Chapter

Prevalence and Treatment of Constipation in Patients with Alpha-Synuclein Pathology

Charles M. Lepkowsky

Abstract

α-Synuclein "Lewy body" pathology is the basis of Parkinson's disease (PD) and neurocognitive disorder with Lewy bodies (NCDLB), sometimes called Lewy body dementia. In patients with α-synuclein pathology, constipation, obstipation and impaction are almost universal symptoms, whose treatment represents a significant burden on health care economies. Description is given of the specific mechanisms through which α-synuclein pathology induces these symptoms, and through which the use of acetylcholinesterase inhibitors (AChEIs) might significantly reduce them. Four case studies are presented testing the hypothesis that the use of the cholinergic agonist donepezil might reduce the symptom of constipation in four patients with NCDLB or PD at different stages of disease progression. Outcomes are presented, as well as follow-up data at 6-, 12-, and 18-month intervals. The potential use of donepezil to reduce the symptoms of constipation in patients with α-synuclein pathology is discussed.

Keywords: constipation, α-Synuclein pathology, Parkinson's disease, neurocognitive disorder with Lewy bodies, Lewy body dementia, acetylcholinesterase inhibitors (AChEIs)

1. Introduction

Longevity has increased significantly over the past four decades [1], bringing with it a significant increase in the number of older adults affected by neurocognitive diseases (formerly called dementias) [2]. Worldwide, the number of people diagnosed with neurocognitive disease was 46.8 million in 2015, and 50 million in 2017. This figure is expected to exceed 75 million by 2030, and 131.5 million by 2050 [3–5]. Approximately 67% of dementia diagnoses are assigned to Alzheimer's disease (AD), 22% to neurocognitive disorder with Lewy bodies (NCDLB) (previously called Lewy body dementia), and the remaining 9% to Parkinson's disease (PD) [2].

According to the US Census Bureau, the Center for Medicare and Medicaid Services (CMS) and the U.S. Burden of Disease Collaborators, the largest increases in annual payments for treatment and long-term care for older adults were for those diagnosed with neurocognitive disease. Per capita, PD and NCDLB represent more than their numeric percentage of this expense, which grew 113 percent between 1990 and 2010. Worldwide in 2015, the estimated economic burden of

AD	Alzheimer's Disease
PD	Parkinson's Disease
NCDLB	Neurocognitive disorder with Lewy Bodies
CNS	Central nervous system
ANS	Autonomic nervous system
PNS	Peripheral nervous system
ENS	Enteric nervous system
MCI	Mild cognitive impairment
ACh	Acetlycholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
REM	Rapid eye movement
RBD	REM behavior disorder
RSWA	REM sleep without dystonia
MP	Myenteric plexus
SMCP	Submucosal colonic plexus
ER	Endoplasmic reticulum
MMSE	Mini mental status exam
QDRS	Quick dementia rating system
LBCRS	Lewy body composite risk score
OTC	Over the counter
HS	Taken daily
PRN	As needed
MRI	Magnetic resonance imaging
CMS	Center for medicare and medicaid services
APA	American Psychological Association

Table 1.
Abbreviations.

neurocognitive disease was $818 billion, representing 1.09% of global gross domestic product. Currently, the global cost of neurocognitive disease is estimated above $1 trillion, and is expected to increase fourfold to more than $4 trillion by 2050 [2, 6, 7]. As the occurrence of neurocognitive disease increases, early and accurate diagnosis becomes increasingly important for appropriate treatment, as well as containment of the cost associated with care delivery.

So what are PD and NCDLB, and why do they cost so much to treat?

PD and NCDLB are α-synuclein "Lewy body "pathologies characterized by a wide range of cognitive, motor, and autonomic symptoms, including constipation, obstipation, and impaction [8]. The disproportionate cost of care for α-synucleopathologies is due to their widely varied symptom presentation, combined with significant, progressive debilitation within systems affected by Lewy bodies. Lewy bodies are abnormal intracellular aggregations of α-synuclein protein [9]. α-synuclein pathology, α-synucleopathology, and α-synucleinopathy are all terms used to describe impairment of neural functioning due to the presence of Lewy Bodies (aggregates of α-synuclein protein) [10].

Pertinent to the topic of constipation, escalating gastric immotility in PD and NCDLB compromises mobility, sleep, cognition, and mood, increasing the cost of care, and potentially debilitating and/or dramatically reducing the quality of life for patients [11–17]. Although gastric immotility is a prevalent symptom characteristic of α-synuclein disorders, constipation, obstipation, and impaction are rarely a focus of treatment for patients with PD and NCDLB [18]. When PD and NCDLB constipation, obstipation, and impaction are addressed, primary care physicians typically recommend conventional (often over-the-counter) treatments, despite data demonstrating that such treatments are ineffective with this population [12]. In order to make accurate diagnosis and assign appropriate and effective treatment, it is necessary to understand constipation, obstipation, and impaction as symptomatic manifestations of Lewy (α-synuclein) pathology in the enteric nervous system (ENS), and the specific mechanisms through which synuclein pathology impairs bowel motility. Medical intervention can then be selected based on the use of medications known to counteract those mechanisms. The effectiveness of evidence-based medical intervention can be evaluated through large data set studies, and/or longitudinal case studies.

