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Donepezil and α-synuclein Constipation: A 60 Month Follow-Up

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Abstract

In a longitudinal case study, the acetylcholinesterase inhibitor (AChEI) Donepezil was used to address the symptoms of constipation, obstipation and impaction in 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). For each of the four patients, the use of Donepezil was associated with significant symptom reduction. Symptom improvement was maintained in follow-up studies conducted at intervals of six, twelve, eighteen, thirty-six, forty-eight and sixty months, with no apparent reduction in bowel motility. After four or five years, even with progression of other α-synucleinopathy, bowel motility was preserved. The results suggest that patients with α-synuclein disorders can experience long-term benefit in the reduction of symptoms including constipation, obstipation and impaction with the use of the AChEI Donepezil.

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

Introduction

The acetylcholinesterase inhibitor (AChEI) Donepezil was used in a case study to treat the symptoms of constipation, obstipation, and impaction in 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) [1].

As defined in the case study, constipation refers to reduced frequency of bowel movements to less than once in two days, obstipation describes severe constipation, with frequency of bowel movements reduced to less than once a week, and impaction refers to complete cessation of bowel function, also referred to as blockage of the lower intestine. The impetus for the case study was a body of research evidence indicating that α-synuclein impairment of the predominantly cholinergic neurotransmitter pathways in the myenteric plexus (MP) and the colonic submucosal plexus (CSMP) induces bowel immotility, presenting symptomatically as constipation, obstipation and impaction [2-10].

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

Cholinergic Agonist Use in NCDLB and PD: Donepezil and Constipation

For decades, acetylcholinesterase inhibitors (AChEIs) have been prescribed for PD and NCDLB patients with α-synucleinopathic cholinergic impairment including PD motor symptoms, gait dysfunction, levodopa-induced dyskinesias, cognitive deterioration, psychosis, sleep abnormalities, autonomic dysfunction, and altered olfactory function [17-22]. 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, is the basis of the pathophysiology of these symptoms [21]. Of all 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].

Pertinent to bowel motility per se, Donepezil has been used to reduce constipation in a nongeriatric affective patient population, and increased bowel contractions 477% in a population diagnosed with severe bowel immotility [29, 30].

Donepezil is a specific, reversible acetylcholinesterase inhibitor that increases acetylcholine levels by limiting the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase, which in turn can mitigate symptoms of cholinergic impairment [31-33]. Donepezil also independently facilitates neuronal nicotinic acetylcholine receptors [34], so that effectively it plays a dual role in reducing cholinergic impairment. Its "dual action" makes Donepezil a long-standing drug of choice for addressing symptoms of cholinergic impairment [22, 23, 25, 31, 34].

Hypothesis

There is a large body of research demonstrating Donepezil's efficacy for reducing cholinergic impairment, including reduction of symptoms of constipation in nongeriatric affective patients and facilitation of bowel contractions in patients with severe bowel immotility [23-30]. It was hypothesized that in patients diagnosed with PD and NCDLB, α-synucleinopathy-based cholinergic impairment in the MP and CSMP and consequent enteric nervous system (ENS) symptoms of constipation, obstipation and impaction would be reduced with the use of Donepezil. A secondary hypothesis was that in patients using Carbidopa-Levodopa, often prescribed to Lewy body patients with Parkinsonian features, Donepezil would reduce bowel immotility.

Methods

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

Results

Assessment two weeks after initial oral administration of Donepezil at daily doses of 5 mg indicated significant reduction of the symptoms of constipation, obstipation and impaction. In quantitative terms in the context of this study, 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. Symptom reduction was increased at assessment intervals of four weeks and six weeks, without exacerbation of existing symptoms, nor the emergence of new symptoms at any assessment interval [1]. Changes in the frequency of bowel movements (BMs) are shown in Table 1.

