

Effects of Cholinesterase Inhibitors in Cognition on Parkinson's Disease Dementia: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Dementia is frequently associated with Parkinson's disease, especially in later stages. Efficacy of cholinesterase inhibitors (ChI) in Alzheimer's dementia is well established. However, treatment with ChI in Parkinson's disease dementia (PDD) remains controversial. The objective of this systematic review and meta-analysis was to assess the effects of ChI in PDD. **Methods:** A comprehensive literature search was performed in MEDLINE, EMBASE and Cochrane library up to March 2014 using the descriptors "*Parkinson's disease*", "*dementia in Parkinson's disease*", "*cognition*", "*acetylcholinesterase inhibitors*", "*cholinesterase inhibitors*", "*anticholinesterase agents*", "*rivastigmine*", "*donepezil*" and "*galantamine*" (Pubmed search strategy). All randomized, double-blinded, placebo-controlled trials that met the eligibility criteria and assessed the effects of ChI in PDD were considered for analysis. There were no restrictions regarding paper language. Summary effect-sizes were presented as standardized mean differences (SMD) and the pooled analysis was performed with a fixed-effects model. Outcomes considered for analysis were the Mini Mental Status Exam (MMSE) score and the cognition scale for evaluation of dementia ADAS-Cog. The degree of heterogeneity between included studies was assessed through the I^2 test. **Results:** After a comprehensive search, 175 references were retrieved. From these, five randomized trials involving 946 PDD subjects were included in the review. Four studies used donepezil and only one study used rivastigmine. The pooled analysis of five studies that assessed the effects of ChI in MMSE total score showed a SMD of 0.24 (CI 95% 0.11 - 0.38). Three studies considered the effects of ChI on Adas-Cog and the pooled results showed a SMD of 0.21 (CI 95% 0.07 - 0.35). There was no significant heterogeneity between the studies. **Conclusions:** The results of this systematic review and meta-analysis suggest that ChI improves cognitive impairment in PDD subjects. Despite statistically significant, the translation of these results into relevant clinical improvement should be taken with caution, as the studies did not address what would be considered a clinically significant result.

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Keywords

Parkinson's Disease, Dementia, Cognitive Impairment, Cholinesterase Inhibitors, Cognition, Non-Motor Symptoms

1. Introduction

Dementia is a very frequent non-motor symptom associated with Parkinson's disease (PDD) and the reported prevalence varies widely ranging from 40% to 80% [1] [2]. Some characteristics were identified as risk factors for the development of dementia in the course of Parkinson's disease (PD) such as severity of motor symptoms, older age, predominant akinetic type, axial impairment and presence of psychosis [1] [3] [4].

Attentional deficits with impaired working memory and visuospatial dysfunctions can be identified in initial clinical phases [5]-[7]. However, the criteria to define a clinical diagnosis of PDD must include the diagnosis of PD according to the United Kingdom Brain Bank criteria and insidious cognition impairment associated with behavioral features, characterized by the presence of attentional deficits, memory and executive function disturbances, visuospatial dysfunction, apathy, humor and personality changes, hallucinations, delirium and excessive daytime sleepiness [8]. Cognitive deterioration is related to advanced phases of PD [3], leading to decreased quality of life in patients and increased caregivers burden [9] [10].

The pathological mechanisms involved in PDD are still not fully understood; however, numerous Lewy bodies can be detected in areas outside the substantianigra, with associated amyloid plaques and neurofibrillary tangles in some cases [11]. The clinical features of PDD suggest impairment of the mesocorticolymbic pathway and cholinergic projections to cerebral cortex originated from the basal nucleus of Meynert [12]-[14]. According to previous published data, the effect of cholinesterase inhibitors (ChI) on cognition in mild to moderate PDD is the modest [14], and side effects on Parkinsonian symptoms such as rising tremor must be considered [15].

Although treatment with ChI in Alzheimer's dementia with significant improvement on cognitive functions is well established, few randomized, double-blind, placebo-controlled trials have assessed the effects of ChI in PDD, with controversial results. The objective of this systematic review and meta-analysis was to assess the effects of ChI in the treatment of PDD.

