Role of Cholinesterase Inhibitors in Parkinson’s Disease and Dementia With Lewy Bodies

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ABSTRACT

This article reviews the cholinergic changes in Parkinson’s disease and dementia (PDD) and dementia with Lewy bodies (DLB), their potential clinical implications, and the available evidence for cholinesterase inhibitors in the treatment of PDD and DLB. Marked neuronal loss of cholinergic nuclei, reduced cholinergic markers in the neocortex, hippocampus, and selected thalamic nuclei, and receptor changes have been reported. One large and 2 small placebo-controlled trials and nearly 20 open-label studies suggest that cholinesterase inhibitors have a positive effect on cognition, psychiatric symptoms, and global function in patients with DLB and PDD. The treatment is well tolerated in most patients without any apparent worsening of extrapyramidal motor features. Given the high risk of severe sensitivity reactions and increased risk of cerebrovascular incidents during treatment with neuroleptics, more clinical trials of cholinesterase inhibitors are encouraged to establish their precise role in DLB and PDD. (J Geriatr Psychiatry Neurol 2004; 17:164-171)

Keywords: cholinesterase inhibitors; dementia with Lewy bodies; Parkinson’s disease; treatment

CHOLINERGIC DISTURBANCES IN PDD AND DLB

Cholinergic Markers

Loss of cholinergic neurons in the basal forebrain has been found in Parkinson’s disease and dementia (PDD) and dementia with Lewy bodies (DLB). A pronounced and significant neuronal loss in the nucleus basalis of Meynert as well as the septal forebrain areas was found by Whitehouse et al1 in PD and by Lippa et al2 in DLB. Extensive reductions of choline acetyltransferase (ChAT), a marker of cortical cholinergic activity, were found in all 4 cortical lobes in PD, and the degree of reduction of ChAT in the temporal lobe correlated with the degree of mental impairment in PD3 and DLB.4 The loss of cholinergic neurons in the basal forebrain is probably the principal pathological cause of impaired cortical cholinergic activity both in PDD3 and DLB.2 Most studies predate the publication of the DLB consensus guidelines,5 making firm conclusions of similarities or differences between DLB and PDD difficult. However, studies reported similar reductions of neocortical presynaptic cholinergic inputs in DLB and PDD, which may even exceed that of Alzheimer’s Disease (AD).6-8 The cortical cholinergic deficit in DLB was independent of the extent of Alzheimer-type pathology.4

In vivo studies have generally supported the results from autopsy studies. Presynaptic cholinergic terminal density in nondemented PD patients was mildly reduced (20%) compared to healthy controls in the parietal and occipital cortices in a SPECT (single photon emission computed tomography) study using a marker of vesicular acetylcholine transporter. PDD patients had extensive acetylcholine-transporter decrease similar to early-onset AD.10 In a PET (positron-emission tomography) study measuring cortical acetylcholinesterase (AChE) activity, the reductions in frontal, temporal, and parietal cortices as well as the right hippocampus were more pronounced.
The Role of Nicotinic Receptors and Butyrylcholinesterase in PDD and DLB

Butyrylcholinesterase (BuChE)

The available cholinesterase inhibitors (ChEIs) differ with regard to some interesting pharmacodynamic effects on the cholinergic system, most important their modulating effect on the nicotinic receptors and the BuChE inhibition. Together with AChE, BuChE is responsible for synaptic breakdown of acetylcholine, and the relative contribution of BuChE is increased in AD and other diseases with reduced cholinergic activity. In addition, BuChE contributes to breakdown of other neuromodulatory peptides, and may play an important role in the maturation of senile plaques in AD.

A highly significant association between temporal cortex BuChE activity and rate of cognitive decline was reported in a prospectively studied autopsy-confirmed DLB series. Few studies have addressed the role of BuChE in PDD. In one study, reduced BuChE cerebrospinal fluid levels, but not AChE levels, were associated with PDD. Taking these findings together, AChE and BuChE inhibitors, such as rivastigmine and tacrine, may have greater clinical efficacy in AD and other diseases with cholinergic deficits than agents solely inhibiting AChE, but clinical studies testing this hypothesis are not available yet.

