Therapy for Alzheimer's disease: how effective are current treatments?

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***Abstract*:** Available symptomatic therapies for the treatment of Alzheimer's disease (AD) have been based on known neurotransmitter dysfunctions associated with the illness. The second-generation cholinesterase inhibitors and the N-methyl D-aspartate receptor antagonist memantine have been widely prescribed and studied. Meta-analyses of these therapies were reviewed, focusing on effectiveness and tolerability. Although many of the meta-analyses demonstrate statistically significant improvements, some question if these benefits are sufficient to justify their current widespread and protracted use. This has spurred the development of new disease-modifying therapies that aim to have a greater impact on this debilitating illness.

***Keywords*:** Alzheimer's disease, cholinesterase inhibitors, meta-analysis, donepezil, galantamine, rivastigmine, memantine, tacrine, beta amyloid, tau protein

Introduction

Alzheimer's disease (AD), the most common cause of dementia [Blennow *et al*. 2006], is characterized clinically by ongoing declines in cognitive and functional ability and the emergence of behavioural and psychological symptoms. With estimated health costs reaching billions of dollars per year and afflicting over 5 million people in North America alone [2008], effective symptomatic and disease-modifying therapies are urgently needed.

The causes of AD have not been fully elucidated and are a focus of current research. Early research, which demonstrated disruptions in the cholinergic [Davies and Maloney, 1976] and glutamatergic [Bleich *et al*. 2003] neurotransmitters, led to currently available symptomatic treatments. Emerging data on risk factors for the development of AD, including the APOE $\varepsilon 4$ allele [Raber *et al*. 2004], cardiovascular risk factors [Cechetto *et al*. 2008] and diabetes [Xu *et al*. 2009] have provided the rationale for other targeted treatments. Recently, more attention has been placed on the role of beta-amyloid and tau proteins since they are recognized as the critical neuropathological findings of the illness. The conversion of the amyloid precursor protein (APP) to the more toxic and highly aggregating $A\beta_{42}$ form [Jarrett *et al*. 1993] is thought to contribute to amyloid plaque formation and ultimately to neuronal death [Hardy and Selkoe, 2002]. A case has also been made for hyperphosphorylation of the tau protein and subsequent neurofibrillary tangles as a cause for neuronal cell death [Anderton *et al*. 2001]. Recent hypotheses recognize the complimentary role of both proteins in the pathogenesis of AD based on animal models demonstrating that amyloid aggregation promotes the hyperphosphorylation of tau protein [King *et al*. 2006; Oddo *et al*. 2003; Gotz *et al*. 2001]. Emerging therapies with proposed disease-modifying effects have targeted these findings.

Presently, the only approved therapies for AD are the cholinesterase inhibitors (ChEIs) and an N-methyl-D-aspartate (NMDA) receptor antagonist. While these agents are being used frequently, and for increasingly long periods of time [Herrmann *et al*. 2007], numerous controversies exist about the clinical significance of their therapeutic effect and thus, their resulting cost-effectiveness [Herrmann and Lanctôt, 2007].

Evidence-based medicine guidelines suggest that the strongest support for interventions is based on meta-analyses of high-quality randomized

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controlled trials (RCTs) [Godloe, 2007]. The purpose of this review was therefore to examine the safety and efficacy of currently available treatments for AD, focussing on meta-analyses of cholinesterase inhibitors and memantine. In addition to this, we will also explore new types of therapies and their potential to become new 'gold standard' treatments.

Methods

We performed a literature search using MEDLINE, Pubmed and the Cochrane Library, specifically searching for tacrine, donepezil, galantamine, rivastigmine or memantine and treatment of AD. Meta-analyses looking at other compounds for the treatment of AD were also examined. We have reviewed all meta-analyses that have been published up to October 2008. We used the national clinical trial registry clinicaltrials.gov as a guide to studies that have recently been completed or are currently recruiting patients.

Cholinesterase inhibitors: efficacy and tolerability

Measurement of outcomes

RCTs for AD have measured cognitive ability, functional ability, behavioural symptoms and overall global function. Cognitive function was a primary outcome variable and predominantly measured using the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) [Rosen *et al*. 1984] with the Mini Mental Status Exam (MMSE) [Folstein *et al*. 1975] as a secondary cognitive outcome. The Clinician's Interview Based Impression of Change (CIBIC) [Schneider *et al*. 1997] was the scale most commonly used to measure global change, while the Alzheimer's Disease Cooperative Studies Activities of Daily Living (ADCS-ADL) [Galasko *et al*. 1997] measured functional ability and the Neuropsychiatric Inventory (NPI) [Cummings *et al*. 1994] measured behavioural and psychological symptoms associated with dementia. Table 1 summarizes the meta-analyses that were reviewed.

Tacrine

The first of the ChEIs approved for AD treatment, tacrine has been replaced as a first-line treatment since the introduction of the second-generation ChEIs. A meta-analysis looking at five studies found that subjects on tacrine had a greater MMSE score compared with placebo after 12 weeks treatment and a significant improvement in global assessment [Qizilbash *et al*. 1998]. Unfortunately this analysis was criticized for ignoring the fact that nonindustry-sponsored studies reported no benefits associated with tacrine treatment [Koepp and Miles, 1999] while another analysis that included five studies comparing tacrine to lecithin and/or placebo found no significant long-term efficacy. Tacrine has been reported to have a high incidence of side-effects [Koepp and Miles, 1999], where a significantly higher proportion of subjects taking the medication discontinued treatment compared to placebo [Qizilbash *et al*. 1998]. In addition, hepatoxicity is a concern [Lagadic-Gossmann *et al*. 1998]. While still available commercially in some countries like the US, tacrine is not available in the UK and is rarely prescribed today, its use supplanted by the better-tolerated 'second-generation' ChEIs [Ringman and Cummings, 2006].