2. Methods

2.1. Literature Search

In accordance to PRISMA guidelines, a comprehensive literature search was performed up to march 2014 in order to identify all randomized, double-blind, placebo-controlled trials that assessed the efficacy of ChI in PDD, without language restrictions. The electronic databases Medline, EMBASE and the Cochrane library for controlled trials were systematically searched including the descriptors "Parkinson's disease", "dementia in Parkinson's disease", "cognition", "acetylcholinesterase inhibitors", "cholinesterase inhibitors", "anticholinesterase agents", "rivastigmine", "donepezil" and "galantamine" with the Boolean operators AND, OR and NOT (Medline search procedures). Other sources of information included the reference list of included trials, identification of ongoing trials in the website www.clinicaltrials.gov and personal contact with worldwide researchers in the field that could provide relevant unpublished data.

2.2. Study Selection and Quality Assessment

All trials retrieved from the search were evaluated for titles and abstracts by three independent researches. Inclusion criteria were randomized, double-blinded, placebo-controlled trials that assessed the efficacy of chI in subjects with diagnosis of PD according to the criteria of the United Kingdom Brain Bank an associated dementia. Outcomes considered for analysis were the Mini Mental Status Exam (MMSE) scale and the cognition scale for evaluation of dementia ADAS-Cog. Studies that did not described clearly the concealment procedure, with paid participants, dropout rate superior to 50% or missing the outcomes considered for analysis were excluded. Quality evaluation of the included studies was performed by two independent reviewers according to Jadad scale [16]. Studies who reached a score of 3 or more were considered as high quality trial. Duplicated publications or

substantial overlap in terms of authors, population, institution, and study period were also excluded. Disagreements concerning whether or not to include a study were resolved by consensus.

2.3. Data Extraction

A standardized form elaborated by the reviewers was used to extract data from each trial that fulfilled the inclusion and exclusion criteria. Information extracted independently by the reviewers from included articles were: first author, publication year, location, number of subjects enrolled in each arm, type of intervention, duration of study, outcomes and intervention. For cross-over trials, only data derived from the first treatment period were considered for analysis. In case of missing data, essential for the analysis, we attempted to contact the authors of the included trials. Inconsistent results among reviewers were resolved by discussion.

2.4. Statistical Analysis

Continuous data that allowed transformation into means and standard deviations (SD) were considered for analysis using the software Comprehensive Meta-analysis version 2.2 (Biostat Inc., Englewood, New Jersey). The standardized mean difference (SMD) and their 95% confidence interval (CI) were calculated for each trial and to estimate the summary effect size. To assess the efficacy of cholinesterase inhibitors in PDD, we calculated the standardized mean difference (SMD) by assessing the baseline and end of study measures of the MMSE and Adas-Cog scores. Only effect-sizes superior to 0.5 were considered as moderate, and measures larger than 0.8 were considered as high [17]. The fixed-effects model was used to assess the results in the meta-analysis, and the degree of heterogeneity was calculated by the I^2 test. A degree of heterogeneity greater than 50% was considered as substantial. Subgroup analysis and metaregression were hampered by the small numbers of studies selected for the analysis.

3. Results

After a comprehensive literature search, 175 references were retrieved from electronic databases and other sources. After title and abstract evaluation, 70 studies were excluded (review articles, case reports, did not present the outcome of interest).

Twenty eighth articles were fully evaluated and 23 were excluded because they not fulfilled the eligibility criteria. A total of five randomized trials [14] [18]-[21], comprising 946 subjects who assessed the effects of cholinesterase inhibitors in PDD were included in the analysis. The steps performed in the study selection process and reasons for exclusion are described in **Figure 1**. The characteristics of the studies included in the revision, their primary outcomes are summarized in **Table 1**.

When analyzing the MMSE, the pooled analysis of 5 studies comprising 568 subjects in the intervention arm and 378 in the placebo arm (**Figure 2**), showed a SMD of 0.25 (CI 95% 0.11 - 0.39). The pooled analysis of Adas-Cog in three studies comprising 555 subjects in the intervention arm and 363 in the placebo arm (**Figure 3**) showed a SMD of 0.21 (CI 95% 0.07 - 0.35). The I^2 test did not show significant heterogeneity across the studies. Sensitivity analysis and metaregression were not performed due to the limited number of articles included in the review.

4. Discussion

The results of this systematic review and meta-analysis suggested that there was an improvement in cognitive functions among patients with PDD treated with cholinesterase inhibitors.

