Mechanisms of α-Synuclein Pathology and Treatment in the Enteric Nervous System

Charles M Lepkowsky

1 Independent Practice, 1143 Deer Trail Lane, Solvang, California, USA

Abstract

α-synuclein (Lewy Body) pathology is commonly found in the enteric nervous system (ENS) of patients diagnosed with Parkinson's Disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB). Lewy pathology in the ENS can produce symptoms of bowel immotility, including constipation, obstipation, and bowel impaction. These symptoms significantly reduce the quality of life for the patient, producing hardship for the patient and care providers. In Lewy body patients, medical intervention using acetylcholinesterase inhibitors (AChEIs) can significantly reduce or alleviate bowel immotility. The specific mechanism through which the cholinergic agonist Donepezil mitigates Lewy Body bowel immotility is explained.

Keywords: Neurocognitive Disorder with Lewy Bodies; Parkinson's Disease; Constipation; Donepezil; AChEI;

Introduction

The purpose of this paper is to explain the biochemical mechanisms responsible for the symptom of constipation in patients diagnosed with Parkinson's Disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB) patients, and the mechanisms through which Donepezil produces symptom relief.

Cholinergic Lewy Pathology in the ENS

Pathological α-synuclein proteins called Lewy bodies have long been known to aggregate in the enteric nervous system (ENS) of patients diagnosed with PD and NCDLB [1-13]. Specifically, in PD and NCDLB, Lewy bodies appear in the myenteric plexus (MP) and the colonic submucosal plexus (CSMP) [8,14-20]. 95% of MP innervation is cholinergic and the CSMP is innervated by the MP [21].

Similarly, cholinergic neural deficits and functional impairment have long been recognized as symptomatic features of PD and NCDLB [22-28]. Increasingly, cholinergic impairments in PD and NCDLB are attributed to Lewy Body pathology (Cholinergic impairment does not appear to be a consistent finding in Alzheimer's disease (AD) [27,42]). Research consistently demonstrates that autonomic dysfunction is a feature of PD and NCDLB, but not AD and that α-synuclein expression is increased in NCDLB and PD, but not in AD [2,7,9,43-46]. For this reason, AD is not included in this discussion) [23,28,29]. The presence of α-synuclein aggregates in the MP predates cognitive and motor functional manifestations of Lewy body diseases so consistently that it has been nominated as a potential biomarker for Lewy pathology [10,17,30].

Symptomatic Manifestations of Cholinergic Lewy Pathology in the ENS

Lewy body cholinergic impairment in the ENS manifests symptomatically as gastric immotility and constipation [13,31-41]. Increased colonic transit time and impaired gastric emptying are frequently found in PD patients [35,42]. The prevalence of constipation in PD is at least three times that of the general population, leading some researchers to suggest that constipation might be a universal feature of PD [47,48]. Bowel immotility can occur 20 years before diagnosis of PD or NCDLB, suggesting that it might be a prodromal symptom for both disorders [5,19,36,44,49-52].

As α-synuclein pathology advances in the ENS, symptoms of gastric immotility advance from constipation to obstipation and impaction. Escalating gastric immotility in PD and NCDLB can interfere with mobility, sleep, cognition, and mood, increasing the cost of care, and potentially debilitating and/or dramatically reducing the quality of life for patients. [4, 34, 36, 53-56].

Potential Exacerbation of ENS Symptoms by Anti-Parkinson Medication

LPD and NCDLB patients with significant Parkinsonian motoric/gait features are often prescribed L-dopa agents like Carbidopa-Levodopa (known also by the brand names Sinemet and Stalevo) in order to preserve gait, balance, and other basic motor functions [40,57,58]. Carbidopa-Levodopa's potential side effects include constipation [59], which can complicate or exacerbate gastric immotility due to ENS Lewy pathology. Medications frequently used for the treatment of resting tremor in PD and NCDLB include Trihexyphenidyl (marketed as Artane or Trihex) and Benzotropinemesylate (marketed as Cogentin), identified as definite anticholinergics that can also exacerbate gastric immotility through suppression of the cholinergic neurotransmitter pathways innervating the ENS [58, 60-62].
Symptom Treatment of Cholinergic Lewy Pathology

Because Lewy pathology produces cholinergic impairment, a practical approach to symptomatic relief for PD and NCDLB patients is the use of a cholinergic agonist, such as an acetylcholinesterase inhibitor (AChEI), to boost cholinergic activity [29,33,63-65]. AChEIs include Tacrine, Galantamine, Rivastigmine, and Donepezil. Low doses of Tacrine and Galantamine have reduced motor symptoms in PD patients [22,66]. Rivastigmine has been shown to reduce neuropsychiatric symptoms and improve cognitive function as measured by the Mini-Mental State Exam (MMSE) in patients with NCDLB [67-71]. However, in PD patients, improvements in cognition with Rivastigmine have also been associated with higher rates of nausea, vomiting, and tremor (Rare, potentially dangerous side effects of cholinergic agonists include rhabdomyolysis and neuroleptic malignant syndrome (NMS) [80-86]). [72].