Donepezil

Donepezil, a specific selective reversible inhibitor of acetylcholinesterase, has been widely studied. A pooled analysis of 15 studies of donepezil compared with placebo looked at treatment outcomes including cognitive function, activities of daily living and behavioural symptoms in mild-to-moderate AD subjects [Birks *et al*. 2006]. This Cochrane Database review found that donepezil demonstrated significant improvement in scores of the ADAS-Cog and MMSE at both 5 and 10 mg/day doses and for treatment periods lasting 12, 24 and 52 weeks. There were also some benefits noted in global function and behavioural symptoms. Those authors concluded that both doses of donepezil demonstrated similar efficacy and that the average improvement in cognitive scores was below what would be considered as clinically beneficial ($\geq$4 point on ADAS-Cog [Rockville, 1989]). Other meta-analyses of ChEIs found similar improvements in cognitive outcomes with donepezil treatment [Hansen *et al*. 2008; Takeda *et al*. 2006; Thompson *et al*. 2004]. Hansen *et al*. [2008] pooled data from eight studies (four studies using 5 mg/day, four studies using 10 mg/day for cognitive function). Weighted mean scores favoured donepezil over placebo, although this change in ADAS-Cog score was less than the clinically beneficial threshold. While 5 and 10 mg/day doses were combined in this analysis, heterogeneity was not

Table 1. Meta-analyses of AD treatments.

Meta-analysis	Daily dose	AD severity	Number of studies	Duration	Outcomes				Major findings
					Cognition	Function	Behaviour	Global	
Donepezil									
Hansen *et al.* (2008)	5 mg 10 mg	Mild to moderate	12	3–6 months	ADAS-Cog	ADCS-ADL ADFACS BADLS CMCS DAD IDDD PDS NOSGER-IADL ADCS-ADL PDS	NPI	CIBIC-plus CGI-C	Significant improvement in 4 outcomes. Both 5 and 10 mg data pooled together
Raina *et al.* (2008)	5 mg 10 mg	All severities	5	12–156 weeks	ADAS-Cog MMSE SIB		NPI NPI	CIBIC+	Statistically significant improvement in cognitive and global outcomes.
Birks *et al.* (2006)	5 mg 10 mg	All severities	15	≤ 6 months	ADAS-Cog MMSE SIB	DAD IADL PSMS		CIBIC-plus GBS CDR	Significant improvement in 4 major outcomes. 10 mg dose demonstrated marginally greater efficacy than 5 mg; not as well tolerated as lower dose
Takeda *et al.* (2006)	5 mg 10 mg	Mild to moderately severe mixed dementia	13	12–26 weeks	ADAS-Cog MMSE				Statistically significant improvement in ADAS-Cog scores *versus* placebo. Less drug related adverse events compared to galantamine and rivastigmine
								CIBIC+	Significant improvement cognitively and globally.
Ritchie *et al.* (2004)	5 mg 10 mg	All severities	9	12–52 weeks	ADAS-Cog MMSE			CDR-SB CGI-C GDS	Greater improvement in ADAS-Cog scores with 10 mg/d *versus* 5 mg/d
Rivastigmine									
Hansen *et al.* (2008)	6–12 mg	Mild to moderate	3	3–6 months	ADAS-Cog	PDS NOSGER		CIBIC+	Significant improvement in cognition, functional and global outcomes. Lack of trials.

(Continued)

Table 1. Continued.

Meta-analysis	Daily dose	AD severity	Number of studies	Duration	Outcomes				Major findings
					Cognition	Function	Behaviour	Global	
Raina *et al.* (2008)	1–12 mg	All severities	4	14–52 weeks	ADAS-Cog MMSE			CIBIC+	Statistically significant improvement in ADAS-Cog scores, significant heterogeneity between studies. Significant improvement in global outcomes.
Ritchie *et al.* (2004)	1–4 mg 6–12 mg	All severities	5	10–26 weeks	ADAS-Cog MMSE				Improvement in cognitive scores. 6-12 mg dose more efficacious in cognitive outcomes
Birks *et al.* (2000)	1–4 mg 6–12 mg	Mild to moderately severe	11	12–26 weeks	ADAS-Cog MMSE SIB	PDS		CIBIC+ GDS	Greater improvement in ADAS-Cog scores from baseline with 6-12 mg/d dose compared to placebo. Improvement in global and functional outcomes.
Takeda *et al.* (2006)	1–4 mg 6–12 mg	Mild to moderately severe mixed dementia	4	13–26 weeks	ADAS-Cog MMSE				Statistically significant improvement in ADAS-Cog scores only with 6–12 mg/d
Galantamine									
Hansen *et al.* (2008)	6–24 mg	Mild to moderate	7	3–6 months	ADAS-Cog	ADCS-ADL DAD	NPI	CIBIC+ CGI-C	Significant improvement in all outcomes. Less improvement in behavioural and global outcomes compared to donepezil
Raina *et al.* (2008)	24–36 mg	All severities	4	12–26 weeks	ADAS-Cog			CIBIC+	Statistically significant improvement in all outcomes
Loy and Schneider (2006)	16–32 mg	Mild to moderate AD MCI	11	12 weeks– 2 years	ADAS-Cog	ADCS-ADL DAD	NPI	CIBIC+ CGIC	Greater improvement in ADAS-Cog scores with 6-month treatments *versus* 3 months. Global outcomes: significant improvements only with higher doses at 6-month timepoint.
Takeda *et al.* (2006)	24–32 mg	Mild to moderately severe mixed dementia	6	12–26 weeks	ADAS-Cog MMSE				Statistically significant improvement in ADAS-Cog scores over placebo. Greater improvement observed with higher doses

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Table 1. Continued.