Each of the four patients was assessed in a follow-up study at an interval of six months. No change in symptoms was evident in Patients A and C. Because Patient B's verbal report and test scores indicated cognitive decline, the diagnosis of NCDLB was assigned. For Patient B and Patient D, both diagnosed with NCDLB, there was evidence of disease progression in α-synucleinopathy-based cognitive and movement pathology, but no increase in the symptoms of constipation, obstipation or impaction, nor was there emergence of any new symptoms [39]. After the six-month follow-up assessment, 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.

Twelve months after the introduction of Donepezil, a second follow-up study was conducted. The same assessment procedure was used with each of the four patients, none of whom showed any increase in symptoms of constipation, obstipation or impaction, apparent progression of any other α-synuclein symptoms, nor the emergence of new symptoms, except Patient C, whose H & Y score indicated some decline in motor functioning (advancement of Parkinsonian symptoms) [40]. Of interest, 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). Assessment at eighteen months using the same methodology indicated no changes in symptom status for any of the four patients [41].

For treatment of depression, Patient B (diagnosed with NCDLB) was prescribed a daily oral dose of 10 mg of

Vortioxetine approximately twenty-four months after initiation of treatment with Donepezil. Patient B 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. Because it has demonstrated efficacy for reducing the symptoms of depression, anxiety, and cognitive impairment, Vortioxetine was added to the patient's prescriptions [42-63]. However, unanticipated symptom consequences quickly followed the introduction of Vortioxetine. Within two weeks of initiating treatment with Vortioxetine, the patient demonstrated increased cognitive impairment, went 10 days without a bowel movement, and required emergency treatment for impaction. Interestingly, within two days after the use of Vortioxetine was discontinued, Patient B's cognition and bowel function returned to their pre-Vortioxetine status [64].

The four patients were again assessed thirty-six, forty-eight and sixty months after the initial introduction of Donepezil, using the same methodology employed at previous intervals. There was no increase in constipation, obstipation, or impaction in any of the four patients. At forty-eight months, Patients B and D showed progression of α-synucleinopathy with declining MMSE scores, and increasing movement disorders with higher H & Y scores. However, neither patient demonstrated any change in bowel motility [65].

At sixty months, there was no increase in constipation, obstipation, or impaction in any of the four patients. All four patients had lower MMSE scores, indicating declining cognitive functioning. Patients A, C and D also had higher H & Y scores indicating progression of Parkinsonian movement symptoms. In particular, Patient D's H & Y and MMSE scores indicate significant α-synucleinopathy, manifesting behaviorally as Parkinsonian motor symptoms with gait dysfunction and dyskinesias, cognitive deterioration, psychosis, sleep abnormalities, autonomic dysfunction, and altered olfactory function. However, there was no evidence of the emergence of new symptoms in any of the other three patients. A summary of findings is shown in Table 1.

Discussion and Conclusions

Four patients at varying levels of disease progression with PD and NCDLB were orally administered Donepezil in doses varying from 5 to 10 mg. Within two weeks, each of the four patients experienced significant reduction in the symptoms of constipation, obstipation and/or impaction, with no apparent symptom progression for cognitive interference, movement disorders or other α-synucleinopathy, nor the emergence of new symptoms. Over time, assessed at intervals of two, four and six weeks, and later, at intervals of six, twelve, eighteen, thirty-six, forty-eight and sixty months, reduction in the symptoms of constipation, obstipation and/or impaction was consistent [1, 39-41, 65, 66].

These findings support the hypothesis that in patients with Lewy body diseases including PD and NCDLB, Donepezil can reduce symptoms of constipation, obstipation and/or impaction thought to be manifestations of α-synucleinopathy-based cholinergic impairment in the in the ENS, specifically the MP and CSMP. The findings also support the hypothesis that Donepezil can counteract bowel immotility associated with the use of Carbidopa-Levodopa.

