REVIEW

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Effects of Cholinesterase Inhibitors in Parkinson's Disease Dementia: A Review of Clinical Data

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SUMMARY

Aims: Cognitive impairment and dementia are common features of Parkinson's disease (PD). Patients with Parkinson's disease dementia (PDD) often have significant cholinergic defects, which may be treated with cholinesterase inhibitors (ChEIs). The objective of this review was to consider available efficacy, tolerability, and safety data from studies of ChEIs in PDD. **Discussions:** A literature search resulted in the identification of 20 relevant publications. Of these, the treatment of PD patients with rivastigmine, donepezil, or galantamine was the focus of six, eleven, and two studies respectively, while one study reported use of both tacrine and donepezil. The majority of studies were small (<40 patients), with the exception of two large randomized controlled trials (RCTs) that are the main focus of this review. In the smaller studies, treatment benefits were reported on a range of outcome measures, though results were extremely variable. While the full results of a large RCT of donepezil in patients with PDD are not yet available, significant treatment differences were reported on the CIBIC-plus at the highest treatment dose. A trend toward improvement was also observed in treated patients on the ADAS-cog. The second large RCT found significant improvements in rivastigmine-treated patients compared with placebo on both the ADAS-cog ($P < 0.001$) and the ADCS-CGIC ($P < 0.007$), as well as on all secondary efficacy outcomes. Consequently, rivastigmine is now widely approved for the symptomatic treatment of mild to moderate PDD. **Conclusions:** Taken together, these studies suggest that ChEIs are efficacious in the treatment of PDD.

Introduction

Parkinson's disease (PD) is a chronic degenerative neurological disease characterized by tremor, muscle rigidity, bradykinesia, and postural instability [1]. PD is one of the most common neurodegenerative disorders, with an estimated incidence of 14 per 100,000 [2]. In addition to the classical motor symptoms of PD, many patients with PD also suffer cognitive impairment and dementia [3], particularly older patients with more severe extrapyramidal signs [4]. The estimated point prevalence of dementia in patients with PD is 30% [5]. Furthermore, a 12-year longitudinal cohort study suggests that the majority of patients with PD develop dementia within 12 years, meaning dementia is a relatively common feature of the disease [6]. The mean duration from the onset of PD to development of dementia is approximately 10 years [7]. Parkinson's disease dementia (PDD) usually manifests with impairment of executive function and attention, although other deficits, including memory and

visuoconstruction impairment, usually develop during the course [8,9]. Behavioral symptoms, including depression, anxiety, hallucinations, and apathy, also commonly occur [10–13]. The emergence of visual hallucinations some time after the onset of Parkinsonian symptoms is highly predictive of PDD. In a cohort of 208 patients with PD, 48% of the patients with visual hallucinations at baseline developed PDD within 1 year [14]. Another study with longitudinal follow-up to autopsy of 42 patients with PD also showed visual hallucinations to be a strong predictor for PDD (odds ratio 21.3) [3]. Where hallucinations are present during the initial onset of Parkinsonism they are more indicative of Lewy body dementia [15,16]. Dementia in PD is associated with more rapid motor and functional decline [17] and increased mortality [18]. It is a great source of distress to patients with PD and their families [19,20], and a more frequent cause of institutionalization in these patients than the motor symptoms of the disease [21].

The pathology of PD initially occurs in the brainstem. Hallmark features include Lewy bodies and Lewy neurites – proteinaceous inclusion bodies – in the neuronal soma and processes of the medulla oblongata [22,23]. The disease progresses to involve other parts of the brain, following a characteristic ascending pathway that next affects the midbrain (most notably the substantia nigra pars compacta), then the mesocortex, and finally the neocortex [24]. In the pars compacta region of the substantia nigra, the formation of PD-related inclusion bodies within dopaminergic neurones finally leads to cell death, and a subsequent deficit of dopamine that is associated with the characteristic motor symptoms of the disease [1,25].

Although the depletion of dopamine is the main neurochemical impairment in PD, significant deficits in cholinergic transmission are also present, particularly in patients with PDD [26]. These deficits are largely localized to the cholinergic system of the basal forebrain and brainstem, in contrast to patients with Alzheimer's disease (AD), where cholinergic deficits are primarily seen in the hippocampus [27]. In patients with PDD, cholinergic deficits may be greater than in AD patients with similar levels of cognitive impairment [28]. Observations of substantial cortical cholinergic deficits in patients with PDD led to the suggestion that the impact of the disease on the cholinergic circuits might be effectively treated with cholinesterase inhibitors (ChEIs). This was first investigated in a small study by Hutchinson and Fazzini in 1996, in which seven patients with PDD treated for at least 2 months with up to 60 mg/day tacrine showed marked improvements in cognition [29]. The results of this study provided the rationale for large randomized controlled trials (RCTs) of ChEIs in PDD. Two large RCTs (one in rivastigmine, the other in donepezil) have now been completed [30,31], as well as several smaller RCTs and a number of open studies and case series.

The present objective is to review available efficacy, tolerability, and safety data from studies of ChEIs in PDD, and consider the value of these agents in the management of this condition. A 2004 review of ChEIs in the treatment of PDD and Lewy body dementia identified a number of publications reporting the use of ChEIs in patients with PD, mostly open studies or small case series [32]. A 2006 Cochrane review of efficacy, safety, tolerability, and health economic data relating to the use of ChEIs in PDD considered the large RCT of rivastigmine only [33]. All other studies were excluded due to being of open-label design or the use of diagnostic criteria for PDD outside those specified by the review authors. This current review will consider all available data retrieved by a systematic literature search, and will focus predominantly on the large RCTs that have been published or presented since 2004.