Ritchie *et al.* (2004)	1–4 mg 6–12 mg	All severities	5	10–26 weeks	ADAS-Cog MMSE				Improvement in cognitive scores. 6–12 mg dose more efficacious in cognitive outcomes
Pooled data from donepezil, rivastigmine and galantamine									
Birks *et al.* (2006)	**Dpz**: 10 mg **Gal**: 24 mg **Riv**: 6–12 mg	All severities	13	≥ 6 months	ADAS-Cog MMSE SIB	ADCS-ADL PDS DAD	NPI	CIBIC+ GBS GDS	Significant difference in mean scores of all 4 outcomes for subjects taking ChEIs vs. placebo
Harry and Zakzanis (2005)	**Dpz**: 5–10 mg **Gal**: 8–36 mg	Mild to moderate	Dpz: 3 Gal: 5	Dpz: 12–24 weeks Gal: 12–24 weeks	ADAS-Cog MMSE				Effect sizes for ADAS-Cog scores demonstrate small improvement No advantage of one drug over the other
Rockwood *et al.* (2004)	**Dpz**: 5–10 mg **Gal**: 8–24 mg **Riv**: ≥ 1.5 mg tacrine metrifonate physostigmine	All severities	20	6–24 weeks	ADAS-Cog			CIBIC+	Small-moderate effect sizes for ADAS-Cog and global scores. Dose response exists, highest dose group demonstrates greatest effect size
Lanctôt *et al.* (2003)	**Dpz**: 5–10 mg **Gal**: 8–24 mg **Riv**: 1–12 mg	Mild to moderate	16	12 weeks–6 months	ADAS-Cog MMSE			CIBIC+ CGIC CDR-SB	Significantly greater proportion of global and cognitive responders for ChEIs vs. placebo Number needed to treat (NNT) 12 for global response and 10 for cognitive
Memantine									
Emre *et al.* (2008)	10 mg	Moderate to severe AD	6 (4 monotherapy + 2 in conjunction with ChEIs)	24 weeks	SIB ADAS-Cog	ADCS-ADL	NPI	CIBIC-plus	Benefits in language, memory and praxis.
Gauthier *et al.* (2008)	20 mg	Moderate to severe AD	6	24/28 weeks			NPI		Significant improvement in individual items of NPI after 24/28 weeks: delusions, agitation/aggression and irritability

(Continued)

Table 1. Continued.

Meta-analysis	Daily dose	AD severity	Number of studies	Duration	Outcomes				Major findings
					Cognition	Function	Behaviour	Global	
Raina *et al.* (2008)	20 mg	All severities	5	12–28 weeks	ADAS-Cog MMSE SIB	ADCS-ADL		CIBIC-plus	Statistically significant but clinically marginal improvement in measures of cognition and global assessment of dementia
Wilkinson and Andersen (2007)	20 mg	Moderate to severe	6(4 monotherapy + 2 in conjunction with ChEIs)	24–28 weeks	ADAS-Cog SIB	ADCS-ADL	NPI	CIBIC-plus	Reduced worsening of clinical symptoms in AD during the 6-month study period compared to placebo
Winblad *et al.* (2007)	20 mg	Moderate to severe AD	6(4 monotherapy + 2 in conjunction with ChEIs)	24–28 weeks	ADAS-cog SIB	ADCS-ADL	NPI	CIBIC-plus	Memantine was well tolerated. Overall incidence rates of adverse events were comparable to placebo. Clinically relevant efficacy in patients with moderate to severe AD
McShane *et al.* (2006)	10 –30 mg	All severities + mixed	12	4-28 weeks	ADAS-cog Syndrom-Kurztest SIB	ADCS-ADL Activities of Daily Living Test BGP NOSGER	NPI NOSIE SCAG BGP NOSGER	CIBIC-+ CGIC Physician' global impression CGI SCAG	**Mild to moderate AD**: Marginally beneficial effect at 6 months on cognition. No effect on behaviour or activities of daily living. **Moderate to severe AD**: Beneficial effect at 6 months on cognition, activities of daily living and behaviour
Gauthier *et al.* (2005)	20 mg	Moderate to severe	2	28 weeks			NPI		Beneficial effect on the behavioural symptoms of patients with moderate to severe AD, with the most pronounced effect on agitation/aggression.
Livingston and Katona (2004)	10–20 mg	Moderate to severe	2	12–28 weeks	SIB	ADCS-ADL		CIBIC+	Small number needed to treat (NNT), 6 for global response, 7 for cognitive response and 8 for functional response

ADAS-Cog: Alzheimer's Disease Assessment Scale- Cognitive.
ADCS-ADL: Alzheimer's Disease Cooperative Study activities of daily living.
ADFACS: Alzheimer's Disease Functional Assessment and Change Scale.
BADLS: Bristol Activities of Daily Living Scale.
BGP: Behavioural Rating Scale for Geriatric Patients.
CDR-SB: Clinical Dementia Rating- Sum of Boxes.
CGI: Clinician's Global Impression.
CIBIC+: Clinician Interview-Based Impression of Change.
CMCS: Caregiver-rated Modified Crichton Scale.
DAD: Disability Assessment for Dementia.
GBS: Gottfries, Brane and Steen scale
GDS: Global Deterioration Scale.
IADL: Instrumental Activities of Daily Living.
IDDD: Interview for Deterioration in Daily Living subscale.
MMSE: Mini Mental State Examination.
NOSGER-IADL: Nurses Observation Scale for Geriatric Patients Activities of Daily Living.
NOSIE: Nurses Observation Scale for Inpatient Evaluation.
PDS: Progressive Deterioration Scale.
PSMS: Physical Self Maintenance Scale.
SCAG: Sandoz Clinical Assessment Geriatric Scale.
SIB: Severe Impairment Battery

significant, indicating that there were no significant between study differences in this outcome. With regard to functional outcomes, a modest improvement was observed in eight studies, however it must be noted that the weighted mean difference was calculated using seven different functional scales. Behavioural symptoms (four studies) and global assessment of change (six studies) scores improved, favouring treatment over placebo. Raina *et al.* [2008] included donepezil *versus* placebo studies in all severities of AD ($n = 5$) and other types of dementia as well. This extensive review found a significant mean decrease (−2.80, 95% CI −3.28 to −2.33, $p < 0.001$) in ADAS-Cog scores, but restricted their analysis to the 10 mg/day dose. MMSE scores were also evaluated in 14 studies, but they found no significant changes with treatment. With regard to global assessments, donepezil also displayed a significant improvement in CIBIC-plus scores (−0.45, 95% CI −0.54 to −0.36, $p < 0.001$) and Clinical Dementia Rating – sum of boxes (CDR) (−0.44, 95% CI −0.65 to −0.23, $p < 0.001$) [Raina *et al.* 2008]. Takeda *et al.* [2006] reviewed donepezil studies, primarily evaluating cognitive outcomes, and to a lesser extent quality of life. However, for quality of life, scales that were used had not been validated in a dementia population. Both ADAS-Cog ($n = 6$) and MMSE ($n = 9$) scores decreased significantly from baseline compared with placebo in the majority of studies that this group compiled, but a quantitative meta-analysis was not conducted [Takeda *et al.* 2006]. Tolerability was also evaluated in many of the meta-analyses and donepezil was found to be well-tolerated at both the 5 and 10 mg/day [Pratt *et al.* 2002]. Significantly more subjects taking donepezil discontinued treatment due to an adverse event compared with placebo [Birks, 2006], though one meta-analysis found that this was only significant for the higher dose of donepezil [Ritchie *et al.* 2004].

