Treatment of Dementia in Parkinsonian Syndromes with Cholinesterase Inhibitors

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Key Words

Dementia · Parkinsonian syndromes · Cholinesterase inhibitor

corticobasal degeneration warrants carefully designed studies including a sufficient number of patients and symptom-adopted dementia scales.

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Abstract

In Parkinsonian syndromes behavioural symptoms and dementia can be even more debilitating than motor symptoms and are an important predictor for nursing home placement and mortality. Neuropathologically, dementia seems to be primarily related to cortical changes rather than to subcortical alterations. Concerning neurotransmitter systems, the cholinergic system has been proposed to play a key role in cognitive disturbances. Based on studies with patients with Alzheimer disease, the application of cholinesterase inhibitors is vividly discussed also for dementia associated with parkinsonian syndromes. This review focuses on the specific symptoms of dementia in different parkinsonian syndromes and critically questions the effect of cholinergic treatment on cognitive functions in patients with extrapyramidal syndromes and dementia. There is evidence that medication with some cholinesterase inhibitors can enhance cognition as well as activities of daily living in dementia with Parkinson's disease and seems to reduce behavioural disturbances in both dementia with Parkinson's disease and dementia with Lewy bodies. The effect of treatment with cholinesterase inhibitors in progressive supranuclear palsy and

Introduction

Behavioural symptoms and dementia are important predictors for nursing home placement and mortality in patients with parkinsonian syndromes [1, 2] and are an important component for the reduction of a patient's quality of life [3]. As a major source of distress both to patients and their families they can be more debilitating than the motor symptoms. Therefore, useful therapeutic strategies and effective management of these deficits is essential. Dementias associated with varying neurodegenerative processes comprise the largest group of dementive diseases, the most frequent diagnosis being Alzheimer disease (AD) at about 60% [4]. The second most common group of the neurodegenerative dementias are those associated with parkinsonian syndromes [5], including idiopathic Parkinson's disease (PD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). In contrast, the atypical parkinsonian syndrome multiple system atrophy is not usually associated with cognitive deteriora-

tion [6]. Some forms of spinocerebellar atrophies [7], the Westphal variant of Huntington's disease [8] and the fragile X tremor ataxia syndrome [9] are other neurodegenerative disorders associated with both extrapyramidal parkinsonian syndromes and dementia [10]. In these disorders, additional neurological features predominate the clinical presentation. Therefore, the focus of the following review will be on dementia associated with PD, DLB, PSP and CBD.

Dementia in parkinsonism is often referred to as a subcortical dementia [11]. In contrast to degenerative disorders with primary cortical involvement such as AD, higher cortical dysfunctions (e.g. aphasia or apraxia) are not an initial component of the disease process; they occur to a lesser extent at later stages. The aetiology of dementia in patients with extrapyramidal motor symptoms is still under investigation. Lewy body (LB) pathology is correlated with the development and severity of dementia in patients with PD and DLB [12, 13], even though additional Alzheimer pathologies can be found [14]. Thus, there is increasing evidence that the occurrence and severity of dementia is primarily related to cortical changes rather than to alterations of subcortical structures [15], therefore, the term subcortical dementia is not appropriate for these disease entities.

Neuropathological and imaging studies in patients with DLB and Parkinson's disease with dementia (PDD) have shown that a number of neurotransmitter systems are affected in the dementive process, including the cholinergic, the noradrenergic and the serotonergic systems [16–18]. In PD, dopaminergic therapy is a favourable therapy for movement symptoms but has limited effects on cognitive functions [19]. The disruption of frontostriatal circuits due to corrupted dopaminergic neurons may cause deficits in executive functions. This dopaminergic contribution may account for an improvement in attentional and frontal functions in patients with PD without dementia by dopaminergic medication [20]. Outside of the dopaminergic system, a cholinergic deficit is the most impressive finding in PDD and the most consistent correlate [16, 21]. In this context, the American Academy of Neurology recently made a recommendation for the use of the cholinesterase inhibitors (ChEIs) rivastigmine and donepezil in the treatment of PDD [22]. Moreover, a cholinergic deficit is also associated with memory decline in DLB [23]. Reduction in choline acetyltransferase activity has not only been found in the basal forebrain in AD but also in DLB, notably in the nucleus basalis of Meynert [16]. In PSP, selectivity for cholinergic lesions led to the suggestion that cholinergic

stimulation is a favourable medicinal option. Several cholinergic regions, basal forebrain, basal ganglia, and mediodorsal thalamic nuclei, are affected, while the cortical neurons and other neurotransmitter systems are relatively spared [24]. Muscarinic blockade with low doses of scopolamine worsens memory and gait function in PSP patients [25]. Furthermore, acetylcholinesterase activity measured in lumbar cerebrospinal fluid of patients with PSP is significantly reduced by 31% relative to healthy controls [26]. Reduction of cholinergic activity is also reported in patients with CBD [27].

This review on the one hand summarizes the specific symptoms of dementia in different parkinsonian syndromes. On the other hand, it critically questions as well as compares the effect of cholinergic treatment on cognitive functions in each patient group. Initial studies indicate that treatment with ChEIs might be more beneficial for patients with PDD and DLB than for patients with AD [28–30]. The results among the studies investigating the effect of cholinergic treatment in patients with PDD are controversial and inconsistent across the individual syndromes.

Methods

To find relevant studies for treatment with ChEIs in patients with PDD, DLB, PSP and CBD, a search in Medline/PubMed and the Cochrane Database was performed (key words: Parkinson's dementia or dementia with Lewy bodies or corticobasal degeneration or progressive supranuclear palsy combined with each of the terms ChEI, rivastigmine, donepezil, tacrine, galantamine and physostigmine). Previous reviews [31–36] also served as basis for literature search.