Methods

A systematic search of literature indexed by MEDLINE or PubMed during the past 10 years was carried out, using combinations of the following terms: ChEI, PD, dementia, cognitive impairment, PDD, rivastigmine, donepezil, galantamine. The bibliographies of included publications were used to supplement the search, as were listings of recent key congress presentations. Each publication or presentation yielded by this search was then assessed for relevance to the current review. Inclusion criteria were English language, human studies, and relevance to PDD and ChEIs. Any publications not reporting on a trial or study of ChEIs in patients with PD were excluded from the results. The literature search returned a total of 20 publications reporting on studies of ChEIs in patients with PD (Figure 1).

Results

Of the 20 publications returned by the literature search, the treatment of PD patients with rivastigmine was reported in 6 publications (Table 1), treatment with donepezil in 11 (Table 2), treatment with galantamine in 2 (Table 3), and treatment with both tacrine and donepezil (with pooled results) in 1 (Table 2). Eleven of the publications reported on open-label studies, two described case series, five reported on RCTs (two of which were crossover studies [34,35]), one described an active extension to one of the larger RCTs [36], and one reported the results of an add-on study of a subgroup of

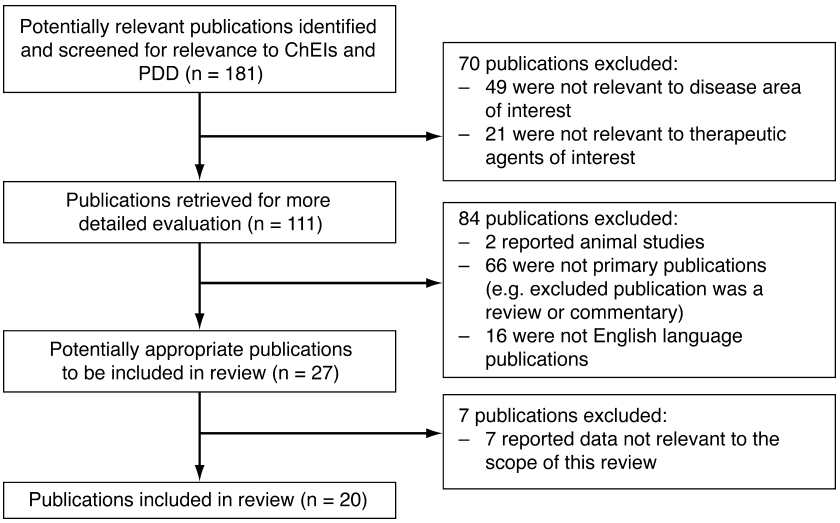

Figure 1 Flow diagram of publication selection for review of ChEIs in PDD.

patients from one of the large RCTs [37]. Most of the studies were small, with only two RCTs [30,31] and active extension [36] including more than 40 patients.

The majority of the studies were restricted to PD patients with dementia, but some studies included nondemented patients with PD suffering from hallucinations and/or delusions [38–41]. The most frequently used outcome measures were the Mini-Mental State Examination (MMSE) [42], the Alzheimer's Disease Assessment Scale (ADAS-cog) [43], and the Neuropsychiatric Inventory (NPI) [44]. The motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) was routinely used to assess any change in motor symptoms over the course of the studies [45].

Each of the smaller studies ($\leq$40 patients) reported some degree of improvement on at least one of the outcome measures assessed, though the outcome measures on which improvements were seen varied, and sometimes conflicted, between studies. Two small RCTs of donepezil in patients with PDD reported significant differences versus placebo on the MMSE and measures of global change [34,35]. The third small RCT of donepezil demonstrated significant treatment differences versus placebo on the memory component of the Mattis Dementia Rating Scale, a measure of global cognitive ability, but no significant differences on the MMSE or on any other outcome measure [46]. While some small open studies of donepezil in PDD reported significant improvements in MMSE versus baseline [47–49], others reported no significant changes on the MMSE, but did show significant improvements on other outcome measures [39,50]. Figure 2 shows mean changes from baseline on the MMSE for all studies where these values were reported.

Improvements in psychotic symptoms, particularly hallucinations, were observed in several studies [38–40,47]. One case series of PD patients given rivastigmine reported that, of four patients with hallucinations at baseline, treatment with rivastigmine for between 5 and 13 months resolved hallucinations in two patients and improved them in the remaining two [38]. In an open study of eight PD patients with hallucinations or delusions given donepezil, the mean score on the hallucinations subitem of the Parkinson Psychosis Rating Scale was significantly improved from baseline after 2 months ($P < 0.05$) [39]. Similarly, an open study following 15 patients with PDD treated with donepezil reported significant improvements on the hallucinations domain of the NPI after 20 weeks ($P = 0.029$). These improvements were lost on withdrawal from treatment, but regained upon recommencement of therapy [47]. A case series of three PD patients treated with donepezil found hallucinations to be reduced in two patients after 3–4 months' treatment, but the third patient experienced delusions that appeared to be linked to donepezil treatment, and discontinued treatment after 17 days [40]. Of the two studies on galantamine, one 8-week study saw improvements in hallucinations, but no significant change on the MMSE [51], while a longer, 24-week study found significant improvements (compared with baseline) on several outcome measures, including MMSE and ADAS-cog [52]. Apart from isolated cases where motor symptoms worsened, the overall trend across all ChEIs was toward no significant change on the motor subscale of the UPDRS.