Compared with other AChEIs, including Galantamine and Rivastigmine, the cholinergic agonist Donepezil has performed favorably for treating cognitive impairment in patients with PD and NCDLB, improving cognition, but with fewer side effects [73,74]. Donepezil has been shown to produce significant improvements in cognition and behavior which disappeared when Donepezil was withdrawn, but treatment gains were restored on recommencement of Donepezil [75]. Donepezil has been shown to improve cognition for up to 52 weeks in long-term treatment of NCDLB patients, without increasing the risk of Parkinsonian features or other clinically significant safety events [76,77].

Donepezil has also been shown to reduce Lewy pathology cholinergic impairment including hallucinations and delusions and psychotic symptoms in PD patients, without apparent side effects or exacerbation of Parkinsonian symptoms [78-79]. Although an early study suggested that treatment of NCDLB with Donepezil was sometimes associated with an increase in Parkinsonian features, a Cochrane database systematic review of previous research using cholinergic agonists to treat PD & NCDLB found that Donepezil produced consistent reduction in neurocognitive symptoms without exacerbation of Parkinsonian features or other side effects [87,88]. These findings have been reproduced in subsequent research [89,90].

More specific to ENS Lewy pathology and impairment, Donepezil has been shown to reduce ANS symptoms including constipation in non-geriatric affective patients, and increase cholinergically mediated bowel contractions as much as 477% in constipation in nongeriatric affective patients, and increase ANS symptoms including rhabdomyolysis and neuroleptic malignant syndrome (NMS) [80-86]). [72].

The mechanisms through which Donepezil mitigates the symptom of constipation in PD and NCDLB patients bears some explanation. Specifically, what are the biochemical mechanisms responsible for the symptom of constipation, and through what mechanisms does Donepezil induce symptom relief?

Because 95% of Myenteric Plexus (MP) innervation is cholinergic, Lewy Body pathology in the MP manifests primarily as α-synuclein protein aggregation in the cholinergic neurons of the MP and the CSMP [8,14-21]. In the MP and CSME α-synuclein pathology does not appear exclusively in the form of large Lewy bodies near the nucleus. Small Lewy bodies and other proteins aggregate even more abundantly in neurites (axons and dendrites) [33].

The specific biochemical mechanisms posited for α-synuclein pathology-based reduction of cholinergic functioning include endoplasmic reticulum (ER) stress, blockade in endoplasmic reticulum (ER)-to-Golgi vesicular trafficking, and mitochondrial dysfunction, all of which contribute to α-synuclein-induced cell death [93,94]. The degeneration of cholinergic neurons leads to a decline in the level of acetylcholine (ACh) [95].

The mechanisms through which Donepezil mitigates these symptoms is twofold. AChEIs like Donepezil inhibit the action of the ACh-hydrolyzing enzyme acetylcholinesterase (AChE), increasing ACh levels, with consequent reduction in symptoms associated with progressive cholinergic dysfunction [95]. Donepezil is a specific, reversible AChE inhibitor [96,97].
Donepezil also interacts independently with neuronal nicotinic ACh receptors [98]. Donepezil’s dual action has made it a long-standing choice for countering cholinergic impairment [74,95,98].

Donepezil’s successful employment in the treatment of constipation in case studies of patients with PD and NCDLB, as well as its demonstrated efficacy in reducing constipation in PD and NCDLB patients using Carbidopa-Levodopa, suggests that the mechanism of boosting ACh levels in the MP and CSMP restores motility to the bowel, significantly reducing constipation without increasing Parkinsonian features or other clinically significant symptoms [39,40].

Discussion and Conclusions

As with the use of any medication, Donepezil’s potential for symptom reduction has to be weighed against its potential side effects. These can include diarrhea, loss of appetite, muscle cramps, nausea, trouble in sleeping, unusual tiredness or weakness, and vomiting, with less common side effects including abnormal dreams, constipation, dizziness, drowsiness, fainting, frequent urination, headache, joint pain, stiffness, or swelling, mental depression, pain, unusual bleeding or bruising, and weight loss (Pfizer US Pharmaceuticals, 2016). AChEIs including Donepezil also have the potential for rare but potentially dangerous side effects, including muscle breakdown (rhabdomyolysis) and a neurological disorder called neuroleptic malignant syndrome (NMS) [80–86].

Donepezil has demonstrated efficacy in mitigating Lewy body impairment of the cholinergic pathways in the MP and CSMP of patients diagnosed with PD and NCDLB, increasing bowel motility and reducing the symptom of constipation, without exacerbating or instigating other symptoms [39,40]. One possible conclusion is that the use of the AChEI Donepezil compensates at least in part for Lewy body impairment of cholinergic pathways in the MP and CSMP, reducing the symptom of constipation in patients with PD and NCDLB.

In case studies, the use of Donepezil was also associated with significant reductions in constipation and the resumption of daily bowel movements in patients using Carbidopa-Levodopa. Another possible conclusion is that Donepezil mitigates constipation in Lewy body patients receiving prescriptive Carbidopa-Levodopa.

The strength of these conclusions is limited by our current understanding of Lewy pathology, its etiology, and progression. Although these early findings suggest that Donepezil might be effective in reducing constipation in patients with PD and NCDLB through a mechanism that directly addresses Lewy body cholinergic impairment in the MP and CSMP, further research is necessary using larger numbers of subjects matched for diagnosis, age, gender, and other variables.

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