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DONEPEZIL FOR BEHAVIOURAL DISORDERS ASSOCIATED WITH LEWY BODIES: A CASE SERIES

KRISTA L. LANCTÔT[1]* AND NATHAN HERRMANN[2]
[1]*Divisions of Clinical Pharmacology and Geriatric Psychiatry, Sunnybrook & Women's College Health Sciences Centre, Kunin-Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care and Department of Psychiatry, University of Toronto, Toronto, Canada*
[2]*Division of Geriatric Psychiatry, Sunnybrook & Women's College Health Sciences Centre and Department of Psychiatry, University of Toronto, Toronto, Canada*

ABSTRACT

Dementia with Lewy bodies (DLB) has been associated with important behavioural disturbances, such as psychotic symptoms. Unfortunately, neuroleptic sensitivity in these patients limits effective pharmacological management of these symptoms. Seven patients, five male and two female (mean age 75.3 ± 4.7 years, range 68–81), diagnosed with DLB were treated with the acetylcholinesterase inhibitor donepezil (5–10 mg once daily) to determine its effect on treating behavioural disorders. Although the intended length of treatment was a minimum of 8 weeks, only three patients completed 8 weeks of therapy, one patient completed 6 weeks, two patients completed 4 weeks and one patient was discontinued after 5 days. The primary outcome (behavioural disturbances) was measured prospectively by the Neuropsychiatric Inventory (NPI), while other outcomes included cognition (Mini-Mental State Examination (MMSE)) and Clinical Global Impression. Three of the seven subjects showed marked improvement in behaviour, with NPI scores dropping significantly over time. Donepezil therapy was discontinued prematurely in three of the cases due to insufficient response and/or adverse events. Overall, five of the seven patients were rated at least minimally improved in behavioural symptoms. Our experience with donepezil in this group of patients shows promise. Given the limited experience with this agent in treating behavioural disorders associated with DLB, further studies are warranted. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS—donepezil; behavioural disorders; dementia with Lewy bodies

Recent neuropathological evidence has suggested that 15–25% of elderly demented patients suffer from dementia with Lewy Bodies (DLB) (McKeith *et al*., 1996). DLB is characterized by motor features of parkinsonism, fluctuating cognitive impairment and marked visual hallucinations (McKeith *et al*., 1996). DLB patients suffer from both psychotic symptoms such as hallucinations and delusions and nonpsychotic behavioural disturbances such as aggression (Allen *et al*., 1995). Unfortunately, these patients are particularly sensitive to neuroleptic medication. Therefore, treatment of behavioural symptoms associated with this form of dementia becomes problematic (McKeith *et al*., 1996).

Recent evidence supports the assertion that certain behavioural disorders may be controlled by manipulation of the cholinergic system. For example, it has been suggested that an imbalance between cholinergic and monoaminergic neurotransmitters is responsible for the high occurrence of visual hallucinations in DLB (Perry *et al*., 1991). Furthermore, post-mortem studies of DLB patients displaying hallucinations show significant reduction in the cholinergic enzyme choline acetyltransferase compared to non-hallucinating patients (Perry and Perry, 1995).

The acetylcholinesterase inhibitors tacrine (Kaufer *et al*., 1996; Raskind *et al*., 1997), physostigmine (Cummings *et al*., 1993), and metrifonate (Morris *et al*., 1998), and the muscarinic agonist xanomeline (Bodick *et al*., 1997) have produced significant

*Correspondence to: Dr K. L. Lanctôt, Department of Psychiatry, Sunnybrook & Women's College Health Sciences Centre, 2075 Bayview Avenue, Room F-G20, Toronto, Ontario, Canada M4N 3MS. Tel: +416 480 6100 ext. 2241. Fax: +416 480 6022. e-mail: lanctot@srcl.sunnybrook.utoronto.ca

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reductions in psychosis, apathy, disinhibition, and aberrant motor behaviour associated with Alzheimer's disease. However, evidence of the clinical efficacy of these medications for behavioural disorders associated with DLB is limited. The acetylcholinesterase inhibitor, donepezil, has been shown to improve cognition and global function in patients with mild to moderately severe Alzheimer's disease (Rogers *et al*., 1998a,b). We report an open-label trial of donepezil for the treatment of behavioural disorders in seven patients with DLB.