While these smaller studies of ChEI treatment in patients with PDD are interesting, the small sample sizes and the uncontrolled design involved in these studies

Table 1 Summary of studies of rivastigmine in patients with Parkinson's disease

Study	Total patients	Patients completing study	Study design	Study duration (weeks)	Mean age (years)	Mean baseline MMSE	Outcome measures	Results
Reading 2001 [41]	15	12	Open/ washout	14/3	71	20.4	MMSE, NPI	Improvements on MMSE[a] (5 points) and NPI[a] (25 points) with deterioration after washout
	Inclusion criteria: PD (UK Brain Bank) for ≥2 years; hallucinations for ≥3 months; stable medication regime not including neuroleptic/anticholinergic agents; caregiver Exclusion criteria: MMSE <10; significant urinary symptoms; history of cardiovascular disease or cardiac arrhythmia							
Giladi 2003 [53]	28	20	Open/ washout	26/8	75	20.5	ADAS-cog, UPDRS, CGI, MMSE	Improvements in mental subscale of UPDRS[a] (1.8 points), ADAS-cog[a] (7.3 points), and attention component of MMSE[a]; no significant change in motor subscale of UPDRS or total MMSE (improvement of 1.4 points)
	Inclusion criteria: PD (UK Brain Bank) for ≥2 years; dementia due to PD (DSM-IV) occurring ≥1 year after PD diagnosis; MMSE 12–26 Exclusion criteria: significant depression; active malignancy; uncontrolled heart disease; diabetes; hypertension; other psychiatric disorders; severe head trauma; stroke; significant brain lesions; anticholinergic drugs; or amantadine							
Bullock 2002 [38]	5	5	Case series	20–52	75	20.6	MMSE	Improvements in cognition (9 points on the MMSE in 1 patient after 5 months) and behavioral symptoms, particularly visual hallucinations
	Inclusion criteria: diagnosis of PDD Exclusion criteria: lack of informed consent; safety concerns over concurrent diseases							
Dujardin 2006 [37]	28 (16 randomized to active group)	16 from active group	RCT	24	73	21.5	MDRS	Improvement in total MDRS score[b] (5.8 points)
	Inclusion criteria: PD (UK Brain Bank); dementia (DSM-IV); MMSE 10–24; onset of cognitive symptoms occurring ≥2 years after PD diagnosis Exclusion criteria: any other neurodegenerative disorder or other cause of dementia; major depression; active, uncontrolled seizure disorder; any disability or unstable disease unrelated to PD; known hypersensitivity to drugs similar to rivastigmine; use of cholinesterase inhibitors or anticholinergic drugs during the four weeks before randomization							
Emre 2004 [30]	541 (362 randomized to active group)	263 from active group	RCT	24	73	19.4	ADAS-cog, ADCS-CGIC, ADCS-ADL, NPI, MMSE, CDR, D-KEFS, Ten Point Clock-Drawing test	Significant treatment differences on ADAS-cog (2.1 points; treatment difference of 2.9 points[c] vs. placebo), ADCS-CGIC (treatment difference of 0.5 points vs. placebo), ADCS-ADL (1.1 points; treatment difference of 2.5 points vs.placebo), NPI (2 points; treatment difference of 2.15 points[c] vs. placebo), MMSE (0.8 points; treatment difference of 1.0 points vs. placebo), CDR (improvement of 31 msec; treatment difference of 294.84 msecond[c] vs. placebo), D-KEFS (1.7 correct responses; treatment difference of 2.8 vs. placebo), and Ten Point Clock-Drawing test (0.5 points; treatment difference of 1.1 points vs.placebo) (all [b])
	Inclusion criteria: PD (UK Brain Bank); dementia (DSM-IV); MMSE 10–24; onset of cognitive symptoms occurring ≥2 years after PD diagnosis; caregiver Exclusion criteria: any other neurodegenerative disorder or other cause of dementia; major depression; active, uncontrolled seizure disorder; any disability or unstable disease unrelated to PD; known hypersensitivity to drugs similar to rivastigmine; use of cholinesterase inhibitors or anticholinergic drugs during the four weeks before randomization							

Table 1 Continued

Study	Total patients	Patients completing study	Study design	Study duration (weeks)	Mean age (years)	Mean baseline MMSE	Outcome measures	Results
Poewe 2006 [36]	334	273	Active treatment extension to RCT [30]	24	72	19.5	ADAS-cog, ADCS-ADL, NPI, MMSE, D-KEFS	Improvements on ADAS-cog (2.0 points), NPI (2.4 points) and MMSE (1.4 points) (vs.baseline at start of RCT); no significant change in motor symptoms
	Inclusion criteria: patients who completed the Emre 2004 double-blind study, or who dropped out but returned for scheduled efficacy assessments and had no significant protocol violations Exclusion criteria: none stated							

[a]Significant versus baseline.

[b]Significant versus placebo.

[c]Difference of least-square means.

UK Brain Bank, criteria for diagnosis of PD as specified by the UK Parkinson's Society Brain Bank [54,55].

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition [56]; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale; UPDRS, Unified Parkinson's Disease Rating Scale; CGI, Clinical Global Impressions scale; NPI, Neuropsychiatric Inventory; ADCS-CGIC, Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR, Cognitive Drug Research Power of Attention tests; D-KEFS, verbal fluency test from the Delis–Kaplan Executive Function System test battery; MDRS, Mattis Dementia Rating Scale.

make it difficult to draw valid conclusions about the results. However, two of the RCTs retrieved by the literature search were large, including more than 500 patients each [30,31], providing a greater degree of statistical certainty when considering the findings.

Rivastigmine

The 24-week, randomized, multicenter, double-blind, placebo-controlled study of rivastigmine in PDD carried out by Emre and colleagues [30] included 541 patients with mild-to-moderate dementia, which developed at least 2 years after a clinical diagnosis of PD (to distinguish PDD from Lewy body dementia). The primary efficacy outcomes in this study were the ADAS-cog and the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC) [57]. Secondary outcomes included the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) [58], the Cognitive Drug Research Power of Attention tests (CDR) [59], the verbal fluency test from the Delis–Kaplan Executive Function System test battery (D-KEFS) [60], the Ten Point Clock-Drawing test [61], MMSE, and NPI.