Inclusion/Exclusion Criteria

Studies restricted to PDD, DLB, PSP and CBD in human subjects up to February 2006, which used at least 1 of the following ChEIs, were reviewed: rivastigmine, donepezil, tacrine, galantamine or physostigmine. Randomized controlled trials, non-randomized controlled trials and open-label studies were included. Only articles focusing primarily on treatment effects on cognition in demented patients were chosen and the presentation of the results had to be either based on a standardized scale, which measures global cognitive decline, or had to include at least the testing of memory function. Therefore, 3 articles were excluded from the review process [37–39]. In addition, studies which either focused only on subgroups of study samples for data analysis [40], or did not report numerous results of cognitive scales [41], or applied the drug only once [25] were excluded from further analysis.

Classification of Evidence

Each article was assigned by 1 reviewer (I.L.) to an a priori defined class of evidence (table 1) adapted from criteria proposed by the American Academy of Neurology. Recommendation for a

therapeutic ‘effective’ intervention was made if at least 2 consistent class I studies in a representative population reported positive treatment effects. Rating as ‘probably effective’ required at least 1 representative class I or 2 positive class II studies. Use of ChEIs was defined as ‘possibly effective’ if 2 consistent studies in a representative population with evidence level III were reported or 1 class II study.

Data Extraction

For comparison of study outcome, the focus was on the frequently used Alzheimer’s Disease Assessment Scale, cognition subscale (ADAScog), and the Mini-Mental State Examination (MMSE) or, if these scales were not used, on other standardized scales for the measurement of global cognitive decline or memory function (e.g. Mattis Dementia Rating Scale). Besides treatment effects on cognition, a worsening of parkinsonian syndromes, the occurrence of other side effects, changes of neuropsychiatric aspects and improvement of activities of daily living (ADL) were looked for. Studies interpreting different aspects of the same study population mentioned beforehand were reported but only counted once for therapeutic recommendation.

Parkinson’s Disease with Dementia

Patients with PD have a 5- to 6-fold higher risk for developing dementia than age-matched control subjects without PD [42, 43]. Possible risk factors for PDD are older age, severe motor signs, depression, less L-dopa responsiveness and the occurrence of hallucinations in the disease course [44, 45].

Cognitive deficits are often associated with PD, although these deficits may be relatively subtle and not clinically apparent. Patients with PD without dementia have poor performance in frontal sensitive tasks including verbal fluency, problem solving and set shifting [46, 47]. Especially attentional deficits and disturbances in visuopraxis tests are among the first cognitive domains to show deterioration in PD. Impairment in memory tests affects mainly the retrieval of learned information [48–50]. In PDD, these deficits are much more pronounced and influence the ADL [51].

The neurobiological mechanisms of dementia in PD are still under discussion. It has been questioned whether LB or AD pathology is the primary contributor to PDD [52]. Recent studies imply that neurodegeneration in PD ascends from the brainstem to the cerebral cortex [53]. This observation of a pathogenic process comprising the whole brain gives valuable information about the development of non-motor symptoms. Furthermore, an individual patient’s neuropathological stage of PD has been suggested to be associated with their cognitive status [54]. The annual rate of brain atrophy has been corre-

Table 1. Classification of evidence

I	Prospective randomized controlled trial with: <div> a Clear and defined primary outcome b Clearly stated inclusion/exclusion criteria c Adequate accounting for dropouts and crossovers with numbers sufficiently low d Presentation of relevant baseline characteristics equivalent among different treatment groups or appropriate statistical adjustment for difference/reported appropriate baseline characteristics for each condition in crossover designs </div>
II	Prospective matched group cohort study with blinded outcome that meets all formerly mentioned quality criteria (see a–d above) or a randomized controlled trial in a representative population that lacks one of these criteria
III	Controlled trial, where outcome is independently assessed
IV	Evidence from uncontrolled studies

lated to global cognitive decline in patients with PD [55], whereas structural cortical changes may be heterogeneous in PDD [56–58]. In addition, PET data showed that cholinergic dysfunction was much stronger in PDD than in non-demented PD [17], and is correlated with performance in tests of working memory and attention [59]. These results support the assumption that treatment with ChEIs might be beneficial for patients with PDD.

Treatment with ChEIs in Patients with PDD

Number of Studies and Patients Enrolled according to the Evidence Classification

We reviewed 3 studies with level I of evidence [60–62], 1 randomized double-blind study [63] classified as level III of evidence (explanation see below), 1 controlled trial [64] and 7 open-label studies [65–71] which examine the effect of ChEIs on cognition in PDD (tables 2, 3). Except for 3 studies [63, 68, 69], the criteria for study inclusion were in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. PD was mostly diagnosed according to the UK Brain Bank criteria [60, 63–67, 69, 70] or established depending on the appearance of clinical core symptoms of PD [61, 62, 68].

Effect of Treatment with ChEIs in PDD

Information of stable coexisting dopaminergic medication was given in 1 class I study using rivastigmine [60]

Table 2. Studies investigating the effect of cholinesterase inhibitors on cognitive deficits in PDD