METHODS

Patients

Participants were consecutive referrals to a geriatric psychiatry service that met the clinical criteria for diagnosis of DLB (McKeith *et al*., 1996), and displayed a sufficient degree of behavioural disturbance, as rated by a global rating of at least mild behavioural disturbance on the Clinical Global Impression scale (CGI), and at total of at least eight on the Neuropsychiatric Inventory (NPI) (Cummings *et al*., 1994). All patients offered this treatment and their caregivers were told that this was an off-label use of donepezil and informed consent was obtained from their substitute decision-makers. Data were collected for clinical purposes to monitor patient response and were within the limits of standard care.

Outcome measures

Following baseline assessments of cognition, using the Mini-Mental State Examination (MMSE) (Folstein and Folstein, 1975), behaviour (i.e. NPI, CGI) and physical health, patients received oral donepezil 5 mg/day. Behavioural changes were assessed after 2 weeks of therapy and every 2 weeks thereafter for 8 weeks. Since the primary objective was to determine the effects of donepezil on behaviour, the major outcome variable was the NPI. The NPI scores 10 behavioural subscales (delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour) on the basis of severity and frequency. The products of severity and frequency scores are summed, giving 0–12 points for each subscale and a total of 0–120 points. Higher scores indicate greater behavioural disturbances. The MMSE, NPI and CGI were done by one experienced assessor (KLL or NH) at each of the visits.

RESULTS

Seven patients with DLB and behavioural disturbances were recruited and received donepezil (five males, two females, mean age 75.3 ± 4.7 years) (Table 1). Three patients completed 8 weeks of treatment, two were discontinued early (6 weeks and 5 days) due to adverse experiences, one did not continue beyond 4 weeks because of insufficient improvement and one was lost to follow-up after 4 weeks of treatment. Changes in behavioural scores are outlined in Tables 1 and 2. Details of the seven cases follow.

Case 1

Mr A, a 68-year-old Caucasian male being seen as an outpatient, was diagnosed with possible DLB, presenting with spontaneous motor features of parkinsonism. He also had angina and was receiving nitroglycerin, and insomnia for which he received lorazepam (1 mg qhs). His initial MMSE score was 12 and his NPI total score was 27. Although he showed moderate behavioural disturbances, including apathy, irritability, aberrant motor behaviour, depression and agitation/aggression, delusions and hallucinations were absent. After 2 weeks of donepezil administration there was a marked reduction in his NPI total score (i.e. 27 versus 1), with mild apathy being the only persistent behavioural symptom. By the end of the 8-week trial, Mr A showed excellent improvement in all symptoms (NPI total score 0). His MMSE score had improved dramatically (score 20) and he began to participate in many previously enjoyed activities, such as painting and gardening. No other medication changes had been made.

Case 2

Mr B was a 77-year-old Caucasian male diagnosed with dementia who was admitted to acute care. He presented with a history of parkinsonism (4 years) as well as hypertension, non-insulin dependent diabetes mellitus, multiple falls and hypothyroidism and met criteria for probable DLB. He was receiving enalapril, metformin, glyburide, ASA, 1-thyroxin, famotidine and levodopa/carbidopa. Vitamin E, risperidone

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Table 1. Patient characteristics and response to donepezil

Case	Age/Sex	Treatment length (weeks)	Initial MMSE	Initial NPI	Final NPI	CGI change	Adverse experiences	Comments
1	68/M	8	12	27	0	Marked improvement	None	Marked improvement in agitation, irritation, depression, apathy
2	77/M	4	15	62	4	Marked improvement	None	Marked improvement in hallucinations, agitation, apathy, irritability
3	75/M	8	14	76	4	Marked improvement	None	Marked improvement in hallucinations, agitation, depression, apathy, irritability
4	77/M	8	19	34	15	Minimal improvement	Moderate sedation	Minimal improvement in hallucinations, irritability, treatment continued
5	70/F	4	5	17	27	Minimal improvement	None	Improvement in apathy but increased depression, increased anxiety and increased aberrant motor behaviour, discontinued due to lack of efficacy
6	81/F	5 days	12	23	N/A	Unchanged or worse	Discontinued due to somnolence, exacerbated COPD	–
7	79/M	6	12	18	21	Unchanged or worse	Discontinued due to syncope, sweating, bradycardia	Unchanged or worse, increased depression, increased irritability

MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory (range 0–120, higher scores indicate greater behavioural psychopathology); CGI = Clinical Global Impression Scale; COPD = chronic obstructive pulmonary disease.