A total of 362 patients were randomized to rivastigmine, and 179 patients to placebo. Of the 362 patients given rivastigmine, 263 (73%) completed the study, compared with 147 patients (82%) given placebo [30]. Sixty-two patients (17%) in the rivastigmine group discontinued due to adverse events, versus 14 patients (8%) in the placebo group. The most frequently occurring adverse events were nausea, which affected 29% of patients in the rivastigmine group and 11% of patients in the placebo group, and vomiting, reported by 17% of patients given rivastigmine and 2% of patients given placebo [30]. Emerging or worsening tremor was reported in 10% of patients in the rivastigmine group, compared with 4% in the placebo group, though this was mild and rarely led to discontinuation. A retrospective analysis of safety data from this trial reported that tremor was usually associated with dose titration and was generally transient, resolving with continued treatment [62]. There were 11 deaths in total, with significantly fewer deaths in the rivastigmine group (4 deaths) compared with the placebo group (7 deaths) ($P < 0.05$) [63].

Statistically significant treatment differences in comparison with placebo were seen with rivastigmine on both primary efficacy variables [30]. On the ADAS-cog, a significant treatment difference was seen in patients given rivastigmine compared with patients in the placebo group ($P < 0.001$) (Figure 3). Mean scores (±SD) indicated that patients in the rivastigmine group experienced an improvement in cognition of 2.1 points (±8.2) on the ADAS-cog over 24 weeks, while patients on placebo deteriorated by 0.7 points (±7.5). If the deterioration on placebo seen here is typical of the rate of decline in the general PDD population, it suggests that treatment with rivastigmine can delay the worsening of PDD symptoms by an average of 1.5 years.

Likewise, on the ADCS-CGIC, the mean change at Week 24 in the rivastigmine group indicated improvement, while that in the placebo group indicated deterioration (rivastigmine versus placebo, $P = 0.007$) (Figure 4)

Table 2 Summary of studies of donepezil in patients with Parkinson's disease

Study	Total patients	Patients completing study	Study design	Study duration (weeks)	Mean age (years)	Mean baseline MMSE	Outcome measures	Results
Bergman 2002 [50]	6	6	Open	6	69	20.2	MMSE, GDS, CGI, SAPS	Improvements on CGI[a] (3.7 points) and SAPS[a] (18.9 points); no change on MMSE (improvement of 0.5 points) or GDS (improvement of 0.1 points)
	Inclusion criteria: PD (UPDRS); diagnosis of dementia based on MMSE and GDS Exclusion criteria: none stated							
Fabbrini 2002 [39]	8	8	Open	8	74	25.2	MMSE, PPRS	Improvement on PPRS[a] (3.9 points); no significant change on MMSE (deterioration of 0.3 points)
	Inclusion criteria: nondemented PD patients experiencing hallucinations and/or delusions Exclusion criteria: use of antipsychotics							
Minett 2003 [47]	15	11	Open treat/ withdraw/ treat	20/6/12	Not reported	17.5	MMSE, NPI	Improvements after 20 weeks on MMSE[a] (3.8 points) and in behavior (particularly hallucinations) which were lost on withdrawal of treatment and restored on recommencement
	Inclusion criteria: probable PDD (UK Brain Bank) Exclusion criteria: severe gastrointestinal, renal or liver disease; history of cardiac bradyarrhythmias, asthma or bladder outflow obstruction; recent history of cerebrovascular disease; use of cholinergic, anticholinergic, nonsteroidal antiinflammatory medication or neuroleptics							
Thomas 2005 [48]	40	35	Open	20	71	18.3	MMSE, NPI	Improvements on MMSE[a] (3.2 points) and NPI[a] (12 points); no significant change in motor symptoms
	Inclusion criteria: PD (UK Brain Bank); dementia due to PD (DSM-IV); MMSE <24; cognitive fluctuations and/or hallucinations; caregiver Exclusion criteria: use of cholinergic, anticholinergic, nonsteroidal antiinflammatory drugs or antipsychotics; severe gastrointestinal, renal or liver disease; history of bradyarrhythmia, asthma or bladder outflow obstruction; recent history of cerebrovascular disease							
Muller 2006 [49]	24	14	Open	12	71	21.6	MMSE, CGI	Improvement in MMSE[a] (3.1 points); no significant change on CGI or in motor symptoms
	Inclusion criteria: PD (UK Brain Bank); dementia due to PD (DSM-IV) occurring ≥2 years after PD diagnosis; MMSE 10–26; stable dopaminergic regime; caregiver Exclusion criteria: history of major depression; any other primary neurodegenerative disorders or other causes of dementia; seizures; prior long-term intake of anticholinergics							
Rowan 2007 [64]	23	23	Open	20	Not reported (range 61–80)	18	CDR	Improvements on Power of Attention[a] and Reaction Time Variability[a] components of the CDR; no significant improvements on Continuity of Attention or Cognitive Reaction Time components
	Inclusion criteria: PD (UK Brain Bank); dementia due to PD (DSM-IV); MMSE <24; cognitive fluctuations and/or hallucinations; caregiver Exclusion criteria: use of cholinergic, anticholinergic, nonsteroidal antiinflammatory drugs or antipsychotics; severe gastrointestinal, renal or liver disease; history of bradyarrhythmia, asthma or bladder outflow obstruction; recent history of cerebrovascular disease							
Kurita 2003 [40]	3	2	Case series	2–56	70	22.6	MMSE, HY	Improvement in hallucinations, some improvement in cognition (5 points on MMSE in 1 patient)
	Inclusion criteria: PD of ≥6 years; visual hallucinations Exclusion criteria: none stated							
Aarsland 2002 [34]	14	12	RCT crossover	20 (10 + 10)	71	20.8	MMSE, CIBIC-plus	Improvement on MMSE[b] (2 points; 1.8 points treatment difference vs. placebo) and CIBIC-plus[b] (treatment difference of 0.8 points vs. placebo)
	Inclusion criteria: mild-to-severe Parkinsonism (HY <5); age 45–95 years; evidence of decline in memory and at least one other category of cognitive function, occurring ≥1 year after onset of Parkinsonism; MMSE 16–26; caregiver Exclusion criteria: brain disease other than PD or other severe medical disorders; use of anticholinergic drugs or psychotropic drugs with anticholinergic effects							