Nicotinic Receptors

Neuronal nicotinic receptors consist of combinations of $\alpha$ and $\beta$ subunits, classified as $\alpha7$ or non-$\alpha7$ nicotinic acetylcholine receptor (nAChR) subunits. They are involved in presynaptic and postsynaptic modulation of neurotransmission of cholinergic and other neurotransmitters, including the dopamine system.

Cortical nicotinic receptor reductions have been reported in PD, DLB, and AD. The $\alpha7$ nAChRs were more reduced in the frontal cortex in DLB than in AD, and nicotinic sites in the striatum and thalamus were decreased in PD and DLB but not in AD. The reduction of nicotinic sites in the striatum was probably secondary to the extensive degeneration of dopaminergic nigrostriatal pathways in PD and DLB, since nicotinic receptors are located on dopaminergic nerve terminals and involved in the regulation of striatal dopamine release. Based on correlations between synapse loss, Ach, and nicotinic receptors, Reid et al suggested that the overall neuronal loss in DLB is predominantly cholinergic, in contrast to a less cholinergic-dominant neuronal loss in AD.

The clinical relevance of changes in nicotinic receptors is not yet clear. However, reductions of $\alpha7$ nAChR subunits in the temporal cortex were associated with visual hallucinations and delusional misidentifications in DLB patients, and disturbance of consciousness in DLB patients was associated with increased temporal binding of non-$\alpha7$ nAChRs. Preliminary evidence suggests that the changes in nicotinic receptor activity in PD and DLB may have potential treatment implications. A beneficial effect of nicotine on parkinsonism, cognition, attention, and sleep has been reported in some, but not all, placebo-controlled studies in PD.

In conclusion, specific disease-related changes of the nicotinic receptor system in PDD and DLB were reported, with some studies suggesting a relationship with key clinical symptoms and preliminary data suggesting clinical implications. ChEIs with an additional effect on the nicotinic receptors, such as tacrine and galantamine, may therefore be especially useful in patients with PDD and DLB. However, clinical studies comparing effects of different ChEIs are lacking, and available studies suggest similar efficacy among all ChEIs.

Cholinesterase Inhibitors in PD and DLB

For this review, we searched the Medline Database from 1966 to 2003 for “Dementia with Lewy bodies respectively Parkinson’s disease dementia” and combined these terms...
with cholinesterase inhibitors/tacrine/donepezil/rivastigmine/galantamine, and treatment effects/side effects/adverse events. Single cases or dual case reports or studies assessing the effect of more than one medication prescribed simultaneously (eg, ChEI and neuroleptics) were not considered. The papers found were read and their references examined to complete the list of references for the present review.

We found a total of 21 reports. Most studies were open-label studies or small case series. Only 1 parallel-group, randomized placebo-controlled trial with a reasonably large study population exists, a 24-week trial with rivastigmine in DLB. In addition, 2 small placebo-controlled studies with donepezil in PDD have been published. Structured assessment of cognition (usually Mini-Mental State Examination [MMSE]) and parkinsonism (Unified Parkinson’s Disease Rating Scale [UPDRS] or Hoehn & Yahr scale) and neuropsychiatric features (Neuropsychiatric Inventory [NPI]) were used in most studies. Large-scale multicenter randomized controlled trials of rivastigmine and donepezil are ongoing.

**ChEI in PD**

Twelve studies were found reporting the use of a ChEI in patients with PD (donepezil, 6 studies; rivastigmine, 3 studies; galantamine, 1 study; tacrine, 1 study; and 1 study reported patients on tacrine and donepezil) (Table 1). There were 2 placebo-controlled studies (1 crossover study and 1 parallel-group study), 8 open-label studies, and 2 clinical case series. Outcome measures were cognition (4 studies), visual hallucinations (1 study), or both (7 studies).

The total number of patients included was 144, with a mean age of 72.4 (SD 3.2) years. Most studies included demented PD patients, but in 2 studies, nondemented patients with visual hallucinations and/or delusions or with cognitive impairment or dementia were included. The median (range) of the study-means of disease duration was 10 (5-13) years, of MMSE score 20 (17-26), and of Hoehn & Yahr stage 3 (2.4-4.4). Median duration of treatment was 12 weeks (6-26).