Authors	Level of evidence	Drug	Patients			Drop-out, %	Procedure and duration		Mean dose mg/day
			n	mean age, years					
Emre et al. [60], 2004	I	rivastigmine	dr. plac.	362 179	73 72	27 18	treatment:	24 weeks	8.6
Poewe et al. [66], 2005 (further analysis of study population by Emre et al. [60], 2004)	(IV)	rivastigmine	RCT OL	(see above) 334	72	18	RCT: OL:	(see above) 24 weeks	7.9
Giladi et al. [67], 2003	IV	rivastigmine		28	75	29	treatment: washout: withdrawal:	26 weeks 2 weeks 6 weeks	7.5
Reading et al. [70], 2001	IV	rivastigmine		15	71	20	baseline: treatment: withdrawal:	10 weeks 14 weeks 3 weeks	8.0
Ravina et al. [62], 2005	I	donepezil	dr./plac. plac./dr.	11 11	75 72	8 9	treatment: washout: crossover design	2 × 10 weeks 6 weeks	10
Aarsland et al. [61], 2002	I	donepezil	dr./plac. plac./dr.	8 6	71	25 0	treatment: crossover design	2 × 10 weeks	9.6
Leroi et al. [63], 2004	III	donepezil	dr. plac.	7 9	71 66	57 22	treatment: withdrawal:	18 weeks 12 weeks	6.4
Thomas et al. [64], 2005	III	donepezil	DLB PDD	30 40	75 71	0 15	treatment:	20 weeks	9.5
Minett et al. [69], 2003	IV	donepezil	PDD DLB	15 9	not stated	27 11	treatment: withdrawal: recommencement:	20 weeks 6 weeks 3 months	not stated 5–10
Werber et al. [71], 2001	IV	donepezil/ tacrine	donepezil tacrine	4 7	75	0 0	treatment:	26 weeks	donepezil: 6.5 tacrine: 100
Hutchinson and Fazzini [68], 1996	IV	tacrine		7	74	0	treatment:	2 months	60
Aarsland et al. [65], 2003	IV	galantamine		16	76	19	treatment:	8 weeks	8

dr. = Drug; plac. = placebo; RCT = randomized controlled trial; OL = open-label study.

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and 2 trials with donepezil [61, 63]. Therefore, the effect of cholinergic treatment in these trials cannot be attributed to changes in antiparkinson medications in these trials. Medication affecting the cholinergic system [60–62, 64, 65, 67, 69, 70] or drugs which influence cognition [60, 65, 68, 69] were mostly withdrawn before the treatment phase.

The treatment effect on cognition in randomized controlled trials was beneficial but small. Emre et al. [60] investigated a large sample (n = 541) and found a significant increase of approximately 1 point on the MMSE as well as 2 points on the ADAScog after 24 weeks of medication with rivastigmine. Furthermore, a significant im-

provement in ADL scales, the global clinical impression score and in the global score of the neuropsychiatric inventory (NPI) was measured under drug condition. Patients in the placebo group (15.6%) reported less frequent worsening of parkinsonism (mainly tremor) than patients treated with rivastigmine (27.3%), whereas no significant difference was measured by the Unified Parkinson's Disease Rating Scale (UPDRS). With rivastigmine, side effects, e.g. nausea, vomiting and dizziness, were more frequently reported than with placebo medication; the amount of serious adverse events was similar in both groups (13.0 placebo vs. 14.5 rivastigmine). A secondary study of Emre et al. [60] in 334 participants with open-

Table 3. Treatment effect of ChEIs on cognition and parkinsonian symptoms in PDD

Authors	Mean cognition ± SD at				Sig-nifi-cance	Effect on parkinsonian symptoms	Other side effects	
	baseline		follow-up after treatment phase					
Emre et al. [60], 2004	ADAScog drug	23.8 ± 10.2	ADAScog drug	21.7 ± 8.2	***	frequency of worsening of symptoms drug 27.3% placebo 15.6% (tremor and other symptoms) no change in UPDRS	frequency of adverse events	
	placebo	24.3 ± 10.5	placebo	25.0 ± 7.5	n.s.		drug 13.0%	
	MMSE drug	19.5 ± 3.8	MMSE drug	20.3 ± 3.8	*		placebo 14.5%	
	placebo	19.2 ± 4.0	placebo	19.0 ± 3.5			(nausea, vomiting, dizziness, hallucinations, orthostatic hypotension, etc.)	
Poewe et al. [66], 2005	ADAScog drug	23.8 ± 10.2	ADAScog differences drug/OL 2.0 ± 7.3		n.t.	frequency of worsening of symptoms OL 18.0% (slight changes in UPDRS)	frequency of adverse events	
	placebo	24.3 ± 10.5	placebo/OL 2.2 ± 8.2				OL 75.4%	
	MMSE drug	19.5 ± 3.8	MMSE differences drug/OL 1.2 ± 4.0				(nausea, vomiting, tremor, falls, confusional state, hallucinations, etc.)	
	placebo	19.2 ± 4.0	placebo/OL 1.7 ± 3.5					
Giladi et al. [67], 2003	ADAScog MMSE	30.8 ± 12.8 20.5 ± 5.1	ADAScog MMSE	23.5 ± 15.0 21.9 ± 5.4	** n.s.	frequency of worsening of symptoms tremor 39%	frequency of symptoms 60.7% more than 1 sign (salivation, confusion, nausea, generalized weakness, hyperhydrosis, diarrhea, etc.)	
Reading et al. [71], 2001	MMSE	20.8 ± 5.4	MMSE	25.4 ± 3.5	**	no change in UPDRS	not stated	
Ravina et al. [62], 2005			ADAScog drug	22.5 ± 6.9	n.s.	no change in UPDRS	frequency of adverse events	
			placebo	24.4 ± 9.4			drug 52.0%	
			treatment effect	-1.9	*		placebo 45.0%	
			MMSE drug	24.5 ± 3.2			(psychosis, agitation, nausea, etc.)	
			placebo	22.5 ± 4.7				
			treatment effect	2.0				
Aarsland et al. [61], 2002			MMSE drug	22.8 ± 3.7	*	no change in UPDRS	frequency of adverse events	
			placebo	21.0 ± 5.0			drug 71.0%	
							placebo 75.0%	
							(dizziness, sweating, salivation, nausea, headache, etc.)	
Leroi et al. [63], 2004	MMSE drug	26.0 ± 2.4	MMSE drug	25.3 ± 3.8	n.s.	no change in UPDRS	frequency of adverse events	
	placebo	25.4 ± 3.3	placebo	25.6 ± 3.8			drug 71.4%	
							placebo 44.4%	
							(acute diplopia, lightheadedness, etc.)	
Thomas et al. [64], 2005	MMSE DLB	17.7	MMSE DLB	21.6	n.s.	no change in UPDRS	frequency of adverse events	
	PDD	18.3	PDD	21.5			hypersalivation 24%	
							nausea/vomiting 18%	
							urinary frequency 15%	
							more lachrymal secretion 15%	
Minett et al. [69], 2003	MMSE PDD	17.5	MMSE PDD	21.3	**	no change in UPDRS	frequency of adverse events	
	DLB	15.8	DLB	19.9	**		nausea 29%	
							hypersalivation 29%	
							tremor 29%	
							cramps 25%	
Werber et al. [71], 2001	ADAScog MMSE	32.6 ± 14.3 18.6 ± 2.7	ADAScog MMSE	29.4 ± 6.0 19.9 ± 3.3	* n.s.	no change in SPES	(nausea, anorexia and dizziness)	