Table 2 Continued

Study	Total patients	Patients completing study	Study design	Study duration (weeks)	Mean age (years)	Mean baseline MMSE	Outcome measures	Results
Leroi 2004 [46]	16 (7 randomized to active group)	2 from active group	RCT	18	69	26.0	MMSE, NPI, MDRS, BTA	Improvement on memory component of MDRS[b] (2.6 points; treatment difference of 5.32 points vs. placebo); no significant change in MMSE (deterioration of 0.67 points) or other outcome measures
	Inclusion criteria: PD (UK Brain Bank) with dementia/cognitive impairment (DSM-IV) Exclusion criteria: MMSE <10; nonambulatory; history of substance abuse or dependence; severe cardiac, vascular or renal disease; inability to tolerate donepezil							
Ravina 2005 [35]	22	19	RCT crossover with washout	10/6/10	73	22.2	ADAS-cog, MMSE, MDRS, CGI, BPRS	Improvements on MMSE[b] (2.3 points; treatment difference of 2 points quoted vs. placebo) and CGI[b] (0.37 points treatment difference vs. placebo); no significant changes on ADAS-cog, MDRS, or BPRS
	Inclusion criteria: clinical diagnosis of idiopathic PD; >40 years of age; dementia (DSM-IV) developing ≥1 year after the motor manifestations of PD; MMSE 17–26 Exclusion criteria: any other causes of dementia; pregnancy or lactation; use of cholinergic/anticholinergic agents except amantadine or tolterodine within the 2 weeks prior to screening; medical conditions or uncontrolled psychosis that might interfere with the safe conduct of the study							
Dubois 2007 [31]	550 (195 to 5 mg/day, 182 to 10 mg/day)	Not reported	RCT	24	72	21	ADAS-cog, CIBIC-plus, DAD, NPI, MMSE, BTA, D-KEFS	Improvements on MMSE[b], BTA[b], D-KEFS[b] and CIBIC-plus (numerical values not provided); no significant improvements on ADAS-cog (treatment difference of 3.42 points vs. placebo for 10 mg/day group), DAD or NPI, and no significant change in motor symptoms
	Inclusion criteria: PD (UK Brain Bank); ≥40 years of age; mild-to-moderate dementia (DSM-IV) occurring >1 year after PD onset; MMSE 10–26 Exclusion criteria: none stated							
Other studies								
Werber 2001 [65]	11 (7 on tacrine, 4 on donepezil; results pooled)	11	Open	26	75	18.6	MMSE, ADAS-cog, GDS, SPES	Improvement on ADAS-cog[a] (3.2 points); no significant change on MMSE (improvement of 1.3 points), GDS (improvement of 0.2 points), or in motor function (SPES; improvement of 2.6 points)
	Inclusion criteria: diagnosis of PD for several years prior to onset of dementia; PDD (DSM-IV); MMSE ≤26; no history of other neurological or psychiatric disorders; no focal findings on CT or MRI; normal thyroid and liver function; normal transcobalamine level and negative for syphilis Exclusion criteria: none stated							

[a]Significant versus baseline.
[b]Significant versus placebo.
UK Brain Bank, criteria for diagnosis of PD as specified by the UK Parkinson's Society Brain Bank [54,55]; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition [56]; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale; GDS, Global Deterioration Scale; SPES, Short Parkinson Evaluation Scale; CIBIC-plus, Clinician's Interview-Based Impression of Change plus caregiver input; UPDRS, Unified Parkinson's Disease Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms; CGI, Clinical Global Impressions scale; PPRS, Parkinson Psychosis Rating Scale; NPI, Neuropsychiatric Inventory; HY, Hoehn and Yahr disability classification; CDR, Cognitive Drug Research Power of Attention tests; D-KEFS, verbal fluency test from the Delis–Kaplan Executive Function System test battery; MDRS, Mattis Dementia Rating Scale; BPRS, Brief Psychiatric Rating Scale; DAD, Disability Assessment for Dementia scale; BTA, Brief Test of Attention.

[30]. Analysis of outcomes in the seven response categories of the ADCS-CGIC (marked, moderate, or minimal improvement; no change; marked, moderate, or minimal deterioration) showed that significantly more patients experienced improvement on rivastigmine than on placebo at Week 24 (40.8 vs. 29.7%, $P = 0.02$). Around a quarter of patients given rivastigmine experienced no change on the ADCS-CGIC, and marked or moderate

Table 3 Summary of studies of galantamine in patients with Parkinson's disease

Study	Total patients	Patients completing study	Study design	Study duration (weeks)	Mean age (years)	Mean baseline MMSE	Outcome measures	Results
Aarsland 2003 [51]	16	13	Open	8	76	17.7	MMSE, Ten Point Clock-Drawing test, verbal fluency measure of MDRS, NPI	Improvements on Ten Point Clock-Drawing test[a] and in hallucinations (improvements seen in 7 of 9 patients with hallucinations at baseline); no significant change in mean MMSE (improvement of 2.3 points)
	Inclusion criteria: PD (UK Brain Bank); dementia due to PD (DSM-IV) occurring ≥1 year after PD diagnosis; caregiver Exclusion criteria: severe disease other than PD; other conditions that could cause neuropsychiatric symptoms; use of anticholinergics, tricyclic antidepressants, or antipsychotic agents							
Litvinenko 2008 [52]	21	21	Open	24	69	17.6	MMSE, ADAS-cog, Ten Point Clock-Drawing test, FAB, NPI, DAD	Improvements on MMSE[a] (3.7 points), ADAS-cog[a] (3.3 points), Ten Point Clock-Drawing test[a] (0.9 points), and FAB[a] (2.5 points)
	Inclusion criteria: PD (UK Brain Bank); dementia due to PD (ICD-10) occurring ≥2 years after PD diagnosis; MMSE <25; ability to perform neuropsychiatric tests; caregiver Exclusion criteria: cardiovascular disease, bronchial obstruction, or hepatic/renal pathology; history of acute cerebrovascular episodes, depression, delusions, or other brain disease; use of cholinolytics, cholinesterase inhibitors, or nootropes							

[a]Significant versus baseline.