Improvement in cognition was found in 10 studies. In 5 studies, improvement of MMSE after treatment was statistically significant. The median and mean (SD) over the study mean improvement on MMSE were 2.1 and 2.3 (2.4), respectively, with a wide range from a mean worsening of 0.7 point to a mean improvement of 7.1. In some studies, very pronounced individual responses were reported. Head-to-head comparison of different ChEIs have not been done yet, and it is thus not possible to disentangle the different effects of ChEIs involved.

Six studies reported the proportion of patients with visual hallucinations who responded to treatment. Of 37 patients with hallucinations, 34 (92%) improved, and in several patients a marked improvement or even complete remission was reported.

Most studies reported no effect on parkinsonism, and worsening of parkinsonism was a rare side effect. Marked improvement of parkinsonism in some patients was found in studies with tacrine and galantamine. In all reports, cholinergic drugs were well tolerated, but 26 patients discontinued treatment, 22 of these (85%; 15% of the total population studied) owing to side effects, most commonly gastrointestinal events or worsening of motor features. Worsening of psychosis and confusion were rarely observed.

**ChEI in DLB**

Nine studies (1 placebo controlled, 6 open studies, and 2 case series) assessed the efficacy of ChEI in patients with DLB (2 donepezil, 4 rivastigmine, 2 tacrine, 1 galantamine) (see Table 2). The total number of DLB patients included was 250. The median (range) of the study-means of baseline MMSE score was 19 (17.9-20.5) and of median treatment duration was 16 weeks (12-96). To be comparable with the other studies, we used effects reported after the first 24 of 96 weeks of the only long-term study.

Seven studies reported cognitive improvement, and 2 studies found no cognitive change during treatment with ChEI. Of the 6 studies assessing MMSE changes, 3 studies revealed significant changes, and in no study MMSE reported deteriorated during the treatment period. Median MMSE improvement was 2.7 (0.7-4.8). One of the studies, which found no treatment effect of ChEI, used a low dose of tacrine (80 mg), and therefore this lack of treatment effect may have been related to underdosage.

In 5 studies, neuropsychiatric symptoms improved, commonly apathy and hallucinations. The focus of the large, multicenter, placebo-controlled study was on neuropsychiatric features. After 20 weeks of treatment, DLB patients taking rivastigmine were significantly less apathetic and anxious and had fewer delusions and hallucinations, and after 3 weeks of drug discontinuation, symptoms relapsed to baseline levels. In 1 study, improvements of sleep quality and fluctuating attentions were reported.

In most studies, ChEIs had no effect on parkinsonism. One case series reported worsening of parkinsonian features (mainly tremor) in 2 of 9 patients, and another study showed a slight progression of parkinsonism during the observation period of 6 months. Improvement of parkinsonism has been reported in 2 studies, and most studies, especially the large placebo-controlled study, found no change. In the only long-term follow-up study, UPDRS motor scores remained below baseline after 96 weeks of treatment with a ChEI.