Open clinical trials have demonstrated that cholinesterase inhibitors improve cognitive functions in subjects with PDD. Litvinenko *et al.* in an open controlled trial including 41 subjects showed significant improvement in cognitive and neuropsychiatric symptoms in patients using galantamine, through the application of several scales and tests such as the MMSE, ADAS-cog, clock drawing test, Frontal Assessment Battery (FAB) and Neuropsychiatric Inventory (NPI) [22]. There were minor side effects and mild increase in tremor in the intervention group. Powe *et al.* in an extension study with 273 PDD patients demonstrated sustained benefits of rivastigmine use in neuropsychiatric symptoms and activities of daily life, as well as executive functions, with mild adverse events [23]. In another open label trial, the results suggest that treatment with galantamine after 8 weeks improved cognition, hallucinations and motor symptoms in PDD patients [24]. Minett *et al.* in an open

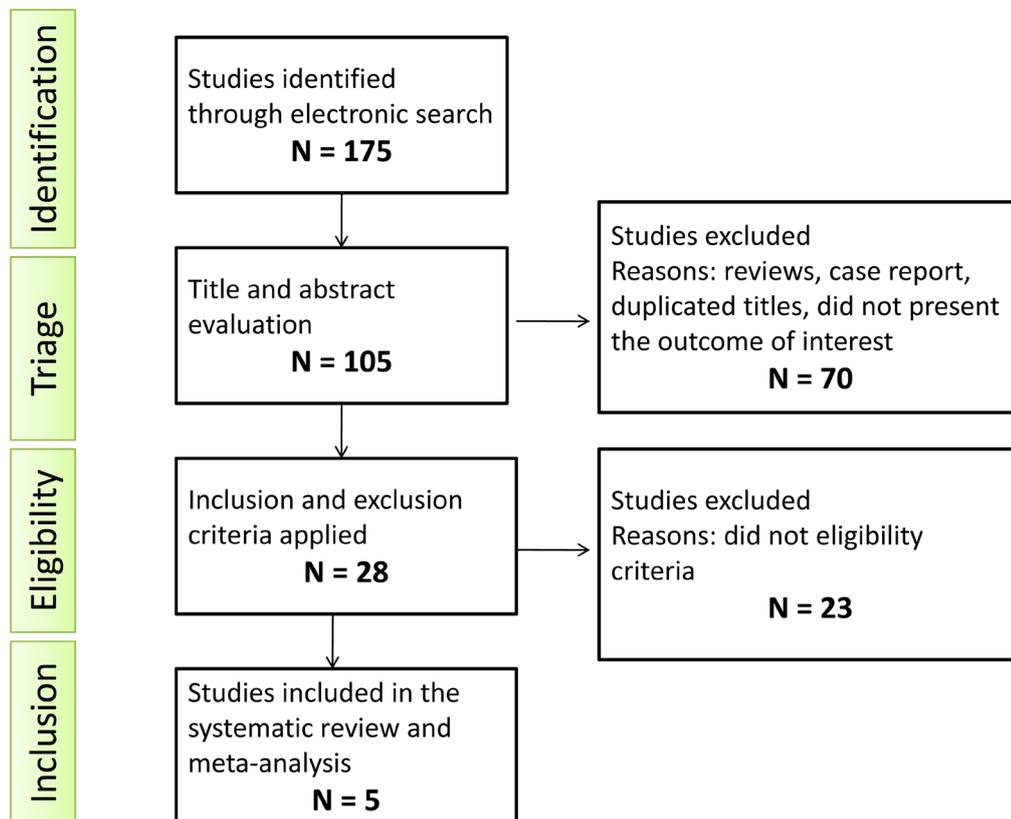
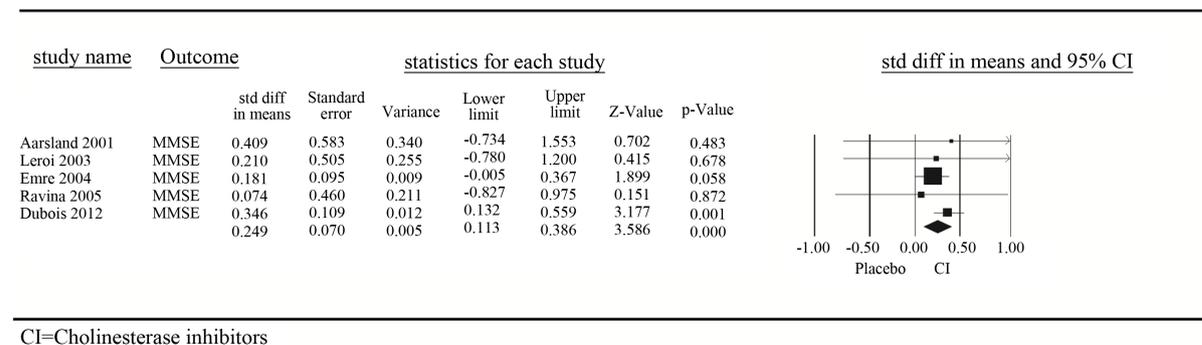
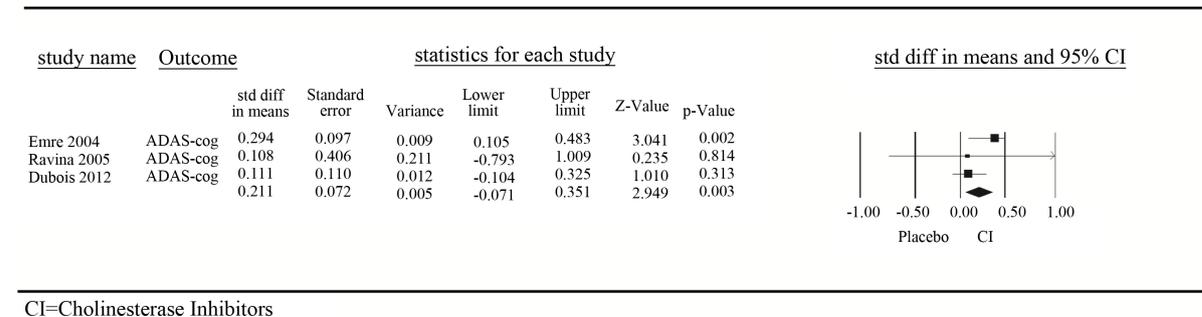