Rivastigmine

Less frequently prescribed and studied compared to donepezil, rivastigmine is a potent inhibitor for both acetylcholinesterase and butylcholinesterase. Pooled analysis from two studies indicated an improvement in ADAS-Cog scores, for both lower (1–4 mg/day) and higher (6–12 mg/day) doses [Ritchie *et al.* 2004]. Pooled safety data indicated that subjects on the higher doses of rivastigmine were more likely to drop out of the study compared with placebo. A more extensive meta-analysis reviewed 11 RCTs of rivastigmine, dividing the studies into lower (1–4 mg/day) and higher (6–12 mg/day) doses and 12, 18 and 26 week durations [Birks *et al.* 2000]. Improvements in both ADAS-Cog and MMSE scores were noted with both doses, although the 6–12 mg/day dose at 26 weeks had the greatest improvement in scores, compared with placebo. With regard to global assessment, an improvement was noted with higher doses at all time points, whereas the lower doses only exhibited an improvement at 26 weeks. An improvement in activities of daily living was only observed with the higher doses. Subjects were more likely to discontinue the medication due to an adverse event compared with placebo with the higher doses. One meta-analysis compared subjects who were experiencing rapid disease progression to subjects who had a slower cognitive decline. Based on the results of four studies, the rapidly progressing group appeared to have a greater cognitive improvements following treatment with rivastigmine [Farlow *et al.* 2005].

Galantamine

In addition to its ability to inhibit cholinesterase, galantamine can also stimulate nicotinic receptors that release acetylcholine. Trials using galantamine were divided into 3-month and 6-month durations in a meta-analysis by Loy and Schneider [2004]. Statistically significant improvements in cognitive outcomes were observed in doses ranging from 18 to 32 mg/day in 3-month and 6-month trials. The proportion of patients who saw an improvement in ADAS-Cog scores greater than 4 points was significantly greater in one 3-month study and at doses of 16 and 32 mg/day in studies lasting 6 months [Loy and Schneider 2004]. Other meta-analyses have confirmed the benefits of galantamine. Hansen *et al.* [2008] pooled data from seven studies that used doses ranging from 16 to 32 mg/day and determined that subjects had significant improvements in the cognitive domain. Galantamine also demonstrated efficacy in functional ability, global assessment of change and behaviour.

Cholinesterase inhibitors: which one is better?

A meta-analysis performed by our own group found that there was a significant improvement in global and cognitive responses compared with placebo when studies using all three ChEIs in mild-to-moderate AD were combined

[Lanctôt *et al*. 2003] In that meta-analysis, 9% more subjects taking a ChEI had a global response compared with placebo, where response was defined as any improvement ≥minimal improvement on the CIBIS+ or the CGIC and the corresponding number needed to treat (NNT) was 12. Global improvement suggests that effects are clinically significant. For cognitive response, 10% more subjects 'responded' while on treatment compared with placebo, where cognitive response was defined as a ≥4 improvement in ADAS-Cog score, and the NNT for that outcome was 10. There was no significant heterogeneity suggesting ChEIs were similar. A Cochrane Database review of all three ChEIs looked at 13 studies comparing ChEIs with placebo in all three disease severities [Birks 2006]. The major finding was that treatment with donepezil, galantamine and rivastigmine demonstrated improvement in cognition, activities of daily living, behaviour and overall global function for the mild and moderate AD groups, although these improvements were characterized as modest at best. The authors found that there was no difference in efficacy between the three ChEIs, but donepezil was better tolerated than rivastigmine. One meta-analysis by Rockwood *et al*. [2004] took a unique approach to investigating the therapeutic potential of ChEIs by pooling data from six different ChEIs and grouping them based on dosing strength (low, mid and high). Effect sizes were greatest in the high doses of ChEIs ($n = 9$) for both cognitive (ADAS-Cog) and global (CIBIC+) outcomes [Rockwood 2004]. Despite pooling data from different ChEIs, that analysis demonstrates in a more general manner that this group of drugs, irrespective of dose strength, displayed at least 20% improvement in ADAS-Cog and CIBIC+ scores over placebo. Hansen *et al*. [2008] compared efficacy between donepezil, rivastigmine and galantamine by combining data from the small number of head-to-head comparative trials with data calculated by adjusted indirect comparison. That method can be used to calculate the relative benefits of different drugs when trials have a common comparator. The results, which must be interpreted with caution due to the lack of rigorous head-to-head data, suggest no significant differences in efficacy in the cognitive domains, although donepezil was more efficacious than galantamine for the treatment of behavioural symptoms. These behavioural data must be taken with some caution, as only four studies were examined and there was a moderate amount of heterogeneity between these studies [Hansen *et al*. 2008]. The lack of superiority of one ChEI over another in cognitive outcomes was supported by a meta-analysis comparing donepezil and galantamine. Effect sizes of ADAS-Cog score change after treatment was described as small and neither drug had an advantage over the other [Harry and Zakzanis, 2005]. In addition to this, the pooled data favoured both donepezil and rivastigmine over galantamine in global assessment of change. In terms of adverse events reported, donepezil was also found to have the least amount while rivastigmine had the greatest. Limitations, as pointed out by the authors include the pooling of AD severity, although there was a lack of viable studies looking at severe AD and dosing strengths.

