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Donepezil and α-synuclein Constipation: A 48 Month Follow-Up

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Abstract

In a case study, four patients diagnosed at different stages of disease progression with the α-synuclein or Lewy body disorders Parkinson's disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB) were treated with the acetylcholinesterase inhibitor (AChEI) Donepezil to address the symptoms of constipation, obstipation and impaction. The use of Donepezil was associated with significant symptom reduction for each of the four patients. In follow-up studies conducted at intervals of six, twelve, eighteen, thirty-six and forty-eight months, symptom improvement was maintained with no apparent reduction in bowel motility, nor the emergence of any new symptoms. The results suggest that the AChEI Donepezil can have long-term benefit in reducing the symptoms of constipation, obstipation and impaction in patients with α-synuclein disorders.

Keywords: Neurocognitive Disorder with Lewy Bodies, Parkinson's disease, constipation, Donepezil, acetylcholinesterase inhibitor

INTRODUCTION

In a case study, four patients diagnosed at different stages of disease progression with α-synuclein protein pathology, or Lewy body disorders including Parkinson's disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB) were treated with the acetylcholinesterase inhibitor (AChEI) Donepezil to address the symptoms of constipation, obstipation, and impaction [1]. In the context of the case study, constipation refers to reduced frequency of bowel movements to less than once in two days, obstipation is defined as severe constipation, with frequency of bowel movements reduced to less than once a week, and impaction is defined as complete cessation of bowel function, also referred to as blockage of the lower intestine. The study was based on research demonstrating that bowel immotility, presenting symptomatically as constipation, obstipation and impaction is a consequence of α-synuclein impairment of the predominantly cholinergic neurotransmitter pathways in the myenteric plexus (MP) and the colonic submucosal plexus (CSMP) [2-10].

Complicating the treatment picture, PD and NCDLB patients with significant Parkinsonian features are often prescribed L-dopa agents including Carbidopa-Levodopa (brand names include Sinemet and Stalevo) to preserve basic motor functions including gait and balance [11, 12]. The potential side effects of L-dopa agents include bowel immotility [13]. Constipation, obstipation and impaction significantly diminish the patient's quality of life, and create daily hardship for providers of care [14, 15]. Conventional forms of treatment including over-the-counter medications have proven largely ineffective for reducing symptoms of constipation, obstipation and impaction in patients with α-synuclein pathology [16].

Donepezil and Constipation: Cholinergic Agonist Use in NCDLB and PD

To counter cholinergic impairment caused by α-synucleinopathy, including PD motor symptoms, gait dysfunction, levodopa-induced dyskinesias, cognitive deterioration, psychosis, sleep abnormalities, autonomic dysfunction, and altered olfactory function, PD and NCDLB patients have long been prescribed acetylcholinesterase inhibitors (AChEIs) [17-22]. The pathophysiology of these symptoms begins with alteration of the cholinergic tone in the striatum and/or to degeneration of cholinergic nuclei, most importantly the nucleus basalis magnocellularis and the pedunculopontine nucleus [21]. Among the AChEI's, Donepezil has demonstrated efficacy for mitigating cholinergic impairment in PD and NCDLB patients, without exacerbating Parkinsonian symptoms or generating new symptoms [23-28]. In a nongeriatric affective patient population, Donepezil was also shown to be effective in reducing constipation [29]. In a population diagnosed with severe bowel immotility, Donepezil increased bowel contractions 477% [30].

Donepezil is a specific, reversible acetylcholinesterase inhibitor [31, 32]. Donepezil increases acetylcholine levels by limiting the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase, effectively mitigating the symptoms of cholinergic impairment [33]. Because it also independently

facilitates neuronal nicotinic acetylcholine receptors [34], Donepezil plays a dual role in reducing cholinergic impairment. Donepezil's "dual action" has long made it a drug of choice for addressing symptoms of cholinergic impairment [22, 23, 25, 31, 34].

Hypothesis

Well documented as an effective agent for reducing cholinergic impairment [23-28], Donepezil has also been shown to reduce symptoms of constipation in nongeriatric affective patients [29] and increase bowel contractions in patients with severe bowel immotility [30]. It was hypothesized thatDonepezil would reduce the enteric nervous system (ENS) symptoms of constipation, obstipation and impaction consequent to α-synucleinopathy-based cholinergic impairment in the MP and CSMP in patients diagnosed with PD and NCDLB. A secondary hypothesis was that Donepezil would reduce bowel immotility in patients using Carbidopa-Levodopa, often prescribed to Lewy body patients with Parkinsonian features.

