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Donepezil and α-synuclein Constipation: A 72 Month Follow-Up

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ABSTRACT

In this longitudinal case study, four patients diagnosed with the α-synuclein or Lewy body disorders Parkinson's disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB) were treated at various stages of disease progression with the acetylcholinesterase inhibitor (AChEI) Donepezil. The off-label effects of Donepezil were observed to reduce the symptoms of constipation, obstipation and impaction in each of the four patients. Symptomatic relief has been consistent, assessed at intervals of six, twelve, eighteen, thirty-six, forty-eight, sixty and seventy-two months. Despite progression of other α-synucleinopathy, bowel motility has been consistent. The results suggest that extended use of the AChEI Donepezil can facilitate long-term reduction in α-synuclein disorder symptoms of bowel immotility including constipation, obstipation and impaction.

Keywords: Neurocognitive disorder with Lewy bodies, Parkinson's disease, Constipation, Donepezil, acetylcholinesterase inhibitor

INTRODUCTION

α-synuclein impairment of the predominantly cholinergic neurotransmitter pathways in the myenteric plexus (MP) and the colonic submucosal plexus (CSMP) characteristically induces bowel immotility symptoms, including constipation, obstipation and impaction [1-9]. Bowel immotility is often exacerbated by the use of L-dopa agents including Carbidopa-Levodopa (brand names include Sinemet and Stalevo), frequently prescribed to preserve basic motor functions including gait and balance in Parkinson's disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB) patients with significant Parkinsonian features. Bowel immotility can significantly diminish quality of life and create daily hardship for patients and providers of care [10-14]. Over-the-counter medications and other conventional treatments are largely ineffective for reducing these symptoms in patients with α-synuclein disorders [15].

α-synucleinopathic cholinergic impairment including PD motor symptoms, gait dysfunction, levodopa-induced dyskinesias, cognitive deterioration, psychosis, sleep abnormalities, autonomic dysfunction, and altered olfactory function has long been treated using acetylcholinesterase inhibitors (AChEIs) [16-21]. These symptoms result from reduction of cholinergic tone in the striatum and/or degeneration of cholinergic nuclei, most importantly the nucleus basalis magnocellularis and the pedunculopontine nucleus [20].

A specific, reversible acetylcholinesterase inhibitor, Donepezil limits the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase, increasing acetylcholine levels which in turn can mitigate symptoms of cholinergic impairment [22-24]. Donepezil performs "dual action" in reducing cholinergic impairment, also independently facilitating neuronal nicotinic acetylcholine receptors [25], historically making it a drug of choice for managing symptoms of cholinergic impairment [21,22,25-27]. In PD and NCDLB patients, Donepezil does not exacerbate Parkinsonian symptoms or generate new symptoms, comparing favorably with other AChEIs [28-31]. In a study with a nongeriatric affective patient population with severe bowel immotility, the use of Donepezil reduced increased bowel contractions 477% [32,33].

Based on the body of research evidence cited above, it was hypothesized that in patients with Lewy body diseases including PD and NCDLB, Donepezil might 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. A secondary hypothesis posited that Donepezil might counteract bowel immotility associated

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with the use of Carbidopa-Levodopa.

CASE PRESENTATION

Donepezil was orally administered in daily doses varying from 5 to 10 mg to each of four PD and NCDLB patients (patients A, B, C and D) diagnosed at varying levels of disease progression with symptoms of constipation, obstipation and/or impaction to see whether Donepezil reduced bowel immotility symptoms including constipation, obstipation, and impaction [34]. In this context, "constipation" is defined as bowel movements less than once in two days, "obstipation" as less than once a week, and "impaction" as blockage of the lower intestine or complete cessation of bowel function [35].

PD was diagnosed for Patient A (male age 51, Donepezil initiated at age 53) and Patient B (male age 70, Donepezil initiated age 70) based on data from MRI's, neurological assessments, CT scans and Modified Hoehn and Yahr (H & Y) scores [36]. NCDLB was diagnosed for Patient C (female age 69, Donepezil initiated age 69) and Patient D (male, age 74, Donepezil initiated age 78) 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 [37-39]. Patient B was also diagnosed with NCDLB six months after the initiation of Donepezil. Symptoms of constipation, obstipation and impaction were measured for each patient prior to and after treatment with Donepezil at intervals of two, four, and six weeks, and six, twelve, eighteen, thirty-six, forty-eight, sixty and seventy-two months.

RESULTS

In each of the four patients, assessment two weeks after initial oral administration of Donepezil at daily doses of 5 mg indicated significant reduction in the symptoms of constipation, obstipation and impaction. Increases in symptom reduction were observed at four weeks and six weeks. At each of these intervals, there was no exacerbation of existing symptoms, nor emergence of new symptoms [34], as shown in **Table 1**.