In many of the RCTs and open-label trials examining ChEIs, behavioural symptoms are often secondary outcomes. A recent review by Cummings *et al*. [2008] demonstrated a large proportion of these studies have reported improvements in NPI scores with treatment, suggesting the benefit for use of ChEIs for the treatment of behavioural symptoms. The effects of ChEIs on neuropsychiatric symptoms was evaluated in a meta-analysis and the results showed that subjects taking any of the three ChEIs improved in NPI and ADAS-non cognitive scores [Trinh *et al*. 2003]. A major shortcoming of these data was that study subjects generally had little in the way of baseline neuropsychiatric symptoms.

A controversial review by Kaduszkiewicz *et al*. [2005] criticized many of the RCTs and the meta-analyses in this area, citing improper study designs that overstated the benefits observed. 'Shortcomings' included a large proportion of trials using observed cases (OC) instead of intent-to-treat analysis (ITT) and a failure to correct for multiple comparisons. Although the majority of the trials included in this review reported significant improvements over placebo, the author points out that these gains should be considered minimal at best, thus putting into question the recommendation of ChEIs for the treatment of AD. Many groups have since contested the criticisms put forth by that review. The use of ITT analysis using last observation carried forward (LOCF) for study dropouts instead of an OC analysis is not without criticism. Molnar *et al*. [2008] outlined drawbacks associated with ITT analysis in a dementia

population, citing that it assumed that patients would remain 'stabilized' if they continued participation in the study, when it could be possible that they would decline further. The authors concluded that ITT analysis could artificially increase or decrease the therapeutic benefit of a drug based on its tolerability profile. Other drawbacks of the review by Kaduszkiewicz *et al.* have been noted, including the failure to pool the data from included RCTs [Herrmann, 2007] and an improper recommendation for a correction for multiple comparisons. In a response by Birks [2008], the author felt that a correction for multiple comparisons only applied to exploratory *post hoc* analysis, not for predetermined outcomes, which applied to most of the RCTs.

Efficacy of memantine in the treatment of AD

Another target in AD therapy has been the glutamatergic system. Research has indicated that activation of the NMDA receptor by excessive amounts of glutamate, as found in AD, can lead to neuronal cell death [Shah *et al.* 2008]. Memantine hydrocholoride, a noncompetitive NMDA receptor antagonist, prevents excitatory activity and has been shown to have a neuroprotective role by preserving and restoring long-term potentiation (LTP) *in vivo* [Frankiewicz and Parsons 1999; Zajaczkowski *et al.* 1997]. It has also been suggested that memantine can influence tau, by decreasing levels of phosphorylated tau protein in CSF [Li *et al.* 2004], but a correlation between decreased levels of phosphorylated tau and an improvement in cognitive scores was not observed [Degerman Gunnarsson *et al.* 2007]. To date, it remains one of the few medications approved for treatment in moderate-to-severe AD in North America and Europe. Pooled analysis by Emre *et al.* [2008] found there was a significant improvement in cognitive domains, specifically memory, language and praxis compared with placebo with 24 weeks of treatment in a total of six studies. In addition to this, a greater percentage of subjects taking memantine had less cognitive decline compared with placebo. Another meta-analysis of six studies examined clinical worsening, defined as a drop in either cognitive, global assessment or functional ratings. The proportion of patients experiencing either any 'clinical worsening' or 'marked clinical worsening' was significantly lower in patients taking memantine *versus* placebo [Wilkinson and Anderson, 2007]. While it is unclear what the magnitude of change was and which domains are actually improving, those results suggest that changes are clinically relevant. A second meta-analysis of six phase III clinical trials of moderate-to-severe AD subjects evaluated cognitive, global, functional and behavioural domains. Pooled analysis showed significant improvement in all four domains and the effect sizes were described as similar in magnitude to the ChEIs for cognitive outcomes [Winblad *et al.* 2007]. A Cochrane Database meta-analysis included studies looking at both mild to moderate AD and moderate to severe AD, as well as studies using subjects with either vascular dementia or mixed dementia. The most benefit was observed in the moderate-to-severe AD cohort, as it was determined that subjects taking memantine saw a significant improvement in the four major outcomes compared with placebo, while subjects with mild-to-moderate AD improved significantly only in the cognitive and global assessment outcomes [McShane *et al.* 2006]. The authors concluded that memantine demonstrated the most efficacy in the moderate-to-severe subject cohort, although there is some cognitive benefit in the mild-to-moderate AD group. This is consistent with the Raina *et al.* [2008] meta-analysis of six studies in all three severities of AD, which found memantine demonstrated efficacy only in global and cognitive domains, but the improvement in scores should not be considered clinically significant. A low NNT was found for cognitive, global and functional response in an NNT analysis of memantine; however, only two studies were examined [Livingston and Katona 2004]. For behavioural outcomes, a meta-analysis evaluated pooled data from two studies, one with monotherapy and the other in combination with donepezil, and found a significant improvement in NPI agitation/aggression scores from baseline, compared with placebo [Gauthier *et al.* 2005]. A more recent meta-analysis using six studies at 12 and 24–28 week treatment periods focused exclusively on the treatment of behavioural symptoms in a moderate-to-severe AD population. A significant improvement in NPI total was observed for both time points using OC and LOCF. When looking at individual items of the NPI, delusions and agitation/aggression improved significantly at 12 and 24–28 weeks, while irritability improved only at 24–28 weeks [Gauthier *et al.* 2008]. That analysis also examined symptom emergence in patients who had not reported behavioural symptoms at baseline. Significantly more subjects taking memantine remained asymptomatic for specific behaviours including agitation/aggression,

delusions and irritability, compared to placebo [Gauthier *et al.* 2008]. These findings were confirmed in another meta-analysis by Wilcock *et al.* [2008], who examined agitation/aggression and psychosis in moderately severe and severe AD subjects. The three 6-month studies that were included in the analysis demonstrated that behaviourally disturbed patients taking memantine (a score >0 on NPI subscales agitation/aggression, hallucination or delusions) improved significantly in this NPI cluster score at 12 and 24–28 weeks, compared with placebo [Wilcock *et al.* 2008].