ChEIs were well tolerated, with dropout rates (10% to 31%) and side effects similar to those found in AD. Discontinuation rates due to side effects were low (10%), and in the large placebo-controlled study, dropout rates of patients on drug or placebo were similar (12% and 11%, respectively). Side effects were mainly gastrointestinal symptoms with nausea, vomiting, and diarrhea.
<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Dropout</th>
<th>Age</th>
<th>Hoehn Yahr</th>
<th>Duration PD, years</th>
<th>Design</th>
<th>Treatment Duration, weeks</th>
<th>Baseline MMSE</th>
<th>Outcome Measures</th>
<th>Mean MMSE Change</th>
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<td>Hutchinson 1996(^3)</td>
<td>Tacrine</td>
<td>7</td>
<td>0</td>
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<td>8</td>
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<td>Leroi 2004(^5)</td>
<td>Donepezil</td>
<td>16</td>
<td>5/7</td>
<td>66</td>
<td>2.5</td>
<td>11</td>
<td>RCT</td>
<td>18</td>
<td>26</td>
<td>MMSE, NPI, H&amp;Y</td>
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<tr>
<td>Kurita 2003(^6)</td>
<td>Donepezil</td>
<td>3</td>
<td>1</td>
<td>70</td>
<td>3</td>
<td>12</td>
<td>Chart review</td>
<td>2-52</td>
<td>22.7</td>
<td>H&amp;Y</td>
<td>–0.7</td>
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<tr>
<td>Reading 2001(^7)</td>
<td>Rivastigmine</td>
<td>15</td>
<td>3</td>
<td>71</td>
<td>32</td>
<td>12</td>
<td>Open/wash-out</td>
<td>14/3</td>
<td>20</td>
<td>MMSE, NPI, UPDRS-motor</td>
<td>ND</td>
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<tr>
<td>Minett 2003(^1)</td>
<td>Donepezil</td>
<td>15</td>
<td>4</td>
<td>ND</td>
<td>34</td>
<td>ND</td>
<td>Open treat/withdraw/treat</td>
<td>20/6/12</td>
<td>18</td>
<td>MMSE, NPI, UPDRS-motor</td>
<td>3.8*/-4.4/5.4</td>
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<td>Bergman 2002(^8)</td>
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<td>69</td>
<td>ND</td>
<td>5</td>
<td>Open</td>
<td>6</td>
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<td>MMSE, GDS, SAPS, CGI</td>
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<td>0</td>
<td>75</td>
<td>ND</td>
<td>10#</td>
<td>Chart review</td>
<td>20-52</td>
<td>20.6</td>
<td>ND</td>
<td>3.7#</td>
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<td>Aarsland 2002(^4)</td>
<td>Donepezil</td>
<td>14</td>
<td>2</td>
<td>71</td>
<td>2.4</td>
<td>11</td>
<td>RCT crossover</td>
<td>10+10</td>
<td>20.8</td>
<td>MMSE, CGI</td>
<td>(0.3 on)</td>
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<td>Open/wash-out</td>
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<td>ADAS, CGI, MMSE</td>
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<td>10</td>
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<td>26</td>
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<td>MMSE, ADAS, GDS, MMSE, NPI</td>
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<td>16</td>
<td>3</td>
<td>76</td>
<td>3.6</td>
<td>13</td>
<td>Open</td>
<td>8</td>
<td>17.7</td>
<td>MMSE, NPI</td>
<td>2.3*</td>
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</table>

Note: ADAS = Alzheimer’s Diseases Assessment scale; CGC-plus = clinical global change plus; CGI = clinical global impression; EPS = extrapyramidal symptoms; GDS = Global Deterioration scale; H&Y = Hoehn and Yahr disability classification; MMSE = Mini Mental State Examination; ND = not determined; NPI = no present illness; PD = Parkinson’s disease; RCT = randomized, placebo controlled trial; SAPS = Scale for Assessment of Positive Symptoms; UPDRS = Unified Parkinson’s Disease Rating scale; VH = visual hallucinations; # = incomplete data; + = improvement; – = worsening; 0 = no effect.

*Statistically significant improvement compared to baseline.

**Statistically significant difference between active treatment and placebo.
<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Dropout</th>
<th>Age</th>
<th>Design</th>
<th>Treatment Duration, weeks</th>
<th>Baseline MMSE</th>
<th>Outcome Measures</th>
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<th>VH</th>
<th>Cognition</th>
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<td>7</td>
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<td>+†*</td>
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<td>Open</td>
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<td>19</td>
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<td>+</td>
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<td>+</td>
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<td>ND</td>
<td>3MS, NPI</td>
<td>+</td>
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</table>

Note: 3MS = Modified Mini Mental State; AD = Alzheimer’s disease; ADAS = Alzheimer’s Diseases Assessment scale; BEHAVE-AD = Behavioural Pathology in AD rating scale; CGC-plus = clinical global change plus; CGI = clinical global impression; DRS = Mattis Dementia Rating Scale; EPS = extrapyramidal symptoms; FAS = controlled oral word association test; FI = fluctuation inventory; GDS = Global Deterioration scale; H&Y = Hoehn and Yahr disability classification; IADL = Instrumental Activities of Daily Living scale; MMSE = Mini Mental State Examination; ND = not determined; NPI = no present illness; PD = Parkinson’s disease; PSQI = Pittsburgh Sleep Quality Index; RCT = randomized, placebo controlled trial; UPDRS = Unified Parkinson’s Disease Rating scale; VH = visual hallucinations; # = incomplete data; + = improvement; – = worsening; 0 = no effect; † = at 24 weeks.