In this chapter, Lewy pathology in PD and NCDLB and its symptomatic manifestations in the ENS will be described. The specific mechanisms through which α-synucleopathology causes those symptoms will be explained, followed by a description of the mechanisms though which specific medications counter those of α-synuclein proteins. A series of case studies will be described, in which four patients at different stages of disease progression with NCDLB or PD were each treated using medication with demonstrated effectiveness for countering the mechanisms underlying α-synucleinopathy in the ENS. Outcomes will be reviewed at 6, 12, and 18 month follow-up intervals, followed by a discussion of implications for future research and practice. Abbreviations used in this chapter are summarized in **Table 1**.

2. α-Synuclein pathology: Lewy bodies in PD and NCDLB

Unlike Alzheimer's disease (AD), which is associated with presence of two proteins in the central nervous system (CNS), amyloid-β (Aβ) and tau, PD and NCDLB are diseases characterized by the presence of Lewy bodies, pathologic aggregates of the synaptic protein α-synuclein. In PD and NCDLB, Lewy bodies appear not only in the CNS, but also in the autonomic nervous system (ANS), the peripheral nervous system (PNS) and the enteric nervous system (ENS), spreading from one nervous system area to the next over time [19, 20]. In PD and NCDLB patients, there is evidence that Lewy bodies travel from the gut to the brain, or vice-versa [21, 22]. Lewy bodies aggregate not only near the nucleus of the neuron, but even more abundantly in neurites (axons and dendrites) [23].

2.1 Symptomatic manifestations of α-synuclein pathology

While amyloid-β (Aβ) and tau pathology in AD are associated almost exclusively with cognitive impairment in the CNS, Lewy pathology in PD and NCDLB is heterogeneous in its presentation. Not every PD or NCDLB patient has the same, or all, α-synuclein pathology symptoms.

Most Lewy body patients present with disordered sleep: REM Sleep Behavior Disorder (RBD), and especially REM sleep without atonia (RSWA). They act out their dreams, sometimes injuring their bed partner, or remaining sleepless at night and drowsy all day [24]. Many Lewy body patients present with ANS dysfunction, including urinary incontinence, constipation, erectile dysfunction, coronary dysfunction, or orthostatic hypotension, which increases the likelihood of injury

due to falling [25, 26]. Lewy body patients sometimes present with sensory dysfunction, losing their sense of smell (anosmia) [27], and/or seeing colors differently [28]. Some Lewy body patients initially present with late life onset depression, with or without visual or auditory hallucinations, delusions, and anxiety [29]. Lewy body patients sometimes initially present with cognitive impairment, including attentional deficits, short-term memory loss, and/or difficulty with concentration or word-finding. Most often these symptoms are functionally diagnosed as Mild Cognitive Impairment (MCI), and frequently, later in symptom progression as AD, which is a common misdiagnosis [30]. Lewy body patients presenting with evolving Parkinsonian features (including shuffling gait, weakness, pain in muscles and joints, and/or tremor) are most often diagnosed with PD, which might be correct, or might be a misdiagnosis overlooking or minimizing the relevance of other symptoms listed above [31]. In some Lewy body patients, Parkinsonian features might not appear at all, or until long after other symptoms have become more prevalent [32].

Constellations of three or more of these symptom presentations are considered reliable prodromal indicators of α-synucleopathology, as well as differential diagnostic indicators distinguishing NCDLB from AD [8]. Proper identification of prodromal Lewy body symptoms for early and accurate diagnosis of α-synucleopathology reduces the likelihood of misdiagnosis, and facilitates early treatment intervention to minimize or delay the emergence of multi-nervous system symptoms that impair functioning and reduce quality of life, with the consequent benefit of containing the cost of care delivery. Early diagnosis has been hindered more by general unawareness of prodromal symptom constellations with demonstrated predictive accuracy for α-synucleopathology [8] than by an actual lack of reliable biomarkers for α-synucleopathology [33].

Although Lewy body patients demonstrate wide variation in symptom presentation, the symptom almost universal to patients diagnosed with PD and NCDLB is constipation, which can lead to obstipation and/or impaction [14, 26, 34–44]. The uniformity of gastric immotility in patients with PD and NCDLB suggests that α-synuclein pathology directly affects the enteric nervous system (ENS).