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Table 2. Effect of donepezil on psychotic and nonpsychotic symptoms based on NPI subscale scores

	Delusions	Hallucinations	Agitation/ aggression	Depression	Anxiety	Euphoria	Apathy	Disinhibition	Irritability	Aberrant motor behaviour
Case 1										
Initial	0	0	2	3	0	0	12	0	6	4
Final	0	0	0	0	0	0	0	0	0	0
Change	0	0	2	3	0	0	12	0	6	4
Case 2										
Initial	12	8	12	0	0	0	8	4	9	9
Final	0	0	0	0	0	0	0	0	0	4
Change	12	8	12	0	0	0	8	4	9	5
Case 3										
Initial	8	12	9	6	9	0	8	6	9	9
Final	0	0	0	0	4	0	0	0	0	0
Change	8	12	9	6	5	0	8	6	9	9
Case 4										
Initial	0	12	6	0	6	0	0	0	2	8
Final	0	3	4	0	0	0	0	0	0	8
Change	0	9	2	0	6	0	0	0	2	0
Case 5										
Initial	4	3	2	0	0	0	8	0	0	0
Final	3	4	0	6	6	0	0	0	0	8
Change	1	−1	2	−6	−6	0	8	0	0	−8
Case 6										
Initial	9	9	2	1	2	0	0	0	0	0
Final	–	–	–	–	–	–	–	–	–	–
Change	–	–	–	–	–	–	–	–	–	–
Case 7										
Initial	4	3	6	0	0	3	0	0	0	2
Final	2	8	2	3	0	3	0	0	3	0
Change	2	−5	4	−3	0	0	0	0	−3	2

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(0.5 mg OD) and lorazepam (0.5 mg bid prn) were started after admission. Three weeks after his admission, he still demonstrated marked behavioural disturbances including delusions, agitation/aggression, irritability, aberrant motor behaviour, hallucinations, apathy and disinhibition. Hallucinations and delusions were very frequency and severe. His baseline MMSE and NPI total scores were 15 and 62, respectively. Donepezil (5 mg OD) was started after two weeks of donepezil treatment, he showed marked improvement overall. NPI total score at 2 weeks had decreased to 14, as had delusion and hallucination scores (Table 2). The patient experienced very mild sedation. Four weeks of treatment resulted in further improvement in hallucinations, agitation, apathy and irritability. His CGI was markedly improved and behavioural disturbances were almost absent (NPI total score = 4). He was unfortunately lost to follow-up after 4 weeks of treatment. Although this patient was also receiving other psychotropic medications such as risperidone, lorazepam and levodopa/carbidopa, no medication changes were made after donepezil was begun.

Case 3

Mr C, a widowed 75-year-old Caucasian male, had a 2-year history of cognitive decline with a more recent onset of visual hallucinations. He was admitted to acute care. He was diagnosed with probable DLB based on the presentation of three core features (i.e. fluctuating cognition, recurrent visual hallucinations and spontaneous motor features of parkinsonism). He had a history of parkinsonism and diverticular disease and a remote possible history of depression and alcohol abuse. Current depression and alcohol abuse were ruled out. He was receiving levodopa/carbidopa, acetaminophen, trazodone (75 mg/day) and lorazepam (0.5 mg prn). Baseline MMSE score was 14 and he exhibited severe behavioural disturbances (NPI total score = 76), including hallucinations, agitation/aggression, anxiety, irritability, aberrant motor behaviour, delusions, apathy, depression and disinhibition. Three days after starting donepezil, his trazodone dose was increased to 100 mg/day, but no other medication changes were made. After 4 weeks of treatment with donepezil (5 mg OD), Mr C showed marked improvement in behavioural symptoms, with the NPI total score dropping to 8. Visual hallucinations were absent and there was no complaint of sedation. He was subsequently placed on 10 mg of donepezil and showed dramatic improvement in cognition and behaviour. After 8 weeks of treatment, his final MMSE score was 24 and his NPI total score was 4. He was maintained on 10 mg daily of donepezil at discharge.