Table 3 (continued)

Authors	Mean cognition $\pm$ SD at				Sig-nifi-cance	Effect on parkinsonian symptoms	Other side effects	
	baseline		follow-up after treatment phase					
Hutchinson and Fazzini [68], 1996	MMSE	16.6 $\pm$ 2.4	MMSE	23.7 $\pm$ 1.5	***	improvement in UPDRS, no change in motor scores	not stated	
Aarsland et al. [65], 2003	MMSE	18.5 $\pm$ 7.1	MMSE	20.8 $\pm$ 5.4	n.s.	improvement 46.2% no change 30.8% deterioration 23.1%	<i>frequency of adverse events</i> 73.5% (vomiting, tremor, anorexia, nausea, gastrointestinal side effects, sedation, headache)	

OL = Open-label study; SPES = Short Parkinson Evaluation Scale; n.t. = not statistically tested; n.s. = test difference statistically not significant; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

label treatment of rivastigmine for 24 weeks showed nearly comparable test performance to baseline testing after 1 year, which was not statistically pointed out [66].

Efficacy of treatment with donepezil was explored in 3 double-blind randomized controlled trials. Ravina et al. [62] examined 22 patients treated 10 weeks with each donepezil and placebo in a randomized order. Improvement in the MMSE (2 points) and of global clinical impression, but not in the ADAScog and in the behavioural scales, was addressed after application of a daily dose of 10 mg donepezil. The frequency of adverse side events of treatment (52%) and placebo (45%) phases did not differ and worsening of parkinsonian syndrome did not occur. Another class I study with donepezil [61] but a low patient number also supports this beneficial effect on cognition. Reduction of psychiatric symptoms was not found. Seventy-one percent of patients reported some adverse side effect with placebo treatment and 75% with the verum, with no statistical difference between the groups. Still there was a tendency that patients reported more specific adverse events like nausea, headache and salivation under the drug condition. In contrast to these consistent outcomes of class I studies, Leroi et al. [63] did not support these positive results under donepezil treatment, which is probably a cause of inconsistent criteria for the diagnosis of dementia and low patient numbers included. In addition, there may also be the possibility of testing bias due to a high rate (57%) of dropouts under drug medication [63]. Open-label studies on average achieved greater differences between medication and placebo in test scores but still have the problem of an uncontrolled placebo effect and testing bias.

There is evidence that medication with the ChEIs rivastigmine or donepezil is moderately effective to enhance cognitive function in PDD. In addition, rivastigmine seems to be probably effective in the treatment of behavioural disturbances and ADL function, but further proof of these aspects is needed [60, 66]. As the sample sizes in the studies using donepezil were small, varying between 14 and 22 patients, the results need to be verified in future studies. However, the crossover design used in the donepezil trials requires fewer subjects than the parallel group structure [72]. Adverse side effects did not primarily worsen parkinsonian syndromes but affected mainly the gastrointestinal system (e.g. nausea, vomiting). Taken together, there is a tendency to a higher dropout rate under medication relative to placebo in 1 trial using rivastigmine [60] and 1 study with donepezil [63]. Presently, there are no controlled studies using the ChEIs galantamine and tacrine so that the effectiveness of these ChEIs cannot be evaluated. The first results of open-label trials indicate that beneficial treatment effects with galantamine and tacrine could be supposed.

Dementia with Lewy Bodies

The central clinical features required for the diagnosis of DLB are progressive cognitive decline that interferes with normal social and occupational function, fluctuation in cognition, recurrent visual hallucinations and/or parkinsonian motor disabilities. The phenomenon of fluctuations in DLB includes both sleepiness and altered arousal. The rapid eye movement sleep behaviour disorder is present in nearly half of the DLB patients and

often a preclinical sign of the disease [73]. Other supportive diagnostic features are repeated falls, syncope, neuroleptic sensitivity, hallucinations in other modalities and depression [74]. As the criteria for DLB are highly specific but the sensitivity of the diagnosis seems to be low [75], the guidelines for the diagnosis of DLB were recently modified [76]. The most common misdiagnosis of DLB is AD [77]. Furthermore, PDD and DLB are 2 syndromes with overlapping clinical symptoms and both diseases are neuropathologically characterized by LB disease [78]. In contrast, additional AD pathology is much more frequent in DLB than in PDD, and LBs are more pronounced in the temporal cortex in DLB [12, 79]. The clinical discrimination to PDD has been set by convention using the time criteria of occurrence of motor symptoms [76].

Cognitive functions of DLB patients are impaired in all areas of cognition and show high variability [80, 81]. Prominent memory impairment may not necessarily occur in the early stages. Rather performance in attentional and visuospatial tasks as well as tests of executive functions are disturbed [82–84]. Nevertheless, memory impairment is usually evident with progression of the disease. Although there are some hints that the neuropsychological test profile may differ between DLB and AD [76, 83], DLB can be suspected but not diagnosed with certainty on the basis of a cognitive profile alone.

Limbic and cortical LB are associated with cognitive decline, both in DLB and PDD [85]. Additionally, it has frequently been demonstrated [86, 87] that in many cases the pathology of DLB involves a combination of LB and AD pathological features (β -amyloid depositions and diffuse plaque formation).