UK Brain Bank, criteria for diagnosis of PD as specified by the UK Parkinson's Society Brain Bank [54,55]; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, American Psychiatric Association [56]; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision, World Health Organization; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale; NPI, Neuropsychiatric Inventory; FAB, Frontal Assessment Battery; MDRS, Mattis Dementia Rating Scale; DAD, Disability Assessment for Dementia scale.

deterioration in symptoms was seen in 13.0% of patients given rivastigmine and 23.1% of patients given placebo. Significant benefits with rivastigmine versus placebo were also seen on all secondary efficacy outcomes: the ADCS-ADL ($P < 0.02$), CDR ($P = 0.009$), D-KEFS ($P < 0.001$), Ten Point Clock-Drawing test ($P = 0.02$), MMSE ($P < 0.03$), and NPI ($P < 0.02$) [30].

Additional analyses showed that significant improvements with rivastigmine in comparison with placebo were present on all four composite measures of the CDR. These measures represent two domains that are characteristically impaired in other forms of dementia (Power of Attention, $P < 0.01$ vs. placebo at Week 24; and Continuity of Attention, $P = 0.0001$ vs. placebo at Week 24), and two domains that are specifically affected in PDD (Cognitive Reaction Time, $P < 0.0001$ vs. placebo at Week 24; and Reaction Time Variability, $P < 0.001$ vs. placebo at Week 24) [66].

A prospective additional analysis of the rivastigmine study data, described in the original study protocol, compared the subpopulations of PDD patients who reported suffering from hallucinations at baseline with those who reported no hallucinations at baseline and found that rivastigmine provided benefits in both groups of patients [67]. However, rivastigmine–placebo treatment differences tended to be larger in hallucinators than nonhallucinators, and patients with hallucinations tended to experience a more rapid decline on placebo in comparison with nonhallucinating patients [67].

Patients completing the 24-week double-blind rivastigmine study [30] were eligible to enter a 24-week open-label extension [36], in which all patients (irrespective of their double-blind treatment) who chose to continue (n = 334) were given 3–12 mg/day rivastigmine. On switching to active treatment in the extension study, patients who had previously received placebo in the double-blind phase experienced treatment benefits similar to those previously seen in the double-blind rivastigmine group. The treatment effects seen in patients receiving rivastigmine, during the double-blind study and open-label

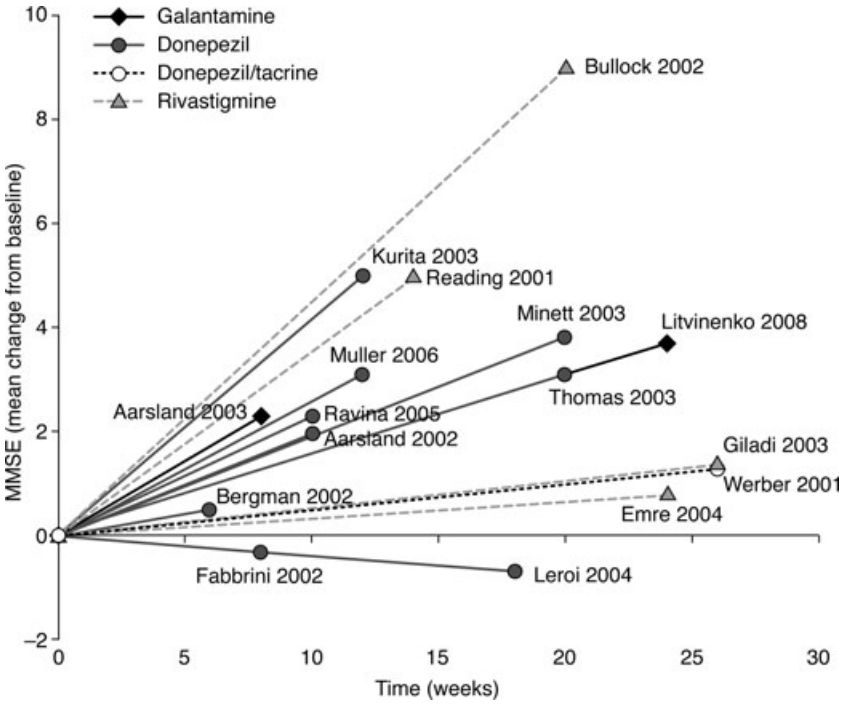

Figure 2 Changes from baseline in mean MMSE score* in studies of galantamine [51,52], donepezil [34,35,39,40,,46,48–50], donepezil or tacrine (with pooled results) [65], and rivastigmine [30,38,41,53]. *Positive changes from baseline on the MMSE indicate improvement; negative values indicate deterioration.