Methods

In order to assess Donepezil's efficacy for mitigating α-synucleinopathy-based bowel immotility, a case study was conducted. Donepezil in daily doses varying from 5 to 10 mg was orally administered to four patients diagnosed with PD and NCDLB at varying levels of disease progression with symptoms of constipation, obstipation and/or impaction. Based on a series of MRI's, neurological assessments, CT scans and Modified Hoehn and Yahr scores[35], two of the patients (Patient A and Patient B) had been diagnosed with PD. Patient A was a male aged 51 years at the time of diagnosis and 53 years at the time Donepezil was initially administered. Patient B was a male aged 70 years at the time of diagnosis and at the time that Donepezil was initially administered. Based on a series of MRI's, CT scans, neurological evaluations, and scores on the Mini-Mental State Examination (MMSE) [36], the Quick Dementia Rating System (QDRS) [37] and the Lewy Body Composite Risk Score [38], the other two patients had been diagnosed with NCDLB (Patient C and Patient D). Patient C was a female aged 69 years at the time of diagnosis and at the time that Donepezil was administered, and Patient D was a male aged 74 years at the time of diagnosis, and 78 years at the time that Donepezil was initially administered. During the subsequent six months, one of the PD patients (Patient B) was also diagnosed with NCDLB, subsuming the PD symptoms leading to the initial PD diagnosis. Each patient was assessed before treatment, and after initiation of treatment at intervals of two, four, and six weeks, and six, twelve, eighteen, thirty-six and forty-eight months.

Results

Two weeks after the introduction of orally administered Donepezil at daily doses of 5 mg, assessment indicated significant reduction of the symptoms of constipation, obstipation and impaction. In the current context, constipation is defined as bowel movements (BMs) 3 times a week; obstipation by BMs 1-2 times a week; and impaction by BMs on a less than weekly basis, e.g., once in 2 weeks. At assessment intervals of four weeks and six weeks, symptom reduction was increased, without exacerbation of existing symptoms, nor the emergence of new symptoms at any assessment interval [1].The increase in the frequency of bowel movements (BMs) is shown in Table 1.

After six months, each of the four patients was assessed in a follow-up study. Patients A and C demonstrated no change in symptoms. Patient B's verbal report and test scores indicated cognitive decline,so the diagnosis of NCDLB was assigned. There was evidence of disease progression in α-synucleinopathy-based cognitive and movement pathology for Patient B and Patient D, both diagnosed with NCDLB, but no increase in the symptoms of constipation, obstipation or impaction, nor was there emergence of any new symptoms [39]. Following assessment at six months, Patient B's daily dosage of Donepezil was increased from 5 to 10 mg to address the increases in cognitive interference (short-term memory loss and difficulty with word-finding) that led to the change in diagnosis from PD to NCDLB.

A second follow-up study was conducted twelve months after the introduction of Donepezil, using the same assessment procedure with each of the four patients. At the twelve-month interval, none of the four patients showed any increase in symptoms of constipation, obstipation or impaction, apparent progression of any other α-synuclein symptoms, nor the emergence of new symptoms [40]. Patient B, the NCDLB patient whose dosage of Donepezil had been doubled at six months, demonstrated some recovery of cognitive function (reductions in short-term memory loss and difficulty with word-finding). Using the same methodology, assessment at eighteen months indicated no changes in symptom status for any of the four patients [41].

About twenty-four months after initiation of treatment with Donepezil, Patient B (diagnosed with NCDLB) was prescribed a daily oral dose of 10 mg of Vortioxetine. The patient had been using Levodopa-Carbidopa (Sinemet) to treat Parkinsonian features, for which Donepezil had appeared effective in countering bowel slowing, and Bupropion for depression and anxiety. Vortioxetine was added to the patient's prescriptions because it has demonstrated efficacy for reducing the symptoms of depression [42-55], anxiety [42, 56-57], and cognitive impairment[58-63]. The introduction of Vortioxetine quickly produced some unanticipated symptom consequences. Within two weeks of initiating treatment with Vortioxetine, the patient went 10 days without a bowel movement, and received emergency treatment for impaction. The patient also demonstrated increased cognitive impairment. The use of Vortioxetine was discontinued, and within two days Patient B's cognition and bowel function returned to their pre-Vortioxetine status [64].