*Statistically significant improvement compared to baseline.
DISCUSSION

The available evidence suggests that patients with DLB and PDD may benefit from treatment with ChEIs, but further evidence is required. Only 1 large (DLB) and 2 small (PDD) placebo-controlled studies have been published. Most published reports were open-label studies, and thus placebo-response, practice effect, and publication bias may lead to overestimating the drug effect. Large-scale placebo-controlled trials using ChEIs are needed.

Although there are pharmacodynamic differences of potential clinical interest between the available ChEIs, no direct comparative studies exist in patients with PDD or DLB, and the existing studies do not indicate that these differences are of clinical relevance. However, the first published study of a ChEI in PDD using tacrine showed the most pronounced treatment effect, with significant improvements of cognition, hallucinations, and parkinsonism. Tacrine is the only drug with combined AChE and BuChE inhibition and an additional modulating effect of the nicotinic receptor. Since there is some preliminary evidence that these additional pharmacodynamic effects are of clinical relevance in PDD and DLB, it cannot be ruled out that tacrine is the most effective drug for these conditions, although tacrine effects in 2 small DLB studies do not support this hypothesis. Studies comparing tacrine with other ChEIs in PDD and DLB using outcome measures sensitive to change would be needed to adequately address this question, and hepatotoxicity limits the use of this drug.

The ChEIs were usually well tolerated. Theoretically, worsening of parkinsonism could be expected, due to the striatal imbalance of acetylcholine and dopamine in PDD and DLB. However, motor deterioration was a rare side effect, and parkinsonism did not worsen in most patients, even after inappropriately high dose treatment. Nigrostriatal dopaminergic degeneration occurs in both DLB and PD, but the anatomical distribution of this and of other striatal neurochemical changes differs between DLB and PD. These differential striatal changes may lead to differences in motor symptoms and to different motor responses to cholinergic and dopaminergic agents in DLB and PDD.

The more pronounced cholinergic changes combined with fewer structural changes in the neocortex of DLB and PDD and the relative preservation or up-regulation of muscarinergic and nicotinic receptors suggest that cholinergic drugs may potentially be more effective in DLB and PDD compared to AD. Controlled studies do not exist, but some preliminary studies suggest that DLB patients may have a greater response to ChEIs than AD patients. Furthermore, the blockade of muscarinic receptors is associated with increased Alzheimer-type pathology in PD, and therefore cholinergic agents may have a potential neuroprotective effect in PD.

Since the cholinergic changes in PDD and DLB are rather similar, one would expect similar responses to pro-cholinergic drugs in these patients. The studies reviewed here support this hypothesis. One study directly compared DLB and PDD patients and found similar treatment effects in both disorders. However, when withdrawn from the drug, deterioration was particularly pronounced in PDD patients, suggesting that DLB and PDD patients, who benefit from ChEIs, will benefit from long-term treatment and that treatment discontinuation may have detrimental effects.

Clinically, decisions regarding risks and benefits of ChEIs should be seen in the context of the presently available treatment alternatives. No studies of drugs other than ChEIs have reliably shown cognitive improvement in PDD or DLB, although dopaminergic agents may have a beneficial effect on some cognitive functions early in course. Atypical antipsychotic drugs have been shown to improve psychosis in PDD and possibly in DLB as well, but risperidone and olanzapine are associated with a higher stroke risk in demented patients, and there is a high risk for marked sensitivity reactions related to neuroleptic drugs in DLB and probably also in PDD, and these potential risks need to be taken into account when prescribing neuroleptics. Studies of nonpharmacological interventions in PDD and DLB do not exist. Thus, if pharmacological interventions are required for the treatment of cognitive and neuropsychiatric symptoms in PDD/DLB, current evidence suggests that ChEIs may be the agents of first choice. However, there is a clear need for large randomized trials to evaluate these promising results.

References


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