Compared to AD, hippocampal and medial temporal lobe atrophy are less pronounced in DLB [88]. However, the global rate of brain atrophy is similar in patients with DLB and patients with other aetiologies of dementia [89]. Patients with DLB suffer from perfusion deficits in the parietal and frontal regions of the brain [90], as do patients with AD [91]. In contrast to AD, occipital hypoperfusion and hypometabolism are found in patients with DLB [92–95]. As we know from DaT-SCAN SPECT, the nigrostriatal dopaminergic function is more severely impaired in patients with DLB compared to patients with AD [96] but does not differ from patients with PD [97].

DLB patients have a pronounced dysfunction of the cholinergic neurotransmitter system which is even greater than that seen in patients with AD [16, 98]. Cholinergic activity is lower in DLB patients with compared to those without hallucinations, which suggests that also hallucinations

might be reduced after therapeutic intervention with cholinergic agents [99–101]. Management of DLB includes an accurate diagnosis, identification of target syndrome, as well as non-pharmacological and pharmacological intervention [102].

Treatment with ChEIs in Patients with DLB

Number of Studies and Patients Enrolled according to the Evidence Classification

We found 1 study that fulfilled the criteria of evidence class I [103], 1 class III study [104], 3 open-label trials that statistically compared the test performance of different patient groups [30, 64, 105] and 3 [106, 107] open-label studies (table 4). Wesnes et al. [108] published a supplementary analysis of the trial of McKeith et al. [103], and 2 open-label follow-up examinations [109, 110] included patients of this large study sample. In all trials, diagnosis was made in accordance with the consensus guidelines of the consortium on DLB obtained at an international workshop [111]. Neuroleptics and anticholinergic agents before or during the treatment phase were not allowed in 5 studies [69, 103, 105, 108, 109], while psychotropics were allowed to be continued in 2 trials [30, 64].

Treatment with ChEIs in DLB

McKeith et al. [103] carried out a randomized double-blind multicenter study with a representative sample size ($n = 120$). Although the slight improvement in the MMSE score of patients treated with rivastigmine compared to the placebo group did not reach significance (table 5), there was a significant reduction in some behavioural domains of the NPI, e.g. apathy, indifference, anxiety or delusions. Comparison of performance on a computerized cognitive assessment system (Cognitive Drug Research) revealed positive changes superior to baseline performance in tests of attention and memory after the drug phase, which decreased to baseline level shortly after withdrawal [108]. More patients on rivastigmine (55.0%) than on placebo (46.8%) had adverse events [103]. However, the frequency of severe adverse events was comparable between the drug and placebo groups. The side effects were predominantly gastrointestinal in nature (e.g. nausea, anorexia, diarrhoea). There was no change in comparison to baseline and placebo in the motor section of the UPDRS after intervention with rivastigmine, whereas patients with severe extrapyramidal symptoms were excluded from the trial due to the risk of worsening of parkinsonism. Performance in cognition after nearly

Table 4. Studies which investigate the effect of ChEIs on cognitive deficits in DLB

Authors	Level of evidence	Drug	Patients			Dropout %	Procedure and duration		Mean dose mg/day
			n		mean age, years				
McKeith et al. [103], 2000	I	rivastigmine	drug placebo	59 61	74 74	31 16	treatment: withdrawal:	20 weeks 3 weeks	9.4
Wesnes et al. [108], 2002 (further analysis of study population by McKeith et al. [103], 2000)	(I)	rivastigmine	drug placebo	59 61	74 74	31 16	treatment: withdrawal:	20 weeks 3 weeks	9.4
McKeith et al. [103], 2000 (members of study population by McKeith [103], 2000)	(IV)	rivastigmine		11	79	0	treatment:	12 weeks	9.6
Grace et al. [110], 2001 (members of study population by McKeith et al. [103], 2000)	(IV)	rivastigmine		29	76	31	treatment:	96 weeks	not stated 3–12
Grace et al. [107], 2000	IV	rivastigmine		6	75	0	treatment:	12 weeks	not stated
Beversdorf et al. [104], 2004	III	donepezil		7	65	14	treatment: placebo: crossover inter-mixed design	2 × 4 weeks 2 × 4 weeks	5
Thomas et al. [64], 2005	III	donepezil	DLB PDD	30 40	75 71	0 15	treatment:	20 weeks	9.5
Samuel et al. [30], 2000	III	donepezil	DLB AD	4 12	80 76	0 0	treatment:	6 months	5
Minett et al. [69], 2003	IV	donepezil	PDD DLB	15 9	not stated	27 11	treatment: withdrawal: recommencement:	20 weeks 6 weeks 3 months	not stated 5–10
Querfurth et al. [105], 2000	III	tacrine	DLB AD	6 6	79 75	17 0	treatment:	24 weeks	80
Edwards et al. [106], 2004	IV	galantamine		25	76	8	treatment:	12 weeks	not stated 8–24

2 years of treatment with rivastigmine was not superior to baseline performance, although no significant deterioration within this time period occurred [110]. In addition, further open-label studies did not characterize improvement on cognitive functions due to rivastigmine in DLB patients [107, 109].

Beversdorf et al. [104] designed a double-blind, double-crossover study (class III, no exclusion criteria and baseline characteristics reported) with the ChEI donepezil in a small group of 7 patients. In spite of the short treatment phase (4 weeks), MMSE and ADAScog scores were significantly more improved after donepezil than after placebo medication, about 2 points each. Functional ability did not improve, neither did achievement of verbal fluency or visuospatial functions. Information concerning side effects was not given. Another class III study compared the performance of patients with PDD

and DLB. The magnitude of improved global cognition and reduced behavioural disturbances did not differ in these disease entities [64]. However, the MMSE score increased by about 4 points after 20 weeks of treatment with donepezil. Samuel et al. [30] reported a 5-fold higher increase in the MMSE score in DLB compared to AD after a 6 months of application of donepezil. However, limitations of the study are the small number of patients with DLB ($n = 4$) and the additional vascular brain defects (lacunes) in 3 of 4 DLB patients. Minett et al. [69] conducted an open-label study and found a significant improvement in the MMSE score (+ 4.1 points). Overall changes of psychiatric symptoms (total NPI score) were not noted, but hallucination, depression and anxiety were affected by medication. Frequently reported adverse events were tremor, vomiting and hypersalivation.