Using the same methodology employed at previous intervals, the four patients were again assessed thirty-six months after the initial introduction of Donepezil. Assessment indicated no increase in constipation, obstipation, or impaction in any of the four patients. Patients A and C showed no progression of cognitive interference, movement disorders or other α-synucleinopathy. Patients B and D both demonstrated progression of PD movement symptoms. None of the four patients showed indication of the emergence of new symptoms.

A summary of findings is presented in Table 1.

Table 1: Changes in Symptoms, Test Scores and Diagnosis over Time

	Patient A **Male** **Age at Dx PD 51** **At start of study:** **Age 53** **MODIFIED HOEHN AND YAHR (H & Y)** **STAGE 2.5** **MMSE 30** **BM 1-2X/week** **Initial dosage Donepezil 5 mg**	**Patient B** **Male** **Age at Dx PD 70** **At start of study:** **Age 70; Dx** **MODIFIED HOEHN AND YAHR (H & Y)** **STAGE 3** **MMSE 23** **BM 1X/2 weeks** **Initial dosage Donepezil 5 mg**	**Patient C** **Female** **Age at Dx NCDLB 69** **At start of study:** **Age 69** **MODIFIED HOEHN AND YAHR (H & Y)** **STAGE 2** **MMSE 25** **BM 3X/week** **Initial dosage Donepezil 5 mg**	**Patient D** **Male** **Age at Dx NCDLB 74** **At start of study:** **Age 78** **MODIFIED HOEHN AND YAHR (H & Y)** **STAGE 3.5** **MMSE 22** **BM 1X/2 weeks** **Initial dosage Donepezil 5 mg**
2 week assessment 2 weeks: 4 weeks: 6 weeks:	H & Y stage 2.5 MMSE 30 Donepezil 5 mg BM 3-4X/wk BM 4-6X/week BM 6-7X/week	H & Y stage 3 MMSE 23 Donepezil 5 mg BM 1-2X/week BM 3-4X/week BM 4-5X/week	H & Y stage 2 MMSE 25 Donepezil 5 mg BM 4-5X/week BM 5-6X/week BM 6-7X/week	H & Y stage 3.5 MMSE 22 Donepezil 5 mg BM 1-2X/week BM 3-4X/week BM 4-5X/week
6 month assessment	H & Y stage 2.5 MMSE 30 Donepezil 5 mg BM 6-7X/week	H & Y stage 3.5 MMSE 20 Donepezil 5 mg BM 4-5X/week Dx now NCDLB	H & Y stage 2 MMSE 25 Donepezil 5 mg BM 6-7X/week	H & Y stage 4 MMSE 19 Donepezil 5 mg BM 4-5X/week
12 month assessment	H & Y stage 2.5 MMSE 30 Donepezil 5 mg BM 6-7X/week	H & Y stage 3.5 MMSE 24 Donepezil 10 mg BM 4-5X/week	H & Y stage 2.5 MMSE 25 Donepezil 5 mg BM 6-7X/week	H & Y stage 2.5 MMSE 19 Donepezil 5 mg BM 4-5X/week
18 month assessment	H & Y stage 2.5 MMSE 30 Donepezil 5 mg BM 6-7X/week	H & Y stage 2.5 MMSE 24 Donepezil 5 mg BM 4-5X/week	H & Y stage 2.5 MMSE 25 Donepezil 5 mg BM 6-7X/week	H & Y stage 2.5 MMSE 19 Donepezil 5 mg BM 4-5X/week
36 month assessment	H & Y stage 2.5 MMSE 30 Donepezil 5 mg BM 6-7X/week	H & Y stage 2.5 MMSE 24 Donepezil 10 mg BM 4-5X/week	H & Y stage 2.5 MMSE 25 Donepezil 5 mg BM 6-7X/week	H & Y stage 2.5 MMSE 19 Donepezil 5 mg BM 4-5X/week
48 month assessment	H & Y stage 2.5 MMSE 30 Donepezil 5 mg BM 6-7X/week	H & Y stage 2.5 MMSE 24 Donepezil 10 mg BM 4-5X/week	H & Y stage 2.5 MMSE 25 Donepezil 5 mg BM 6-7X/week	H & Y stage 2.5 MMSE 19 Donepezil 5 mg BM 4-5X/week