Data regarding adverse events have indicated that memantine is well tolerated, as there have been no significant differences between reported adverse events (AEs) between the treatment and placebo groups [Wilcock *et al.* 2008; Winblad *et al.* 2007; Areosa *et al.* 2003]. In summary, studies to date demonstrate a modest improvement in cognitive impairment in moderate-to-severe AD in addition to benefits on global assessment, functional ability and behavioural symptoms with excellent tolerability. It is unclear whether some of these improvements are clinically relevant.

Statistical significance *versus* clinical significance

A general issue that has arisen in many of the meta-analyses reviewed is the importance of clearly understanding the differences between statistical significance and clinical significance. The ChEIs and memantine have demonstrated statistically significant improvements in outcomes including cognitive and behaviour when compared with placebo, but how do these improvements translate in a clinical setting? A recent review by Hogan [2007] cautioned that many of the reported results from RCTs may be statistically significant but researchers must go a step further to prove that these benefits are clinically relevant. In order to avoid this exaggeration of results, methods including the reporting of effect sizes, NNT, or setting a minimum change in score in order to be labelled a 'responder' should be considered [Hogan, 2007].

Other therapies

Besides the ChEIs and memantine, meta-analyses have been conducted looking at other forms of AD treatments. A Cochrane Database review looking at the benefits of huperzine A, a plant-derived ChEI found that there were improvements in MMSE with this compound alone or in conjunction with vitamin E, compared with placebo [Li *et al.* 2008]. Improvements in other outcomes were also observed, but further studies will need to be conducted in order to confirm this, as many of the trials were excluded from their final analysis due to questionable quality of data. Pooled data from RCTs investigating the effects of hydergine have demonstrated efficacy in global assessment, but many of the outcomes used were not standard scales like the CGI-C or the ADAS-Cog [Olin *et al.* 2001]. Meta-analyses have also been done on metrifonate [Lopez-Arrieta and Schneider, 2006], vitamin E [Isaac *et al.* 2008] and ginkgo biloba [Kurz and Van Baelen, 2004].

Future directions

What's old is new again

Because it may be many years before new interventions are approved, further clinical trials are being conducted with the available therapies in an attempt to clarify their spectrum of activity. Trials of donepezil hydrocholoride now underway are evaluating long-term efficacy across the spectrum of AD severities. Other trials include comparative designs with memantine or galantamine. Recently completed or currently recruiting studies with galantamine have looked at the efficacy over 2 years, and evaluation of an extended release formulation. With rivastigmine, efficacy studies are now focusing on the transdermal patch for delivery of the drug. A recent study comparing variable doses of the transdermal patch with the capsule found that the patch had the similar efficacy with significantly less adverse events [Mercier *et al.* 2007; Winblad *et al.* 2007]. Current studies of memantine are looking at comparative/adjunct therapy with vitamin E, off-label uses and switching from drugs with poorer tolerability profiles.

Therapies targeting amyloid plaque formation

The conversion pathway of the precursor protein APP to the more toxic, highly aggregating Aβ_{42} is a target being evaluated for future AD therapies. Past studies have linked plaque deposition to AD [Wilcock and Esiri, 1982; Blessed *et al.* 1968], although plaques have also been detected in healthy, nondemented controls [Henriksen *et al.* 2008; Knopman *et al.* 2003] and beta-amyloid as a predictor for AD has been challenged [Hansson *et al.* 2009]. High levels of Aβ_{42} in the plasma has

been linked with an increased risk of developing AD and plasma and CSF Aβ_{42} concentrations have been shown to decrease with conversion from mild cognitive impairment to AD [Schupf *et al.* 2008].

APP is cleaved by either α or β then γ secretase, the latter two forming major products Aβ_{40} and Aβ_{42} [Blennow *et al.* 2006]. New therapies under development seek to disrupt this process through the inhibition of either isoform of secretase and, to date, both *in vitro* [Rajendran *et al.* 2008] and *in vivo* [Wong *et al.* 2004] studies have demonstrated promising results. Activation of α-secretase was shown to decrease levels of Aβ_{40} and Aβ_{42} *in vivo* [Etcheberrigaray *et al.* 2004]. Recently, testing on human subjects has begun, evaluating the tolerability and efficacy of a γ-secretase inhibitor LY450139. The medication was well-tolerated in a phase II safety trial with no significant changes in Aβ_{40} and Aβ_{42} CSF levels or significant improvements in cognitive or functional outcomes observed at 14 weeks of treatment [Fleisher *et al.* 2008]. Immunization against β-amyloid protein is another treatment that may prove beneficial. A number of studies using transgenic mouse models that overexpressed mutant human APP found that immunization against Aβ_{42} led to a decrease in amyloid plaque formation [Bacskai *et al.* 2002; Bard *et al.* 2000; Schenk *et al.* 1999] and protected neuronal synapses [Buttini *et al.* 2005]. Initial trials looking at immunization against β-amyloid in humans evaluated efficacy and tolerability using variable doses in 20 patients with AD [Bayer *et al.* 2005]. Due to the emergence of meningioencephalitis in 18/300 or 6% of patients, that study was ended prematurely [Gilman *et al.* 2005]. A number of newer studies using antibodies directed against β-amyloid are in various phases and are currently recruiting patients.