Table 5. Treatment effect of cholinesterase inhibitors on cognition and Parkinsonian symptoms in DLB

Authors	Mean cognition ± SD at				Signifi- cance	Effect on parkinsonian symptoms	Other side effects	
	baseline		follow-up after treatment phase					
McKeith et al. [103], 2000	<i>MMSE</i> drug placebo	17.9 ± 4.7 17.8 ± 4.4	<i>MMSE</i> drug placebo	18.4 17.7	n.s.	no change in UPDRS	<i>frequency of adverse events</i> drug 54.9% placebo 46.8% (nausea, vomiting, anorexia, somnolence)	
Wesnes et al. [108], 2002 (further analysis of study population by McKeith et al. [103], 2000)	<i>CDR: overall quality of memory</i> drug placebo	1.8 1.8	<i>CDR: Overall quality of memory</i> drug placebo	1.9 1.6	*	not stated	not stated	
Mc Keith et al. [103], 2000 (members of study population by McKeith et al. [103], 2000)	MMSE	18.9 ± 5.1	MMSE	19.6 ± 5.1	n.s.	reduction in UPDRS score	no severe adverse side effects occurred (nausea and diarrhoea)	
Grace [110], 2001 (members of study population by McKeith et al. [103], 2000)	MMSE	19.2	MMSE	15.5	n.s.	no change in UPDRS	not stated	
Grace et al. [107], 2000	MMSE	18.5	MMSE	23.0	n.t.	not stated	not stated	
Beverdort et al. [104], 2004	ADAScog MMSE	25.4 ± 20.1 18.7 ± 10.7	<i>ADAScog</i> drug placebo <i>MMSE</i> drug placebo	23.5 ± 18.1 27.2 ± 19.2 20.7 ± 7.4 19.0 ± 8.6	* *	no change in UPDRS	not stated	
Thomas et al. [64], 2005	<i>MMSE</i> DLB PDD	17.7 18.3	<i>MMSE</i> DLB PDD	21.6 21.5	n.s.	no change in UPDRS	<i>frequency of adverse events</i> hypersalivation 24% nausea/vomiting 18% urinary frequency 15% more lachrymal secretion 15%	
Samuel et al. [30], 2000	<i>MMSE</i> DLB AD	20.5 ± 3.1 19.6 ± 4.1	<i>MMSE</i> DLB AD	25.3 20.1	*	not stated	not stated	
Minett et al. [69], 2003	<i>MMSE</i> PDD DLB	17.5 15.8	<i>MMSE</i> PDD DLB	21.3 19.9	** **	no change in UPDRS	frequency of adverse events nausea 29% hypersalivation 29% tremor 29% cramps, etc. 25%	
Querfurth et al. [105], 2000	<i>DRS</i> DLB AD	93.8 ± 19.8 113.7 ± 8.7	<i>DRS</i> DLB AD	77.0 ± 47.7 106.3 ± 9.9	n.s. (n.s) (*)	worsening of parkinsonism	not stated	
Edwards et al. [106], 2004			ADAScog change MMSE change	−2.8 1.6	n.s. *	no change in UPDRS	frequency of adverse events (nausea, vertigo, anorexia, dyspepsia, etc.)	48.0%

DRS = Mattis Dementia Rating Scale; CDR = Cognitive Drug Research computerized attention battery; n.s. = test difference statistically not significant; n.t. = not statistically tested; * $p < 0.05$, ** $p < 0.01$.

Querfurth et al. [105] did not confirm a superior treatment effect of tacrine in patients with DLB. However, 1 open-label study that investigated the treatment effect of galantamine [106] reported a significant improvement in the MMSE and in 4 subscales of the NPI (delusion, hallucination, apathy and depression) after 12 weeks of medication. Further controlled trials in a representative study sample for the evaluation of the treatment effect of tacrine and galantamine are needed.

First results in DLB show only slight improvement of cognitive dysfunction due to treatment with rivastigmine. However, ChEIs are probably effective in the reduction of behavioural disturbances. Only one third of all studies focused on safety analysis [103, 106, 109]. There, adverse side events tended to be more frequent in patients treated with rivastigmine than with placebo. In addition, treatment with ChEIs can cause hypersalivation, hypertension and falls in patients with DLB [102]. Worsening of parkinsonian symptoms did not occur after 20 weeks of blinded drug treatment [103, 104], which is supported by most of the open-label trials [64, 69, 106, 109, 110].

Progressive Supranuclear Palsy

PSP is characterized by mostly asymmetrical parkinsonism, postural instability, supranuclear vertical gaze palsy, axial rigidity with abnormal posturing of the neck, frontal lobe syndrome and dementia [112, 113]. Personality changes occur frequently in the disease course, particularly apathy and disinhibition. Approximately 40–50% of the patients have signs of depression [114] and sleep disturbances [115]. Occurrence and severity of depression, however, seem to be independent of the cognitive state [116].

Cognition is not necessarily disturbed in PSP but dementia occurs in more than 50% of patients. Usually, executive functions are most severely affected [117, 118]. Patients have slowed information processing and motor execution, affected long-term memory, limited attentional resources and difficulties in planning and problem solving as well as in set shifting [115, 119]. Breakdown in verbal memory is less pronounced than in AD [120]. On the other hand, phonematic and semantic fluency are severely disturbed and more affected than in patients with PD or multiple system atrophy [121, 122]. Although limb apraxia is an important diagnostic sign of CBD, it is also found in patients with PSP [123]. Apraxia is predominantly classified as ideomotor apraxia [124, 125] and associated with dementia [126].

