5mg -2.49 p<0.0001 10 mg -2.88 p<0.0001	5mg 0.36 p=0.0047 10 mg 0.44 p<0.0001
Rogers, 1998[B 25]	RDB, MC, PC	468	15 weeks	19.35-19.8	Donepezil 5 and 10 mg	5mg -2.1 p<0.0001 10 mg -2.7 p<0.0001	5mg 0.3 p=0.008 10 mg 0.4 p=0.07
Burns, 1999[26]	RDB, MC, PC, parallel group	818	30 weeks	20	Donepezil 5 and 10 mg	5mg 1.5 p=0.0021 10 mg 2.9 p<0.0001	Scores < 3 at 24 weeks 5mg 21% 10 mg 25% placebo 14%
Greenberg, 2000[27]	RDB, MC, PC, crossover	60	24 weeks	21.8	Donepezil 5 mg	Net improvement 2.17 (CI 0.2-4.10)	
Agid, 1998[28]	RDB, MC, PC	402	15 weeks	NR	Rivastigmine 4 mg and 6 mg after 3 weeks of titration		Used CGIC Higher percentage responders with 6 mg p=0.05
Corey-Bloom, 1998[29]	RDB, MC, PC	699	26 weeks	mild	Rivastigmine 1-4 mg and 6-12 mg	6-12 mg 3.78 p<0.001	6-12 mg -0.29 p<0.010
Forette, 1999[30]	RDB, MC, PC	114	18 weeks	19.5	Rivastigmine mean dose 9.6 mg/day	Non-significant	57% improved p=0.027
Rosler 1999[31]	RDN, MC, PC	725	26 weeks	mild	Rivastigmine 1-4 mg and 6-12 mg	6-12 mg 0.26 p<0.1 ITT	6-12 mg 3.91 p<0.001 ITT
Wilcock, 1997[32]	RCT, PC (Phase II)	253	12 weeks	NR	Galantamine 22.5 mg/day, 30 mg/day and 45 mg/day	30 mg 0.875 p=0.008	
Tariot, 2000[33]	RDB, MC, PC, parallel group	978	5 months	17.7-18.0	Galantamine 8, 16 24 mg	16mg -1.4 p<0.001 24 mg -1.4 p<0.001	Percent improved 16 mg 66% 24 64% p<0.001
Raskind, 2000[34]	RDB, MC, PC, parallel group	636	6 month and 6 month extension	19.1-19.5	Galantamine 32 mg after 3 weeks	-1.4 p<0.001	Higher proportion improved by score P<0.05

Table 5 continued

Trial	Type	N	Duration	Mean Baseline MMSE	Treatment	Results and significance (Difference from baseline) CDR-SB	IDDD
Winblad, 2001[35]	RDB, MC, PC	286	12 months	19	Donepezil 5mg for 28 days then placebo or donepezil 10 mg for 12 months	Used PDS P<0.05	
Feldman, 2001[36]	RDB, MC, PC	290-community or assisted living	24 weeks	12	Donepezil 5 mg for 28 days then 10 mg	Used DAD, IADL+, PSMS+ and FRS P<0.0001, p=0.0015, p=0.0002	
Tariot, 2001[37]	RDB, MC, PC	208, nursing home	24 weeks	14	Donepezil 5 mg for 28 days then 10 mg	P<0.05	
Homma, 2000[38]	RDB, MC, PC	268	24 weeks	17	Donepezil 5 mg	P<0.001	
Burns, 1999[26]	RDB, MC, PC, parallel group	818	30 weeks	20	Donepezil 5 and 10 mg	5mg p=0.034 10 mg p=0.003	10 mg p=0.007
Agid, 1998[28]	RDB, MC, PC	402	15 weeks	NR	Rivastigmine 4 mg and 6 mg after 3 weeks of titration	Used NOSGER-not significant	
Corey-Bloom, 1998[29]	RDB, MC, PC	699	26 weeks	mild	Rivastigmine 1-4 mg and 6-12 mg	GDS 6-12 mg 0.19 p<0.030	
Forette, 1999[30]	RDB, MC, PC	114	18 weeks	19.5	Rivastigmine mean dose 9.6 mg/day	Used NOSGER only significant for memory p=0.037	
Rosler 1999[31]	RDN, MC, PC	725	26 weeks	mild	Rivastigmine 1-4 mg and 6-12 mg	GDS Both doses p<0.05	
Tariot, 2000[33]	RDB, MC, PC, parallel group	978	5 months	17.7-18.0	Galantamine 8, 16 24 mg	ADCS/ADL 16 mg at 5 month p<0.01	
Raskind, 2000[34]	RDB, MC, PC, parallel group	636	6 month and 6 month extension	19.1-19.5	Galantamine 32 mg after 3 weeks	DAD 32 mg at 12 months p<0.001	