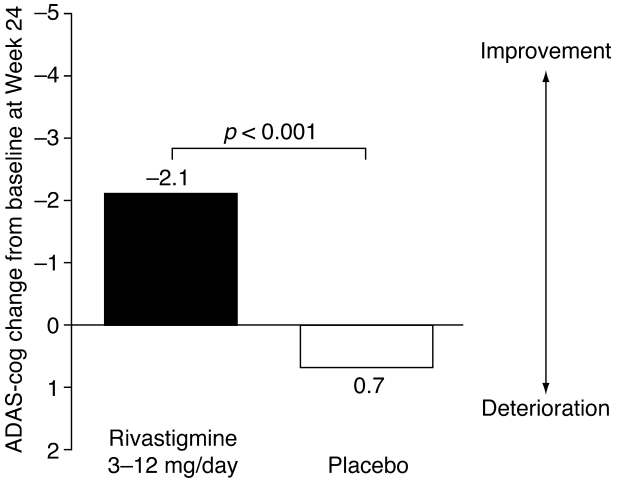

Figure 3 Changes from baseline in ADAS-cog scores at 24 weeks in patients with PDD in an RCT of rivastigmine (efficacy population*) [30]. *All randomized patients receiving at least one dose of study medication who were assessed at baseline and at least once after baseline.

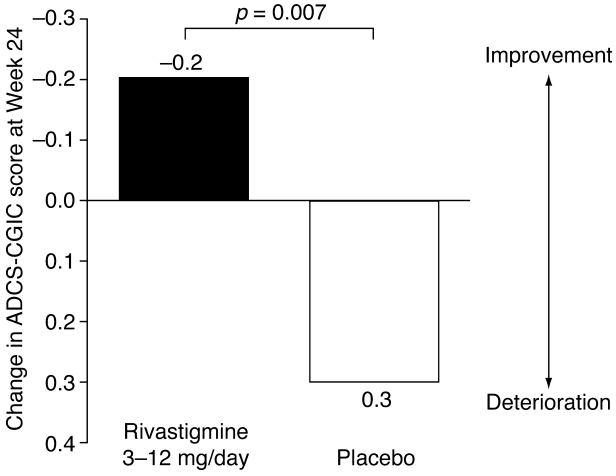

Figure 4 Changes at Week 24 in ADCS-CGIC scores in patients with PDD in an RCT of rivastigmine (efficacy population*) [30]. *All randomized patients receiving at least one dose of study medication assessed at baseline and at least once after baseline.

extension, were largely maintained for the full 48-week period. The profile of adverse events seen in the open-label extension was similar to that of the original double-blind trial.

Donepezil

While full publication of the results of the RCT of donepezil in patients with PDD by Dubois et al. is pending, preliminary findings were presented in 2007 at the Eighth International Conference on Alzheimer's and PDs in Salzburg, Austria [31]. Because of the clinical importance of this large RCT, the results as presented at this International Congress will be discussed here, although that poster was not subject to formal peer-review. However, due to the nature of the poster presentation, the amount of information provided is limited, and a detailed

review of the study is not possible until the results are published in a peer-reviewed journal.

Like the rivastigmine study [30], the donepezil study was a 24-week, randomized, multicenter, double-blind, placebo-controlled trial [31]. Primary efficacy outcomes were the ADAS-cog and the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus). Secondary efficacy outcomes included the MMSE, the Brief Test of Attention (BTA) [68], the D-KEFS, the Disability Assessment for Dementia scale (DAD) [69], and the NPI.

A total of 550 patients with PDD were randomized to 5 mg donepezil (n = 195), 10 mg donepezil (n = 182), or placebo (n = 173). Mean age was 72 years, and mean baseline MMSE was 21/30. Sixty-eight percent of the patients were male. The number of patients completing the full 24 weeks of the study was not provided, nor was the number of deaths occurring during the study. The most common adverse events were nausea (occurring in 21, 17, and 7% of patients given 10 mg donepezil, 5 mg donepezil, and placebo, respectively) and Parkinsonian side effects (10, 11, and 7%, respectively).

Results on the CIBIC-plus for the group given 10 mg donepezil, but not the group given 5 mg donepezil, were reported to be statistically superior compared with placebo (*P*-values not provided). However, while there was a trend toward improvement on the ADAS-cog for both 5 mg and 10 mg donepezil at 24 weeks, the treatment difference versus placebo was not significant for either dose (Figure 5). Mean scores (±SD) indicated that patients in the 5 mg donepezil group experienced an improvement of 2.45 points (±5.28) on the ADAS-cog over 24 weeks, while patients in the 10 mg donepezil group improved by 3.72 points (±7.05), and those on placebo improved by 0.3 points (±6.49). Significant treatment differences were seen on secondary measures including the MMSE ($P < 0.001$), BTA ($P < 0.01$), and D-KEFS ($P < 0.01$). No significant differences were observed on measures of activities of daily living (DAD), or behavior (NPI).

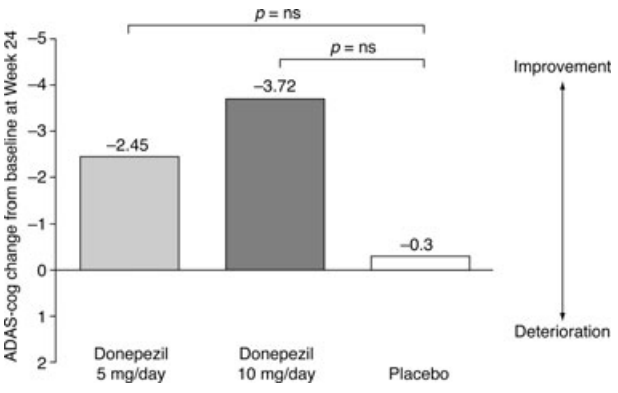

Figure 5 Changes from baseline in ADAS-cog scores at 24 weeks in patients with PDD in an RCT of donepezil (ITT-LOCF population) [31].

Discussion

The data reviewed here support the suggestion that ChEIs may be efficacious in the treatment of PDD. The collection of open studies and case series described in this review consistently observed discernable treatment benefits (albeit on varying outcome measures) relative to baseline values for all three ChEIs. These open studies do not make any attempt to control against placebo effects, but the observations they make are corroborated by the evidence provided from RCTs. However, as Figure 2 shows, the results of small RCTs, open studies, and case series are extremely variable, demonstrating the need for robust evidence-based medicine in the form of large, randomized, placebo-controlled trials.