Case 4

Mr D was a 77-year-old Caucasian male who had been institutionalized for 1 year. He was diagnosed with probable DLB, exhibiting recurrent hallucinations and spontaneous motor symptoms of parkinsonism. He had a history of asthma and depression and was receiving lorazepam (0.5 mg prn), salbutamol and acetaminophen. Baseline MMSE was 19, NPI was 34 and he was rated as having moderate behavioural disturbances. At initial assessment, he had frequent and marked, well-formed visual hallucinations. Some of these hallucinations were disturbing to the patient. In addition, he exhibited aberrant motor behaviour, agitation/aggression, anxiety and irritability. After administration of donepezil (5 mg OD) for 2 weeks, there was little change in his CGI and NPI scores. His hallucinations did not change. Moderate sedation was reported, but this did not impair his ability to continue on the drug. After 4 weeks, Mr D showed minimal improvement in his behavioural disturbances, though his NPI score for hallucinations showed a substantial drop. This trend continued through to the end of the trial and after 8 weeks of donepezil treatment, his total NPI score dropped from 34 to 15.

Case 5

Mrs E, a 70-year-old Caucasian female diagnosed with dementia over 7 years ago and parkinsonism, was diagnosed with probable DLB. She was being seen as an outpatient and was receiving levodopa/carbidopa, and lorazepam (0.5 mg prn). At initial assessment, she scored 5 on the MMSE with a total score of 17 on the NPI. She presented with moderate behavioural disturbances, including apathy, delusions, hallucinations and agitation/aggression. Donepezil administration (5 mg OD) resulted in minimal improvement in behaviour scores after 4 weeks. Donepezil was discontinued however after this visit because of the spouse's concerns of insufficient improvement and trazodone was started. Her final recorded MMSE was 12.

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Case 6

Mrs F was an 81-year-old Caucasian female who presented with behavioural disturbances. She was admitted to acute care from emergency with a medical history of congestive heart failure, myocardial infarction, non-insulin dependent diabetes mellitus, coronary artery disease and hypertension. She was previously diagnosed with parkinsonism and was found to be extremely sensitive to neuroleptics. In addition to parkinsonism, diagnosis of probable DLB was based on her fluctuating consciousness, confusion and visual hallucinations. She was stabilized on the acute care ward. Her medications included nitroglycerin, cisapride, enalapril, levodopa/carbidopa, furosemide, acetaminophen, ASA, and vitamin E. At baseline assessment, her MMSE score was 12 and her NPI total score was 23. She had persecutory delusions (i.e. people were trying to poison her, the nurses were rough with her) and visual hallucinations (i.e. delusion and hallucinations, NPI scores = 9). Additional behaviours included mild agitation/aggression, anxiety and depression. During the first week of treatment with donepezil (5 mg OD), the patient experienced side effects that included somnolence and exacerbation of her previously stable chronic obstructive pulmonary disease (COPD). Donepezil was therefore discontinued.

Case 7

Mr G was a Caucasian male, age 79, who had been diagnosed with dementia and behavioural disturbances 2 years ago and met criteria for probable DLB. He has a history of COPD and alcohol abuse, as well as arteriosclerotic heart disease and glaucoma, and was receiving pilocarpine/timolol and nitroglycerin. He was institutionalized and his behaviours had previously been unsuccessfully treated with loxapine, trazodone, risperidone, olazapine, and lorazepam. His baseline MMSE score was 12 and his NPI total score was 18. He had well-formed hallucinations and reported seeing snakes and would talk to people not present in the room. Other behaviours included agitation/aggression, euphoria and aberrant motor behaviour. Upon administration of donepezil (5 mg OD), he showed little improvement and was mildly sedated. After approximately 4 weeks, he developed adverse events, including syncope, bradycardia and sweating. After 6 weeks of therapy, donepezil was discontinued due to these adverse effects. His final MMSE and NPI scores were not significantly different from baseline (i.e. 12 and 21, respectively).