Cost Effectiveness Analysis

There are many studies investigating the cost effectiveness of the CIs. Variable outcome measures, study types, duration and costs limit a comparison of results among these studies. From a global perspective CIs have been shown to offer benefit by delaying nursing home placement or by reducing costs of care in the home as well indicating that the use of cholinesterase inhibitors in treatment of Alzheimer's disease may prove cost neutral. **Table 6, 7, 8** describe the literature available for cost effectiveness of the CIs.

Table 6: Cost Effectiveness of donepezil

Authors	Study type	Country	Time horizon	Costs included	Cost difference*	Outcome	Outcome difference
Stewart, 1998[44]	CEA model (Markov)	UK	5 years	Not specified but included direct costs and informal care	£ 841	Expected years with non-severe AD	0.12
Small, 1998[45]	Case control study	US	6 months	Medications, medical expenses, institutionalization	$US -33	Institutionalization	5% vs. 10%
Jonsson, 1999[46]	CEA model (Markov)	Sweden	5 years	Medication, home help, institutionalization	SEK –237K – -277K	Time in non-severe disease state	0.72-0.85
O'Brien, 1999[47]	CEA model (decision analysis and Markov)	Canada	5 years	NH care, community services, medications, unpaid caregiver time	$Can -882	Expected years with non-severe AD	0.20
Neumann, 1999[48]	CUA model (Markov)	US	1 year	Direct medical and non-medical costs, unpaid caregiver time	$US 489	QALYs	0.015
Fillit, 1999[49]	Retrospective review	US	Variable	Medical and medication costs	$US 2.11/day	NR	NR
Hill, 2002[50]	Case control	US	1 year	Cost for medical services and prescription drugs	$US -3,891	NR	NR
Ikeda, 2002[51]	CUA model (Markov)	Japan	2 years	Costs covered by a health insurance (including long-term care)	Mild AD ¥ -38697 Moderate AD ¥ -330809	QALY	Mild AD 0.08 Moderate AD 0.09

*Negative number indicates cost savings due to donepezil use, SEK = Swedish krone, QALY=quality-adjusted life-years

Table 7: Cost effectiveness of rivastigmine

Authors	Study type	Country	Time horizon	Costs included	Cost difference*	Outcome	Outcome difference
Fenn & Gray, 1999[52]	Cost savings model (survival analysis, patient data)	UK	26 weeks	Formal care, medications	£ -29	NR	NR
Hauber, 2000[53]	CEA model (survival analysis, patient data)	US	2 years	Total costs including medications	$US –4,839	NR	NR
Baladi, 2000[54]	Delphi panel	Canada	2 years	Total costs including medications	$Can -1,923	NR	NR
Hauber, 2000[55]	Cost-consequence analysis (survival analysis, patient data)	Canada	2 years	Cost of AD treatment in Canada not including drug cost	$Can –351 - -5,023	Delay in progression to more severe AD	Mild AD 188 days, moderate AD 44 days