PSP is a sporadic neurodegenerative disorder, neuropathologically defined as a tauopathy with prominent subcortical and cortical neurofibrillary degeneration [127]. The exact aetiology of tau pathology in PSP is unknown. First studies show pathologic tau composed of aggregated 4-repeat (E10+) tau isoforms that accumulate in neurons and glia in subcortical and cortical areas [128]. Cortical tau aggregation is mainly found in the motor and the frontal cortex [129–131]. The amount of frontal lobe atrophy and the existence of cortical tau pathology in PSP patients are suggested to be associated with behavioural changes and dementia [132–134]. However, subcortical changes are traditionally considered to play a decisive role in the development of cognitive loss in PSP [135].

Treatment with ChEIs in Patients with PSP

PSP progresses inevitably and presently there is no effective therapy [136]. Cholinergic dysfunction is related to changes of cortical and subcortical neurotransmitter systems (for review see [34]). Therefore, it has been proposed that cholinergic treatment can be helpful for symptoms related to cholinergic dysfunction in PSP patients. However, there are also studies that failed to show any abnormalities in cholinergic cortical activity in contrast to PD [137, 138].

Treatment with Physostigmine in PSP Patients

Two double-blind, placebo-controlled crossover studies investigated the effect of physostigmine, a short-acting ChEI, on cognition in PSP. Due to lack of information concerning the methodological background, both articles have to be rated as class III studies. Litvan et al. [139] included 8 patients (median age: 64 years) who received 0.5–2.0 mg of physostigmine 6 times a day for 10 days. Diagnosis of dementia was based on the criteria of the revised third edition of the DSM. Improvement in long-term memory was assessed, but no change in the performance of short-term memory functions was noticed. Drug-induced improvement in cognition correlated with global motor impairment, which indicated that only the less impaired PSP patients respond to physostigmine stimulation. Worsening of motor performance or other side effects was not seen after treatment with physostigmine. Moreover, the levels of acetylcholine in the cerebrospinal fluid (CSF) did not change during drug administration. Blin et al. [140] examined the influence of physostigmine on neuropsychological test performance and

on changes in FDG-PET in 6 PSP patients aged 68–74 years. Both physostigmine and placebo infusions were given for the duration of one week, each in randomized order. Some improvement was noted in tasks of attention and memory. Brain glucose metabolism was altered in every brain region because of drug application. The transfer of glucose from blood to brain was increased with physostigmine from 8% in the frontal cortex to 32% in the thalamus. Motor symptoms were not modified between drug and placebo phases. No severe adverse events were recorded.

The Efficacy of Donepezil in PSP

Two studies investigated treatment effects of longer acting ChEIs, both with the ChEI donepezil. One [141] double-blind placebo-controlled randomized crossover trial (level I of evidence) randomized 22 patients (mean age: 66 years). One patient dropped out before the treatment had started. The remaining 21 patients were treated for 6 weeks with placebo (11 patients) or with donepezil 10 mg/day (10 patients) and, after a 4-week washout phase, were treated for 6 weeks with the reverse medication. The deterioration in cognition of patients at baseline was only mild ($24 \leq \text{MMSE} \leq 30$). The trial was completed by all patients of the placebo group and by 8 patients treated with donepezil. Efficacy analyses revealed no significant changes in a broad range of standardized tests for memory, executive function, attention and behavioural aspects. A slight improvement was observed in two tests of memory function. On the other hand, a worsening in motor ADL occurred. Post-hoc testing marked an important influence of dopaminergic co-medication on ADL function and memory. Thus, in this study it was impossible to differentiate whether worsening in motor ADL function was primarily caused by insufficient drug medication or due to progression of parkinsonian syndromes. Litvan et al. [141] reported 3 patients who did not tolerate the full dose of donepezil because of considerable deterioration of motor functions. The frequency of diarrhoea was higher in the donepezil phase compared with the placebo period. One open-label trial (class IV) with 6 patients (mean age: 67 years) failed to show improvement of cognitive functions after 3 months of treatment with donepezil (10 mg/day) [142]. The neuropsychological performance at baseline ($18 \leq \text{MMSE} \leq 28$) was compared with that after the 3-month treatment phase, and no changes in cognition, motor scores and ADLs were found. No significant adverse events during the treatment phase with donepezil were stated.

In summary, in PSP the outcome of 1 class I study indicates a minor improvement in some but not all tests of memory function after treatment with donepezil. Therefore, the results are not unequivocal. Moreover, there is an increased risk of gastrointestinal side effects. The weak beneficial effect on memory functions was not supported in an open-label trial with a small sample size. Studies (class III) with the short acting ChEI physostigmine noted amelioration in memory and frontal sensitive tests. Unfortunately, the number of patients was very low in these 2 investigations. In addition, it is questionable whether the doses used in these studies were sufficient to have any central effect [26, 34]. Therefore, the level of evidence for treating PSP with donepezil and physostigmine is poor and needs further verification in studies with sufficient numbers of patients.

Corticobasal Degeneration

Patients with CBD may present with a wide range of different symptoms, which leads to poor diagnostic accuracy [143]. Clinical characteristics are asymmetric signs of parkinsonism, usually from the akinetic-rigid syndrome with or without tremor, and asymmetrical cortical signs [144, 145]. Similarly to PSP there is usually only little or no beneficial response to levodopa therapy [146]. Dystonia, dysarthria as well as alien limb phenomenon are common in CBD [147–150]. Abnormalities of eye movements may occur [151]. Most prominent, however, and helpful for differential diagnosis, is the occurrence of apraxia presented in up to 70% of patients with clinically diagnosed CBD [152]. Ideomotor and limb-kinetic apraxia are the most striking features of CBD [153, 154] and both forms of apraxia can be combined in the same limb [123].

