

Establishing the comparative efficacy of Alzheimer's disease therapy through systematic review and comparative analysis

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Introduction

Alzheimer's disease (AD) is an incurable, progressive and fatal neurodegenerative disorder causing cognitive deterioration [1]. For therapeutic augmentation of impaired cholinergic transmission in AD, acetylcholine-esterase-inhibitors (AChEIs: galantamine, donepezil and rivastigmine) are approved therapies in mild to moderate AD. An alternative is memantine, a N-methyl-D-aspartate receptor partial antagonist; memantine is licensed for moderate to severe AD and may prevent excitatory neurotoxicity in dementia [2]. In order to inform the clinical decision-making about efficacy, safety and broader non-cognitive outcomes, we identified the evidence from comparative and non-comparative studies.

Methods

A comprehensive search aimed to identify the relevant studies was conducted in MEDLINE, EMBASE and Cochrane Central Trials Register (till 10 March 2010). Relevant conference proceedings were hand searched from 2007 to 2010. Clinical study reports from Janssen-Cilag and bibliographic searching of systematic reviews in this disease area also provided relevant data for the review. The inclusion criteria were:

- **Study design:** Randomised controlled trials with any blinding status
- **Patient population:** Adult (≥ 18 years) diagnosed with AD
- **Interventions:** Galantamine, donepezil, rivastigmine and memantine
- **Control:** Other included intervention, placebo or BSC (no treatment/observation alone)
- **Study duration:** A minimum of 12 weeks duration of randomised phase
- **Licensed dose and disease severity:** Studies assessing intervention within their licensed indication with respect to severity of AD and dose

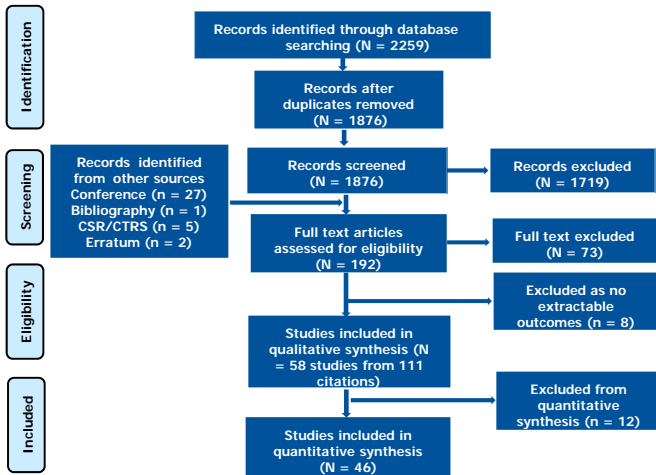
Eligibility of trials was assessed by two blinded reviewers with discrepancies resolved by a third independent reviewer. Quality of the included studies was assessed using the CONSORT checklist. Data from the use of interventions within their licensed severity were extracted. Data from direct evidence were meta-analysed using the metan function in Stata® using the Mantel-Haenszel and DerSimonian-Laird methods for effect-size estimation, through fixed and random effects model respectively. Standardised mean differences (SMD) were used for combining trials where different scales to measure cognitive outcome (ADAS-cog, MMSE, and SIB) and behavioural outcomes (NPI-10 and NPI-12) were used. Random effects meta-analyses results have been presented here.

Results

Search results

- Our search provided 2259 citations for initial screening that resulted in selection of 58 potentially relevant studies for data extraction (Figure 1).
- After assessing the clinical and methodological heterogeneity, 33 studies were included in quantitative efficacy analyses. In total 46 studies contributed to at least one efficacy, safety or tolerability analysis.
- In several publications the data were presented graphically/qualitatively only and some studies did not report the measures of variance around the point estimate. Thus, limiting the evidence which could contribute to the quantitative analyses.

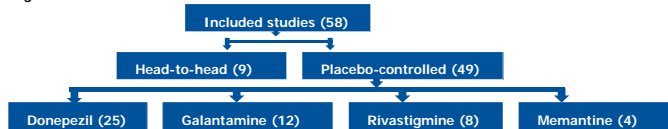
Figure 1: Trial flow



Overview of evidence base

- An overview of the available evidence base is presented in Figure 2. Almost all placebo controlled studies (46 studies) were double-blind. However open-label design was used in six head-to-head trials. The typical duration for randomised controlled phase was 12-30 weeks. Nine studies assessed the long term treatment outcomes, up to 24 months.
- Based on CONSORT check-list; the quality of overall reporting was good. The introduction sections were reported adequately, however, major short-comings were observed in reporting of the methodology sections with respect to the description of randomisation and blinding.
- In one trial comparing memantine and placebo, the study participants were receiving donepezil prior to and throughout the study duration. Hence, meta-analysis for memantine vs. placebo was run with and without the results of this trial.

Figure 2: Overview of included trials



Efficacy results: Cognitive outcomes

- Meta-analysis of 5, 7, and 4 trials respectively for donepezil (Figure 3), galantamine (Figure 4) and oral rivastigmine (Figure 5) for cognitive outcomes showed superiority of the AChEIs over placebo at 6 months. Results for memantine indicated non-significant improvement (Table 1).
- Cognitive function measured as 'an improvement of 4 points or more in ADAS-cog' also showed a significant improvement with AChEIs compared to placebo (Table 1).