Commonly prescribed for insulin resistance in the treatment of diabetes mellitus, the thiazolidinediones are peroxisomal proliferator-activated receptor-gamma (PPAR-γ) agonists and have been evaluated in preliminary trials for the treatment of AD. Considered a risk factor for the eventual development of dementia [Ott *et al.* 1999], a strong association has been found between diabetes and AD pathology [Miklossy *et al.* 2008], as a recent study demonstrated that delivery of insulin intranasally led to both cognitive improvement in APOE4 ε4- subjects and increased plasma levels of Aβ_{42} [Reger *et al.* 2008]. Studies have shown the efficacy of both pioglitazone [Nicolakakis *et al.* 2008; Heneka *et al.* 2005] and rosiglitazone [Pedersen *et al.* 2006] in mouse models of AD. One small scale RCT ($n = 30$) evaluating treatment with rosiglitazone for 6 months found a significant improvement in some aspects of memory, but standard cognitive tests like the ADAS-Cog were not utilized in this study [Watson *et al.* 2005]. A larger scale, 24-week treatment RCT ($n = 511$) found no significant difference between rosiglitazone and placebo. When patients were stratified based on the APOE4 status, ε4 negative subjects demonstrated a significant improvement in ADAS-Cog scores with the highest tested dose of drug, compared with ε4 subjects, although a correction for multiple testing was not done and it is likely that the significance would subsequently be lost [Risner *et al.* 2006]. Nonetheless, further RCTs have since been conducted, although controversies surrounding the potential cardiac risk of rosiglitazone have recently arisen and may negatively impact its viability as a potential AD treatment [Selvin *et al.* 2008].

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, or 'statins', typically used in lowering cholesterol, have also been tested as potential treatments for AD based on prospective studies that found an association between statin use and a decreased risk of developing AD [Haag *et al.* 2009]. Subsequent RCTs evaluating efficacy of various statins have found no decrease in CSF levels of Aβ_{42} [Carlsson *et al.* 2008; Riekse *et al.* 2006; Hoglund *et al.* 2005; Simons *et al.* 2002] and no significant improvement in ADAS-Cog scores at the 1-year-study endpoint [Sparks *et al.* 2008]. There are two clinical trials currently recruiting subjects looking at pitavastatin and simvastatin and a number of studies on simvastatin and atorvastatin that have recently been completed.

Finally, one phase II RCT ($n = 58$) looked at the efficacy of 3-amino-1-propanesulfonic acid (3APS), a compound that selectively binds to soluble forms of Aβ_{40} and Aβ_{42}, in mild-to-moderate AD for a 3-month period [Aisen *et al.* 2006]. Although a dose dependent decrease was observed in Aβ_{42} levels following treatment, there were no significant improvements in either cognitive or global outcomes. Further tests in a larger sample size and over a longer treatment period are ongoing.

Therapies targeting tau protein

The phosphorylation of tau protein in frontal cortex regions of the brain has been observed in AD patients in various stages of the disease [Muntane *et al*. 2008] and is believed to lead to the neurofibrillary tangles that eventually lead to neuronal cell death [Alonso *et al*. 2001; Alonso *et al*. 1994]. One main target in the tau phosphorylation pathway is glycogen synthase kinase-3b (GSK-3b), a kinase that has been associated with an increased risk of AD [Schaffer *et al*. 2008]. This kinase has previously been shown to be upregulated in the frontal cortex of AD brains [Leroy *et al*. 2007]. Treatment with a GSK-3b inhibitor in a rat model was found to decrease levels of phosphorylated tau [Selenica *et al*. 2007]. *In vivo* studies have previously shown that lithium could decrease the expression of GSK-3b in specific brain regions [Mendes *et al*. 2008] and both lithium and sodium valproate had the ability to inhibit GSK-3b and decrease phosphorylated tau [De Sarno *et al*. 2002]. Lithium's ability to decrease Aβ levels can best be described as contradictory, where some studies have demonstrated an association [Su *et al*. 2004; Phiel *et al*. 2003], and other groups have found no significant association [Caccamo *et al*. 2007]. In a recent case-control study, bipolar geriatric subjects taking lithium had a decreased risk of developing AD over a 6-year period compared with an age-matched group not taking lithium [Nunes *et al*. 2007]. Further clinical trials in larger populations are warranted in order to confirm these results. Besides targeting GSK-3b in the tau phosphorylation pathway, immunization against tau protein has been investigated in an animal model; however, results demonstrated that tauopathies were induced in mice vaccinated against neuronal tau [Rosenmann *et al*. 2006].

Other potential therapies

Other drugs that may or may not act through the amyloid or tau pathways (outlined in Figure 1)