DISCUSSION

This series of cases suggests some clinical effect of donepezil in managing both psychotic and non-psychotic behavioural symptoms in patients with DLB. Response to donepezil was varied with three of seven patients showing marked improvement in behavioural disorders (Cases 1, 2 and 3), and two patients exhibiting minimal improvement (Cases 3 and 4). Delusions were improved in all four of the four patients who initially reported them and hallucinations were improved in three of five patients with these symptoms (Table 2). The improvement in hallucinations provides supporting evidence for the putative relationship (Perry *et al.*, 1991) between cholinergic deficits and visual hallucinations.

Recently, two case reports have been published documenting the effect of donepezil in patients with DLB, showing varying results with respect to managing hallucinations (Aarsland *et al.*, 1999; Kaufer *et al.*, 1998). In addition, Shea and colleagues (Shea *et al.*, 1998) published a case series in which nine patients received 5–10 mg of donepezil daily for the management of DLB. Their outcomes of interest included cognition, function and hallucinations. With respect to hallucinations, some of their patients showed improvement overall, while others worsened, although this was determined qualitatively without the use of a standardized behavioural rating scale. To date, this case series is the first to demonstrate similar results prospectively utilizing the NPI, which is a sensitive measure of both psychotic and non-psychotic behavioural disturbances in patients with dementia.

Three of the patients (Cases 1, 3 and 5) had marked improvements in their MMSE scores over the course of donepezil treatment. There are several possibilities for these dramatic improvements. In trials with tacrine, Alzheimer's patients with Lewy bodies were thought to be amongst the best responders on cognitive outcomes (Levy *et al.*, 1994). Although delirium can also be suspected (Kaufer *et al.*, 1998; Wengel *et al.*, 1998), these patients were stable and delirium and other treatable causes of behavioural changes had been ruled out before donepezil was initiated. For all three cases, donepezil treatment was associated

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with marked improvements in apathy that can be expected to influence performance on the MMSE. Case 3 also had improvements in delusions, hallucinations, agitation, depression, anxiety, disinhibition, irritability and aberrant motor behaviour. Thus, in addition to a possible cognitive effect of donepezil and the contribution of expected fluctuations in cognition with DLB, improvements in behaviours such as apathy may also explain the substantial improvements noted on cognitive testing.

Three of the seven patients treated reported side-effects after initiation of donepezil, and two discontinued donepezil because of the severity of the adverse events. Although we report on only seven patients here, effective treatment of behavioural disturbances associated with DLB was limited by side-effects in this group. The previous case series with DLB patients (Shea *et al*., 1998) did not report on side-effects except for the exacerbation of parkinsonian features in three of nine patients. In clinical trials with Alzheimer's patients, only 4–9% of patients receiving 5 mg per day of donepezil withdrew from the trials (Burns *et al*., 1999; Rogers *et al*., 1998a,b). Those treatment limiting side-effects were mostly gastrointestinal. However, the clinical trials involved patients selected to be free from many co-morbid illnesses and those patients are not likely representative of the patients seen in the 'real world'. It may also be possible that DLB patients are more susceptible to certain cholinergic side-effects than Alzheimer's patients. Since the motor features of parkinsonism are thought to be controlled through a dopaminergic/cholinergic balance, an increase in parkinsonian symptoms might be expected with cholinergic therapy in LBD. Contrary to this, no increases in symptoms of parkinsonism were noted in these patients. Future trials are needed to quantify treatment limiting side-effects in different populations.

These results are preliminary and must be interpreted with caution. The participants received donepezil in an unblinded-fashion. Hence the magnitude of the effect on behaviour cannot be firmly established, especially given the small sample size. As well, DLB cannot be diagnosed with certainty pre-morbidly. In these cases, the diagnosis of DLB was made based on consensus guidelines (McKeith *et al*., 1996) that have been supported by a prospective investigation indicating 100% accuracy of 'probable' DLB in a small number of patients (Ballard *et al*., 1998). Because of the difficulties in making a pre-morbid diagnosis of DLB, efforts are being made to produce standardized and validated criteria (Holmes *et al*., 1999; Litvan *et al*., 1998). These findings, though, suggest that donepezil has potential as a therapy for the behavioural and psychotic symptoms suffered by DLB patients. The benefit of donepezil for psychotic and non-psychotic behavioural symptoms in DLB patients should be clarified in controlled trials.

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