Figure 3: Forest plot for change in ADAS-cog or MMSE or SIB at 6 months: Donepezil vs. placebo

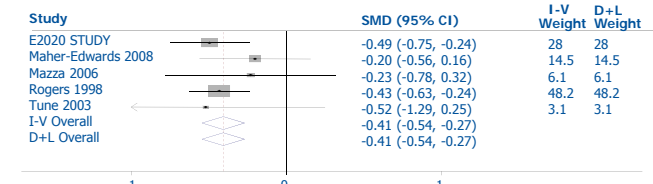


Figure 4: Forest plot for change in ADAS-cog or MMSE or SIB at 6 months: Galantamine vs. placebo

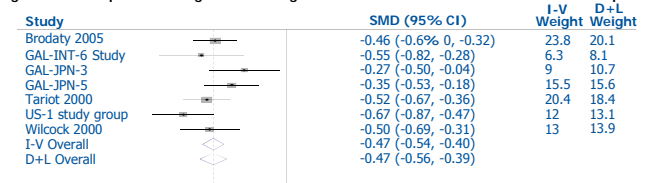


Figure 5: Forest plot for change in ADAS-cog or MMSE or SIB at 6 months: Rivastigmine vs. placebo

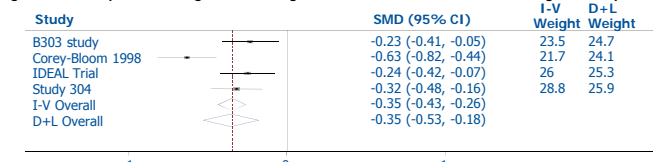


Table 1: Meta-analysis results for cognitive outcomes

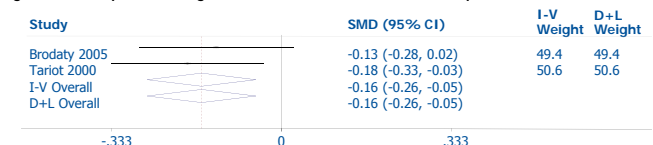
Outcome	Treatment	Control	Studies	N	Effect size*(95% CI)
ADAS-cog or MMSE or SIB change at 6 m	RIV (patch)	PBO	1	529	-0.24 (-0.41 to -0.07)
	MEM + DON	PBO + DON	1	394	-0.36 (-0.55 to -0.16)
	MEM	PBO	2	583	-0.14 (-0.35 to 0.07)
	GAL	DON	1	156	-0.52 (-0.84 to -0.2)
ADAS-cog improved: 4 points or more at 6 m	DON	PBO	3	717	1.64 (1.11 to 2.4)
	GAL	PBO	6	2961	1.64 (1.4 to 1.91)
	RIV (oral)	PBO	2	1016	1.43 (1.13 to 1.81)
	RIV (patch)	PBO	1	529	1.38 (1.01 to 1.88)

DON = Donepezil; GAL = Galantamine; RIV = Rivastigmine; MEM = Memantine; PBO = Placebo; CI = Confidence interval; *Effect sizes are SMD for ADAS-cog or MMSE or SIB change outcomes and relative risks for ADAS-cog 4 points improvement; Highlighted cells represent statistically significant (p < 0.05) results

Efficacy results: Behavioural outcomes

- Behavioural outcomes were assessed less frequently across the included studies. An improvement in behavioural symptoms was indicated with galantamine compared to placebo (Figure 6). Memantine + donepezil showed a significantly higher improvement behavioural symptoms compared to placebo + donepezil (SMD -0.28; 95% CI: -0.48, -0.08).
- Donepezil showed no significant difference compared to placebo in improving behavioural symptoms measured using NPI at 6 months (SMD 0.17; 95% CI: -0.59, 0.93).
- Only one trial including rivastigmine (patch and oral formulation) assessed behavioural outcomes. This trial showed no evidence of any benefit with rivastigmine oral (SMD -0.04; 95% CI: -0.21, 0.13) or patch (SMD 0; 95% CI: -0.17, 0.17) compared to placebo.

Figure 6: Forest plot for change in NPI at 6 months: Galantamine vs. placebo



Safety and tolerability outcomes

- Gastrointestinal AEs were commonly reported with AChE-Is: reported frequency of nausea, vomiting or diarrhoea is around 10-20%. The typical treatment discontinuation rate was around 20% in 3-6 months trials and was mainly attributed to adverse events.

Conclusions

- There is abundant evidence for the efficacy, safety and tolerability of AChEIs in the treatment of patients with mild to moderate AD. AChEIs were beneficial in improving cognitive symptoms among patients with mild to moderate AD. Memantine showed less deterioration in cognitive function compared to placebo.
- Data for improved behavioural functioning are limited: there is some evidence of advantage for galantamine and for the addition of memantine to donepezil.

References

1. Alzheimer's Disease International (2009) World Alzheimer Report <http://www.alz.co.uk/research/worldreport>
2. Jones R, Sheehan B, Phillips P, Juszczak E, Adams J, Baldwin A et al. (2009). DOMINO-AD protocol: donepezil and memantine in moderate to severe Alzheimer's disease - a multicentre RCT. *Trials*. 10:57, 1-11.