Figure 1. Studies identified through electronic search and reasons for exclusion.



CI=Cholinesterase inhibitors

Figure 2. Effect of cholinesterase inhibitors in the MMSE in Parkinson's disease dementia.



CI=Cholinesterase Inhibitors

Figure 3. Effect of cholinesterase inhibitors in the ADAS-cog score in Parkinson's disease dementia.

Table 1. Characteristics of the studies included in the review and outcomes.

Author, year	Study design	Population	Intervention	Outcomes	SMD (CI 95%)
		Treatment/Placebo			
Aarsland, 2001	Clinical trial	6/6	Donepezil 10 mg/Placebo	MMSE	0.41 (-0.73 to 1.55)
Leroi, 2003	Clinical trial	7/9	Donepezil 10 mg/Placebo	MMSE	0.21 (-0.78 to 1.2)
Emre, 2004	Clinical trial	362/179	Rivastigmine 12 mg/Placebo	MMSE Adas-Cog	0.18 (-0.00 to 0.37) 0.29 (0.10 to 0.48)
Ravina, 2005	Clinical trial	11/11	Donepezil 10 mg/Placebo	MMSE Adas-Cog	0.07 (-0.82 to 0.97) 0.11 (-0.79 to 1.00)
Dubois, 2012	Clinical trial	182/173	Donepezil 10 mg/Placebo	MMSE Adas-Cog	0.34 (0.13 to 0.55) 0.11 (-0.10 to 0.32)

label study with 11 PDD patients showed that suddenly withdrawing donepezil led to rapid clinical cognitive deterioration with restoration of treatment gains as soon as the treatment was reinitiated [25].

Among the studies included in the review, only two outcomes (MMSE and ADAS-cog) presented with comparable results and could be pooled in a meta-analysis. The MMSE is a worldwide applied test used for screening of cognitive impairment, due to its feasibility and high reliability test-retest [26]. However, there is a lack of specificity to discriminate clinical syndromes associated with dementia [27]. In addition, greater changes in MMSE total score would be necessary to correlate with a clinical significant improvement.

Despite statistically significant, the changes observed in MMSE and ADAS-cog scores in the intervention group may be not clinically relevant, as the effect-sizes demonstrated in the results for these outcomes were not substantial (<0.5), considering that an enhance of 30% in these scores would perhaps translate into clinical improvement.

Worsening motor symptoms in PDD due to cholinesterase inhibitors use have been reported, especially minor increases in tremor. However, open trials showed mild effects in motor features, usually associated to the initial phase of the treatment [15].

The absence of comparable and reliable outcomes for PDD evaluation has limited the interpretation of the results achieved in this meta-analysis. In addition, the absence of information in the trials included of what would be considered as a clinically relevant improvement should be taken into account.

Further clinical trials with extended intervention analysis and standardized scales to assess outcomes may optimize the results and allow a better evaluation of the efficacy of cholinesterase inhibitors in PDD.

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