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

Assessments	Patient A	Patient B	Patient C	Patient D
2-week assessment	• 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	• 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	• 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	• 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 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	• H & Y stage 3 • MMSE 20 • Donepezil 5 mg	• H & Y stage 2 • MMSE 25 • Donepezil 5 mg	• H & Y stage 3 • MMSE 19 • Donepezil 5 mg

	• BM 6-7X/week	• BM 4-5X/week Dx now NCDLB	• BM 6-7X/week	• 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
72-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

At six months, Patients A and C demonstrated no change in symptoms. For Patient B, self-report and test scores indicating cognitive changes led to the diagnosis of NCDLB, and increased dosage of Donepezil to 10 mg. Testing indicated α-synuclein disease progression in cognition and movement for both Patients B and D without increased bowel immotility or emergence of new symptoms [40].

Assessment at twelve months showed no symptom exacerbation, except in Patient C, whose H & Y score indicated advancement of Parkinsonian symptoms [41]. Testing demonstrated recovery of some cognitive function (short-term memory and word-finding) in Patient B, whose dosage of Donepezil had been doubled at six months. At eighteen and twenty-four months, testing indicated no symptom change in any of the four patients [42].

Patient B had been using Levodopa-Carbidopa (Sinemet) for Parkinsonian features and Bupropion for depression. At twenty-four months, Patient B was prescribed Vortioxetine for its reported efficacy in reducing anxiety, depression, and cognitive impairment [43-64]. Within two weeks, he reported exacerbation of cognitive impairment and was hospitalized with bowel impaction. Less than 48 hours after discontinuing Vortioxetine, his bowel function and cognition returned to their pre-Vortioxetine levels [65].

At forty-eight months, Patients B and D showed progression of α-synucleinopathy manifesting as declining MMSE scores and increasing movement disorders with higher H & Y scores [66]. At sixty months, MMSE scores indicated cognitive change in all four patients, and advancement of Parkinsonian movement symptoms in Patients A, C and D (with higher H & Y scores). However, even at seventy-two months there was no increase in bowel immotility for any of the patients. A summary of findings is shown in **Table 1**.

DISCUSSION AND CONCLUSION

Case study findings support the hypothesis that 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 in patients with Lewy body diseases including PD and NCDLB, well as the secondary hypothesis that Donepezil can counteract bowel immotility associated with the use of Carbidopa-Levodopa.

A bonus finding was that Vortioxetine can inhibit serotonergic and cholinergic transmission, and importantly, that such inhibition is reversible [64]. Vortioxetine is metabolized by cytochrome P450 enzymes (e.g., CYP450 2D6) and subsequently by uridine diphosphate glucuronosyltransferase, and was initially thought to have relatively low risk for pharmacodynamic drug interactions [68-70]. The current case study demonstrated that significant increases in Vortioxetine peak plasma concentration and systemic exposure can occur when Vortioxetine is co-administered with the potent CYP450 2D6 inhibitor Bupropion [67], as well as Levodopa-Carbidopa (Sinemet) [71,72].

The molecular mechanisms underlying Vortioxetine's site binding appear to utilize the same 5-HT3 receptor binding site used by serotonin selective reuptake inhibitors (SSRIs). Varying from currently known 5-HT3Aorthosteric ligands, Vortioxetine binds through interaction with residues of the aromatic box motif in the orthosteric binding site in a manner similar to the setron class of competitive antagonists and 5-HT. Vortioxetine 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 [71]. Vortioxetine's partial agonist activity can induce persistent and insurmountable inhibition, so that its peak plasma concentration and systemic exposure can more than double through its combined interactions with Bupropion and Levodopa-Carbidopa, significantly increasing its serotonergic inhibitory potential [68-72].

In the current case study, the combination of Vortioxetine, Bupropion and Levodopa-Carbidopa appears to have significantly increased Lewy Body α-synuclein cholinergic suppression in Patient B's ENS, rapidly inducing bowel immotility. It also produced significant cognitive interference due to the apparent combination of Vortioxetine's cholinergic and serotonergic inhibition. These unanticipated findings contribute to a growing understanding of potential drug interactions for Vortioxetine [65,67].

However, the case study's primary focus continues to be the efficacy of Donepezil, whose "dual action" independently facilitates neuronal nicotinic acetylcholine receptors, while specifically and reversibly limiting the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase [22-25]. The apparent elevation of acetylcholine levels through the combination of these two mechanisms appears to significantly mitigate symptoms attributable to cholinergic impairments, which include bowel slowing and cognitive interference [24].

The findings of this longitudinal case study are consistent with 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 [16-20]. Moreover, 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. Future research is recommended over an extended time frame using larger numbers of subjects matched for diagnosis, age, gender and other variables.

AUTHOR CONTRIBUTION

The author warrants that he has reviewed and approved the manuscript prior to its submission, and assumes responsibility for the contents of the manuscript.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

The author declares no conflicts of interest in the manuscript, including financial, consultant, institutional, and other relationships that might lead to bias or a conflict of interest. The author also declares no sources of funding for the manuscript. The Santa Barbara Cottage Hospital Institutional Review Board granted a waiver (#18-81ix) for this case study.

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