*Negative number indicates cost savings due to rivastigmine use

Table 8: Cost effectiveness of galantamine

Authors	Study type	Country	Time horizon	Costs included	Cost difference*	Outcome	Outcome difference
Getsios, 2001[56]	Algorithm to predict need for full-time care	Canada	10 years	Full time care	Mild $Can –788 Moderate $Can –3,718	Duration of full-time care	-10%
Garfield, 2002[57]	Algorithm to predict need for full-time care	Sweden	10 years	Full time care	Mild EUR 3131 Moderate EUR 5,594	Duration of full-time care	-10%
Caro, 2002[58]	Algorithm to predict need for full-time care	Netherlands	10.5 years	Full time care	NLG 3,050 ($US 1,676)	QALYs	0.05

*Negative number indicates cost savings due to galantamine use, QALY=quality-adjusted life-years
CEA = cost-effectiveness analysis (measures costs in relationship to a clinical measures); CUA = cost-utility analysis (compares the cost of treatments on the basis of a weighted and valued outcome)

Safety /Tolerability

Generally the agents are well tolerated with common adverse effects managed by titration and dose adjustments. **Table 9** compares the treatment emergent side effects of the CI. It should be remembered that titration is a key determinant in the development of adverse effects. Lanctot[65] evaluated the NNH (number needed to harm) 1 additional patient with CI treatment. This was defined as 12 (95% CI 10-18).

Additional safety concerns may be found the drug interaction profile of agents. These interactions may be pharmacokinetic, pharmacodynamic or a combination of the two. There have been reports of pharmacokinetic interactions with the CIs , **Table 10** lists several of these interactions.

Table 9: Treatment-emergent adverse events

	Donepezil	Galantamine	Rivastigmine(titration)	Rivastigmine(maintenance)
Headache (%)	10	8	13	17
Insomnia (%)	9	5	9	
Somnolence (%)	2	4	5	
Abnormal dreams (%)	3	9		
Diarrhea (%)	10	9	13	16
Pain (%)	9			9
Nausea (%)	11	24	30	13
Vomiting (%)	5	13	15	4
Depression (%)	3	7	6	
Dizziness (%)	8	9	14	7

Table 10: Cholinesterase Inhibitor drug interactions

Precipitant drug	Object drug *		Description
Donepezil	Anticholinergics	↓	Because of their mechanism of action, CI may interfere
Donepezil	NSAIDS	↑	Donepezil increases gastric acid secretions. Therefore patients may be predisposed to develop active or occult GI bleeding
Donepezil	Furosemide, digoxin, warfarin, theophylline, cimetidine	↔	No significant effects on binding or pharmacokinetic properties of these agents
Ketoconazole, quinidine	Donepezil	↑	Theoretical based on inhibition of CYP3A4 and 2D6. Clinical significance is unknown
Donepezil, galantamine, Rivastigmine	Succinylcholine, bethanecol	↑	Synergistic effect
Cimetidine	Galantamine	↑	Bioavailability of galantamine is increased 16%
Ketoconazole, paroxetine, erythromycin	Galantamine	↑	Galantine area under the curve increased up to 30%

↑ = object drug increased; ↓ = object drug decreased; ↔ = undetermined clinical effect

Conclusion

All of the cholinesterase inhibitors presented in this review appear to mildly enhance or delay deterioration of symptoms associated with Alzheimer's disease. It is difficult to compare the different treatments in terms of efficacy without the utility of head to head trials. The lack of definitions of what constitutes a widely accepted standard of clinically meaningful change on the multitude of AD assessments compounds the difficulty of interpreting the results. In addition, the efficacy measures utilized in the clinical trials may not reflect the methods used to guide therapy in community practice. The comparisons made in this review were based on available published controlled trials for each drug therapy. Well-designed, controlled, comparative trials are needed to accurately examine the efficacy and safety of cholinesterase inhibitors in a similar population of AD patients.

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