Dementia is one of the most common signs of pathologically confirmed cases with CBD [155, 156]. Cognitive deficits are present early in the disease course, sometimes even before the onset of motor symptoms [157]. Estimation of the dementia rate in patients with CBD varies between 25 and 100% [144, 156]. Cognitive symptoms in CBD share common clinical and pathological features with PSP and with fronto-temporal dementia (FTD) [158–160]. Impairments of frontal lobe functions, e.g. problems in set shifting [161] or reduced word fluency [162] as well as constructional apraxia are also usual findings in CBD [163, 164]. Impairment in handwriting occurs frequently and is not exclusively related to apraxia [165]. Episodic memory function disturbance seems to be

less severe than that seen in AD [166]. It is supposed that disturbances in episodic memory are caused by frontal rather than hippocampal loss of function [164]. However, further verification of this hypothesis is needed. Speech problems have been reported in CBD and it is now generally accepted that aphasia may either occur as one of the initial symptoms or in the course of the disease [157, 167]. Additionally, many patients suffer from neuropsychiatric disturbances like depression, apathy, irritability and agitation [168].

Atrophy in CBD is usually cortical and subcortical in nature. Loss of neurons and gliosis, especially astrocytic plaques, can be found in the pars compacta of the substantia nigra as well as in the brainstem and cerebral grey matter [145]. Cortical atrophy is mainly asymmetric and affects the superior parietal and frontal lobes with relative sparing of the temporal and occipital lobes associated with the presence of swollen achromatic cells and secondary degeneration of the corticospinal tracts [169, 170]. Studies of tau protein demonstrate that CBD shares a common genetic background with PSP and primary progressive aphasia [171, 172]. Cholinergic neuropathological changes in CBD have been found in the nucleus basalis of Meynert, as well as the dorsolateral tegmental and the pedunculopontine tegmental nuclei [27]. Reduction of cholinergic neurons and activity in the nucleus basalis of Meynert seem to be more pronounced than in PSP [27]. However, reports of treatment effects with ChEIs in patients with CBD are lacking. The symptomatology and neuropathology of CBD show great overlap with FTD [173]. Cases presenting with progressive aphasia and the behavioural variant of FTD frequently develop features of CBD [157] or had CBD neuropathology [158, 160]. Therefore, some authors claimed that CBD should be considered as part of the Pick complex [160]. One study examining the use of rivastigmine in FTD [174] gives rise to the expectation that treatment may reduce neuropsychiatric symptoms but does not primarily affect cognition.

Discussion

Up to now the aetiology of dementia in parkinsonian syndromes is only partly understood. The greatest similarity exists between DLB and PDD, where the classification of the diagnosis depends mainly on the sequence of appearance of symptoms [76]. In contrast to AD, reduction in cognition mostly concentrates on executive functions, and here especially on visuospatial functions, oc-

curing very early in the course of the disease. Neuropsychiatric symptoms are characteristic for dementia in parkinsonian disorders, particularly depression, hallucination, apathy, disinhibition and altered sleep behaviour.

In all the discussed disorders, PDD, DLB, PSP and CBD, the cholinergic system is affected [16, 27, 29, 34]. However, the benefit of ChEIs on dementia might differ between the different entities. ChEIs may be moderately effective to increase cognition in PDD and rivastigmine may reduce behavioural disturbances in these patients. Further verification of these aspects is needed. Varying treatment effects of ChEIs in these patient groups may be additionally caused by blockage of different cholinesterase subtypes (i.e. acetyl- and butyrylcholinesterase). The amount and relation of these 2 enzymes have been shown to change in the course of AD, and it may well be that a specific relation of these metabolizing systems may account for the different responses within PDD [175, 176]. Recently, the ChEI rivastigmine was authorized for the treatment of mild to moderately severe PDD. At present, there are only some hints of the beneficial effect of cholinergic treatment on cognition in DLB. However, behavioural aspects might be positively affected, which may increase the quality of the patient's life and reduce caregiver distress. Heterogeneity of patient samples is likely to be one reason for the lack of evidence of effects of treatment with ChEIs on cognition in DLB. The definition may include various subgroups of patients, e.g. patients with and without additional Alzheimer pathological cortical changes [102], which differ in severity and progression of the disease. Identification of clinical characteristics of patients and definition of subgroups that will respond well to ChEIs medication are needed. Furthermore, it can only be suggested that patients with PSP and cognitive disturbances did not benefit from use of ChEIs. Cognitive impairment in PSP has been attributed to prefrontal deafferentation and lesions and only secondarily to degeneration of the ascending cholinergic basal or striatal neurons [25]. In contrast, cognitive dysfunction may be related to impairment of the ascending cholinergic system [137], which can also cause diverse action of pharmacological intervention with ChEIs. Only studies with low patient numbers have been performed. A systematic study on cholinergic treatment in CBD has not been conducted.

When discussing the effect of ChEIs in parkinsonian syndromes associated with dementia, some key issues should be considered. (i) To date there are only few double-blind randomized placebo-controlled trials in a rep-

representative population. (ii) Improvements in the MMSE and ADAScog scores were about 2 points, which rises the question of clinical relevance and of subgroups which benefit most (or not) from medication. These scales also primarily focus on aspects of cognitive decline in AD; therefore, screening instruments which assess other core symptoms of dementia in parkinsonian syndromes are needed. These should also include improvement in clinical impression as in some class I studies [61, 62, 103] and in ADL function [60]. (iii) Although there is some data that ChEIs do not worsen parkinsonian motor symptoms in PDD and DLB, it is indispensable for future trials to concentrate on the exact registration of these adverse effects. Most side effects are gastrointestinal in nature (e.g. nausea, vomiting) and do not obviously differ between treatment and placebo group in class I studies, but there

was often a tendency of a higher patient dropout rate under drug medication. However, reported adverse events may be merely transient in duration and therefore inferior to the overall beneficial effect of ChEIs. (iv) Randomized controlled trials that directly compare different ChEIs in a representative population as well as the proof of long-term efficacy are still lacking and have to be investigated in future trials.

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