The two large RCTs of rivastigmine and donepezil [30,31] and the three small RCTs of donepezil [34,35,46] that have been carried out to date all report at least one outcome with a statistically significant treatment difference versus placebo, though not all donepezil studies reached primary endpoints. Rivastigmine is now widely approved by regulatory authorities for the symptomatic treatment of mild-to-moderate PDD, on the basis of the positive results observed in the RCT of this ChEI. Donepezil and galantamine are not approved for this indication. It should be noted that the primary endpoints in the large RCTs reviewed here are primarily indicated for research in AD, not PDD. However, although the ADAS-cog – a primary endpoint in both the large RCTs of donepezil and rivastigmine – was originally designed for use in patients with AD, its validity and reliability in the assessment of patients with PD has been demonstrated [70].

Most recent American Academy of Neurology (AAN) guidelines on the treatment of depression, psychosis, and dementia in PD recommend that both rivastigmine and donepezil should be considered for the treatment of PDD [71]. This advice was based on a review of the results of the large RCT of rivastigmine by Emre [30] and two small RCTs of donepezil [34,35], despite one of the latter studies failing to see a significant treatment difference on its primary outcome measure [35]. The larger RCT of donepezil was not available for the AAN panel's review at the time of developing their guidelines. If all currently available evidence is considered, including the recent large RCT of donepezil in PDD [31], the most robust demonstration of treatment benefits without the

risk of worsening Parkinsonian symptoms is seen with rivastigmine.

A marked or moderate deterioration on the ADCS-CGIC was reported in 13% of patients on the treatment arm in the large RCT of rivastigmine [30]. It is possible that some of the patients experiencing decline on rivastigmine were those who were unable to tolerate the recommended target dose of 6–12 mg/day. At 24 weeks, 23.5% of patients in the rivastigmine group were receiving less than the target dose, with 2 patients (0.6%) on less than 3 mg/day. A transdermal patch formulation of rivastigmine, now approved in many countries for the treatment of PDD, may make it easier for patients to titrate to higher doses due to its improved tolerability profile compared with capsules [72]. However, this formulation was not available at the time of the study.

There are several reasons why the large RCT of rivastigmine in PDD patients may have proved more successful in terms of meeting primary efficacy outcomes defined in its trial design, compared with the large RCT of donepezil. Firstly, differences in demographics between the patient populations included in these two trials may have affected the relative success of these studies. For example, the patients included in the RCT of donepezil had an average baseline MMSE two points higher than that of the patients in the rivastigmine RCT. Secondly, there may have been differences in trial design that affected statistical certainty. On the other hand, mean group differences in change on the ADAS-cog were rather similar between the two large RCTs, and it is possible that the lack of statistical significance in the donepezil study is due to reduced statistical power since three groups were compared. However, it is difficult to consider such differences, due to the limited availability of information about the donepezil study, which has only been presented in poster format to date.

Differences between the therapeutic agents themselves may also have contributed to the outcomes of the studies. In PDD, the pathology of the disease predominantly affects frontal regions of the brain. Interestingly, butyrylcholinesterase (BuChE) appears to be the predominant cholinesterase in many key regions affected in PDD, and it has been postulated that BuChE inhibition might be particularly important in this type of dementia [73]. It could be hypothesized that inhibitors of BuChE and acetylcholinesterase (AChE), such as rivastigmine, might have potential for added therapeutic effects, compared with AChE-selective inhibitors.

Several studies provided evidence for a reduction in, or elimination of, hallucinations upon treatment with ChEIs. These observations add further weight to claims that ChEIs are more appropriate for the treatment of behavioral and psychotic symptoms in patients with PDD and other dementias than the atypical antipsychotics that are still commonly used. ChEI therapy may provide effective treatment of hallucinations in PDD, without the increased risks of extrapyramidal Parkinsonian features, stroke, and mortality associated with antipsychotic use in the elderly [74,75]. However, there are no studies yet demonstrating that ChEIs can improve psychotic symptoms in PDD patients selected for having such symptoms at baseline. Hallucinations may also be a clinical marker for greater underlying cholinergic deficits [76], which may explain recent findings suggesting that PDD patients with hallucinations receive increased benefits from ChEI therapy on measures of cognition, activities of daily living, and behavior, in comparison with patients not suffering from hallucinations [67]. Patients with hallucinations at baseline tend to experience more rapid cognitive decline on placebo, leading to greater rivastigmine versus placebo treatment effects. In *post hoc* analyses, rivastigmine has also been associated with greater treatment benefits in other specific subgroups of patients with dementia. Such subgroups include PDD patients with elevated levels of plasma homocysteine in comparison with patients with normal or low levels [77], and female AD patients homozygous for the BuChE wild-type genotype compared with males or females with the BuChE-K variant allele and males homozygous for the BuChE wild type [78]. To our knowledge, no equivalent evidence has been published to date for donepezil or galantamine.

While this review focused on the efficacy of ChEIs in PDD, trial data with rivastigmine in PDD patients for up to 48 weeks suggest that this agent is well tolerated with a favorable safety profile [36]. No unexpected safety issues arose in this population. In fact, rivastigmine was associated with significantly fewer deaths than placebo in the RCT [30]. In summary, ChEIs have shown beneficial effects in the treatment of PDD. Both donepezil and rivastigmine have been evaluated in large RCTs, although full data are in the public domain for the rivastigmine study only. Regulatory approval of rivastigmine for PDD was based on those data. Until the full results of the donepezil study are published, the efficacy, safety, and tolerability of donepezil in patients with PDD remain to be confirmed.

Author Contributions

All authors contributed to, reviewed, and approved this manuscript. The decision to submit this article to peer review, for publication, was reached by consensus among all of the authors.

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Conflict of Interest

The authors have no conflict of interest.

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