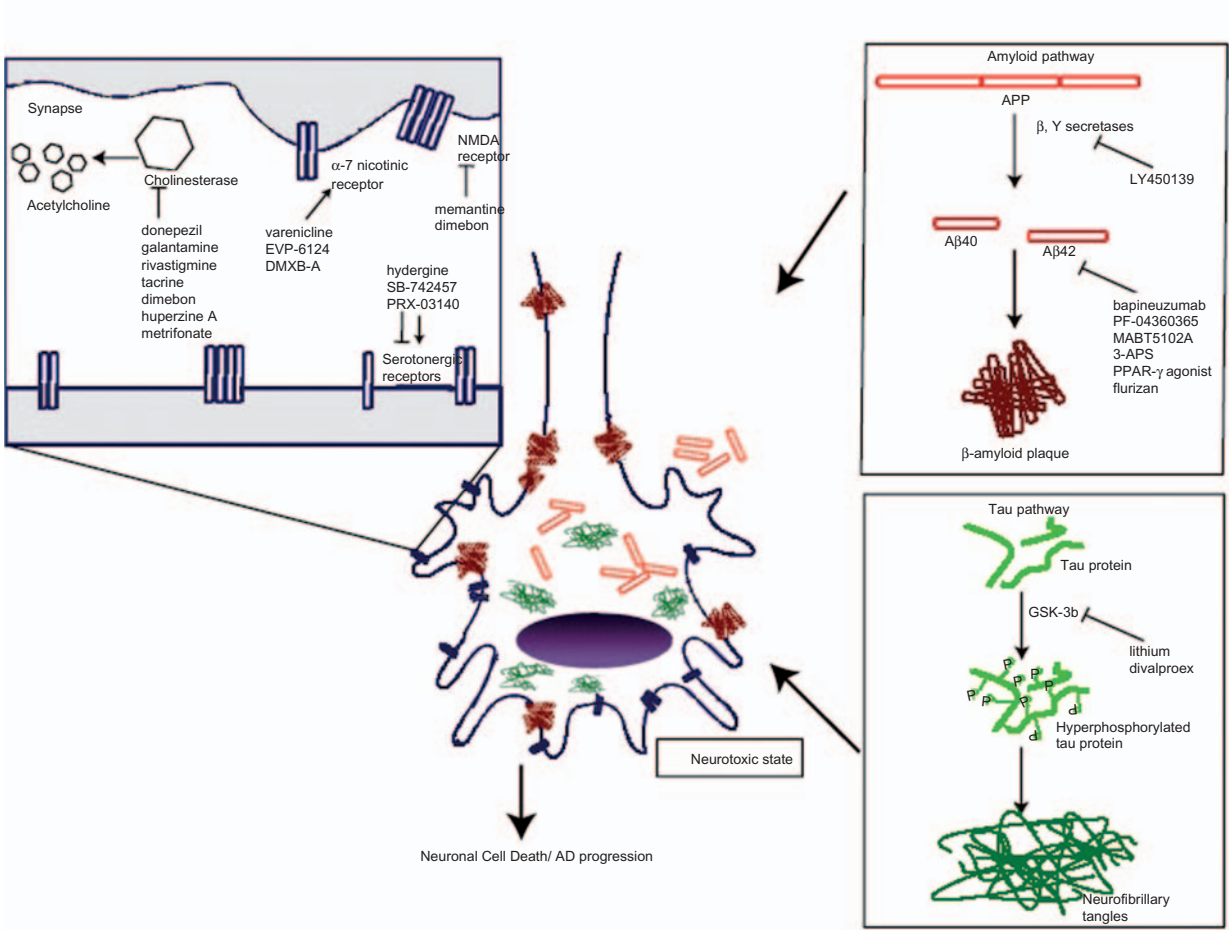

Figure 1. Targets of Alzheimer's disease (AD) therapies. APP, amyloid precursor protein; 3-APS, 3-amino-1-propanesulfonic acid; GSK-3b, glycogen synthase kinase 3b; NMDA: N-methyl-D aspartate; PPAR-γ agonist, peroxisomal proliferator-activated receptor-gamma.

are being studied for their potential to be used in AD therapy and are outlined in Table 2. One such drug is the H1 antagonist dimebon [Doody *et al.* 2008]. Once used as an antihistamine, it is believed that this drug has multiple mechanisms of action that may improve symptoms associated with AD [Burns *et al.* 2008].

Conclusions

The meta-analyses of current AD treatments, including the ChEIs and memantine, have examined numerous trials that included thousands of AD patients. While the results of these analyses consistently show efficacy with statistical significance, conclusions about their clinical significance differs between clinicians. Some believe that ChEIs have demonstrated important improvements for most outcomes including cognition, global assessment, behaviour and function. Even these proponents agree that a limitation of many of these studies is that the treatment period (usually 6 months) is too short, and studies looking at the long-term effects of ChEIs are needed. Others believe that much of the reported data are flawed based on methodological limitations of the pivotal studies, and the improvements documented cannot be considered clinically significant. Adding to these controversies are the results and interpretation of cost-benefit analyses. For example, a cost–benefit analysis led to the recommendation that ChEIs should not be used in the treatment of mild AD by the National Institute for Health and Clinical Excellence (NICE) in England, citing that the benefits gained did not justify the cost of the medication. As of May 2008, this decision was overturned by the appeal court [Dyer, 2008] and ChEI use in mild AD patients continues, for now.

A review of new drugs has shown an exciting array of possibilities with the potential for disease-modifying therapies. Unfortunately, it will likely be many years before any of these therapies are deemed efficacious and approved.

Table 2. New AD therapies under development.

Intervention	Proposed mechanism of action	Sponsor	Phase of study
Therapies targeting β-amyloid			
Antibody targeting amyloid plaque/ vaccine	Monoclonal antibody targeting A-beta 42, disruption of amyloid plaque		
bapineuzumab		Elan/Wyeth	III
PF-04360365		Pfizer	II
MABT5102A		Genentech	I
tarenflurbil	Selective $A\beta_{42}$ lowering agent	Myriad Pharmaceuticals	III
γ-secretase inhibitor LY450139	Inhibition of γ-secretase. Block conversion of APP to $A\beta_{42}$	Eli Lilly	III
PAZ-417	Plasminogen activator	Wyeth	I
3-APS (homotaurine)	Selective binding to soluble $A\beta_{42}$ and $A\beta_{40}$	Bellus Health Inc.	III
HMG CoA reductase inhibitors	Reduction of $A\beta_{42}$ levels	National institute on Aging (NIA)	II
PPAR-γ agonist	Reduction of A-beta plaque formation and $A\beta_{42}$ brain levels in-vivo	GlaxoSmithKline	III
Therapies targeting the tau pathway			
lithium and divalproex	GSK-3b	National Institute of Neurological Disorders and Stroke (NINDS)	II
Other therapies			
α-7 nicotinic receptor partial agonist	↑acetylcholine, neuroprotective		
varenicline		Pfizer	I
EVP-6124		EnVivo Pharmaceuticals	I
DMXB-A		CoMentis	II
PRX-03140	5-HT4 agonist, ↑acetylcholine, ↑ soluble APP	Epix	II
dimebon	Cholinesterase inhibition, NMDA receptor antagonist	Medivation	II
T-817MA	Neurotrophin	Toyama	II
ZT-1 (Huperzine A)	Cholinesterase inhibition	Debiopharm	II
SB-742457	5HT6 receptor antagonist	GlaxoSmithKline	II

Until then, new strategies using currently available treatments will need to be devised in order to optimize treatment response in this growing population.

Conflict of interest statement

Dr Nathan Herrmann has received research support and/or speaker's honoraria from Lundbeck Canada Inc., Pfizer Canada Inc., Janssen Ortho, Neurochem, Novartis and Eli Lilly. Dr. Krista Lanctôt has received research support and/or speaker's honoraria from Abbott Laboratories, Lundbeck Canada Inc., Neurochem, Pfizer Canada Inc., Janssen Ortho, Eli Lilly and Wyeth. Ryan Rajaram has no financial disclosures to make.

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