Discussion and Conclusions

In four patients at varying levels of disease progression with PD and NCDLB, daily oral administration of Donepezil in doses varying from 5 to 10 mg was associated with significant reduction in the symptoms of constipation, obstipation and/or impaction. After initiating use of Donepezil, the four patients demonstrated no symptom progression for cognitive interference, movement disorders or other α-synucleinopathy, nor the emergence of new symptoms. Reduction in the symptoms of constipation, obstipation and/or impaction was consistent over time, assessed at intervals of two, four and six weeks, and later, at intervals of six, twelve, eighteen, thirty-six[1, 39-41, 65] and forty-eight months.

The findings from this series of case studies support the hypothesis that Donepezil can reduce α-synucleinopathy-based cholinergic impairment in the in the ENS, specifically

the MP and CSMP, as evidenced by reductions in the symptoms of constipation, obstipation and/or impaction. The case study findings also support the hypothesis that Donepezil can counter bowel immotility consequent to the use of Carbidopa-Levodopa.

The findings from this series of case studies also provide a demonstration of Vortioxetine's potential for serotonergic and cholinergic inhibition, and importantly, its reversibility [63]. Vortioxetine is metabolized by cytochrome P450 enzymes (e.g., CYP450 2D6) and subsequently by uridine diphosphate glucuronosyltransferase [66]. Initially believed to have relatively low risk for pharmacodynamic drug interactions [67, 68], Vortioxetine peak plasma concentration and systemic exposure are significantly increased when Vortioxetine is co-administered with the potent CYP450 2D6 inhibitor Bupropion [66]. When co-administered, Levodopa-Carbidopa (Sinemet) also significantly increases Vortioxetine peak plasma concentration and systemic exposure [69, 70]. The NCDLB patient in the case study prescribed Vortioxetine was using Bupropionand Levodopa-Carbidopa (Sinemet).

Apparently utilizing the same 5-HT3 receptor binding site as serotonin selective reuptake inhibitors (SSRIs), the molecular mechanisms underlying Vortioxetine's site binding appear to vary from currently known 5-HT3Aorthosteric ligands. In addition to binding in a similar manner to the setron class of competitive antagonists and 5-HT by interacting with residues of the aromatic box motif in the orthosteric binding site, Vortioxetine also interacts with residues not previously described to be important for the binding of either setrons or 5-HT, including Thr176 on loop B and Val202 on loop F [71]. Following partial agonist activity, Vortioxetine mounts what has been described as a persistent and insurmountable inhibition [71]. Vortioxetine'speak plasma concentration and systemic exposure can be more than doubled by its combined interactions with Bupropion and Levodopa-Carbidopa [66, 69, 70], so its serotonergic inhibitory potential is also significantly increased.

As illustrated by the case study, the combined interaction of Bupropion and Levodopa-Carbidopa with Vortioxetine can be dramatic, in this instance apparently exacerbating Lewy Body α-synuclein cholinergic suppression in the ENS, while the combination of Vortioxetine's serotonergic and cholinergic inhibition also significantly interfered with cognition. Although painful for the patient, this serendipitous finding contributed to the growing body of information about potential drug interactions for the relatively new drug Vortioxetine [64].

The primary focus of the case studies, however, continues to be Donepezil. Its "dual action" specifically and reversibly limits the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase [31, 32], while independently facilitating neuronal nicotinic acetylcholine receptors [34]. In combination, these two mechanisms effectively increase acetylcholine levels, with significant mitigation of symptoms attributable to cholinergic impairment [33].

The consistency of the current case study's findings over a four-year period in four patients diagnosed with degenerative α-synuclein neurocognitive and movement disorders is encouraging. It corroborates previous research indicating that Donepezil slows or reverses cognitive symptom progression in α-synucleinopathy, including short-term memory loss, difficulty with word-finding, hallucinations and cognitive interference [17, 18, 19, 20, 21]. It also provides a viable treatment protocol for mitigating α-synucleinopathy-based ENS suppression of the cholinergic pathways in the MP and the CSMP, providing relief from the symptoms of constipation, obstipation, and impaction that can so dramatically reduce the Lewy Body patient's quality of life.

Further research is recommended following patients over an extended time frame to establish longitudinal outcomes, and using larger numbers of subjects matched for diagnosis, age, gender and other variables.

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