The case study's findings also demonstrate Vortioxetine's potential for serotonergic and cholinergic inhibition, and of equal importance, its reversibility [63]. Patient B, the NCDLB patient in the case study prescribed Vortioxetine, was simultaneously being administered Bupropion and Levodopa-Carbidopa (Sinemet). Metabolized by cytochrome P450 enzymes (e.g., CYP450 2D6) and subsequently by uridine diphosphate glucuronosyltransferase, Vortioxetine was initially believed to have relatively low risk for pharmacodynamic drug interactions [67- 69]. However, the case study provided a dramatic demonstration of significant increases in Vortioxetine peak plasma concentration and systemic exposure when Vortioxetine is co-administered with the potent CYP450 2D6 inhibitor Bupropion [67]. Similarly, when co-administered, Levodopa-Carbidopa (Sinemet) significantly increases Vortioxetine peak plasma concentration and systemic exposure [70, 71, 72].

The same 5-HT3 receptor binding site used by serotonin selective reuptake inhibitors (SSRIs) appear to be utilized by the molecular mechanisms underlying Vortioxetine's site binding, varying from currently known 5-HT3A orthosteric ligands. Vortioxetine not only binds 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, but also interacts with residues not previously considered relevant for the binding of either setrons or 5-HT, including Thr176 on loop B and Val202 on loop F [72]. Through partial agonist activity, Vortioxetine can induce a persistent and insurmountable inhibition causing Vortioxetine's peak plasma concentration and systemic exposure to more than double through its combined interactions with Bupropion and Levodopa-Carbidopa, so that its serotonergic inhibitory potential is also significantly increased [67-72].

For Patient B in the current case study, the combination of Vortioxetine, Bupropion and Levodopa-Carbidopa apparently exacerbated Lewy Body α-synuclein cholinergic suppression in the ENS, with significant cognitive interference apparently due to the combination of Vortioxetine's cholinergic and serotonergic inhibition. This unanticipated finding contributes to a growing body

of research data facilitating understanding of potential drug interactions for Vortioxetine [64, 66].

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:** **6weeks:**	H & Y stage 2.5 MMSE 30 Donepezil 5 mg BM3-4X/wk BM4-6X/wk BM6-7X/wk	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 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 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 3 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 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 3 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 3 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 3 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 3 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 3 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 4 MMSE 22 Donepezil 10 mg BM 4-5X/week	H & Y stage 2.5 MMSE 25 Donepezil 5 mg BM 6-7X/week	H & Y stage 4 MMSE 17 Donepezil 5 mg BM 4-5X/week
60 month assessment	H & Y stage 3 MMSE 26 Donepezil 5 mg BM 6-7X/week	H & Y stage 4 MMSE 20 Donepezil 10 mg BM 4-5X/week	H & Y stage 3 MMSE 22 Donepezil 5 mg BM 6-7X/week	H & Y stage 5 MMSE 15 Donepezil 5 mg BM 4-5X/week

The primary focus of the case study, however, continues to be the efficacy of Donepezil, whose "dual action" specifically and reversibly limits the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase, while independently facilitating neuronal nicotinic acetylcholine receptors [31-34]. In combination, these two mechanisms appear to effectively increase acetylcholine levels, producing significant mitigation of symptoms attributable to cholinergic impairments including bowel slowing and cognitive interference [33].

Over a five-year period in what has become a longitudinal study, the findings have been encouragingly consistent for four patients diagnosed with degenerative α-synuclein neurocognitive and movement disorders. Consistent with data from previous research, the findings indicate that Donepezil slows or reverses cognitive symptom progression in α-synucleinopathy, including short-term memory loss, difficulty with word-finding, hallucinations and cognitive interference [17-21]. Although it appears that with advancing age and over a longer time frame α-synucleinopathy eventually erodes cognitive and motor function, the current study's findings suggest that the oral administration of Donepezil is a viable treatment protocol for mitigating α-synucleinopathy-based ENS suppression of the cholinergic pathways in the MP and the CSMP, providing reduction in the symptoms of constipation, obstipation, and impaction.

In order to establish more longitudinal outcomes, additional research using larger numbers of subjects matched for diagnosis, age, gender and other variables over an extended time frame is recommended.

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