2.2 Symptomatic manifestations of α-synuclein pathology in the ENS

Because gastric immotility is such a consistent symptom feature of PD and NCDLB, much research has focused on whether or to what extent Lewy pathology occurs in the ENS of PD & NCDLB patients. Research data consistently demonstrate that abnormal α-synuclein proteins aggregate in the ENS of patients diagnosed with PD and NCDLB, with symptomatic manifestation as gastric immotility [14, 26, 34–44]. In patients diagnosed with PD, symptoms frequently include increased colonic transit time [45] and impaired gastric emptying [46]. In PD patients, constipation is at least three times as prevalent as it is among the general population [47], and several researchers believe that constipation is a universal feature of PD [48]. In both PD and NCDLB, the symptom of bowel immotility often presents years before other diagnostic features [47, 49–53] sometimes as much as 20 years before the emergence of others symptoms leading to the diagnosis of PD or NCDLB [17]. This occurs so frequently that many experts suggest that bowel immotility is a prodromal symptom for both PD and NCDLB [17, 21, 25, 37, 54–57].

3. The mechanism of α-synuclein impairment of the ENS

In patients with PD and NCDLB, high concentrations Lewy bodies (α-synuclein protein aggregates) are found in the myenteric plexus (MP) [56, 58–63] and the

colonic submucosal plexus (CSMP) [40]. 95% of innervation in the MP and the CSMP is cholinergic, and the CSMP is innervated by the MP [64]. As in other neurotransmitter pathways, Lewy bodies in the MP and CSMP do not appear exclusively in the form of large aggregations of α-synuclein protein near the nucleus. Small aggregations of α-synuclein and other proteins aggregate even more abundantly in neurites (axons and dendrites) [65]. The abundance of Lewy bodies in the predominantly cholinergic neurotransmitter pathways innervating the MP and CSMP interferes with cholinergic neurotransmission.

The specific biochemical mechanisms posited for α-synuclein pathology-based reduction of cholinergic functioning include endoplasmic reticulum (ER) stress, blockage in endoplasmic reticulum (ER)-to-Golgi vesicular trafficking, and mitochondrial dysfunction, all of which contribute to α-synuclein-induced cell death [66–68]. The degeneration of cholinergic neurons leads to a decline in levels of acetylcholine (ACh) [69]. The loss of cholinergic function in the MP and the CSMP reduces or eliminates signals that induce and maintain peristalsis, symptomatically manifesting as constipation, obstipation, and/or impaction [8, 13, 17, 23, 44, 46, 52, 70–73]. The presence of Lew bodies in the MP and CSMP predates cognitive and motor functional manifestations of α-synuclein diseases [42, 61] so consistently that it has been nominated as a potential biomarker for α-synuclein pathology [74].

3.1 Potential exacerbation of ENS symptoms by anti-Parkinson medication

In both PD and NCDLB, α-synuclein patients with Parkinsonian features are often prescribed L-dopa agents such as carbidopa-levodopa (known also by the brand names Sinemet and Stalevo) in order to preserve gait, balance, and other basic motor functions [18, 75, 76]. Complicating or exacerbating gastric immotility due to α-synuclein ENS pathology, carbidopa-levodopa's potential side effects include constipation [77]. Other medications frequently used to mitigate resting tremor in PD and NCDLB include trihexyphenidyl (marketed as Artane or Trihex) and benztropine mesylate (marketed as Cogentin). Each has been identified as an anticholinergic medication, which accordingly can also exacerbate gastric immotility through suppression of the cholinergic neurotransmitter pathways innervating the ENS [76, 78–80].

4. The mechanism of symptom relief for cholinergic α-synuclein pathology: cholinergic agonist use in NCDLB and PD

The symptomatic features of PD and NCDLB have long been known to include cholinergic neural deficits and functional impairment [81–87]. Over time, it has become increasingly evident that α-synuclein pathology is the basis of cholinergic impairments in PD and NCDLB [82, 87, 88].[1] With the hope of mitigating α-synuclein cholinergic impairment [29, 65, 88, 91, 92], cholinergic agonists such as acetylcholinesterase inhibitors (AChEIs) are prescribed to NCDLB and PD patients. AChEIs include tacrine, galantamine, rivastigmine, and donepezil.

Low doses of tacrine have been associated with reductions of motor symptoms in PD patients [80] and galantamine [93]. Rivastigmine has been used to reduce neuropsychiatric symptoms and improve cognitive function as measured by the

[1] Cholinergic impairment does not appear to be a consistent finding in Alzheimer's disease (AD) [86, 91]. Research consistently demonstrates that autonomic dysfunction is a feature of PD and NCDLB, but not AD [25, 39, 82, 89], and that alpha-synuclein expression is increased in NCDLB and PD, but not in AD [35, 41, 90]. For this reason, AD is not included in this discussion.

Mini-Mental State Exam (MMSE) [94] in patients with NCDLB [95–98]. In PD patients, however, the use of Rivastigmine to improve cognition has also been associated with higher rates of nausea, vomiting, and tremor [99].[2]

Donepezil has been used to improve cognition and reduce hallucinations and delusions in PD patients with cognitive impairment (suggesting that they are in fact NCDLB patients) [107]. 5–10 mg daily dosages of donepezil used in conjunction with antiparkinsonian therapy produced significant reduction in psychotic symptoms in PD patients (again, likely misdiagnosed NCDLB patients), without apparent side effects or exacerbation of Parkinsonian symptoms [108]. An early study suggested that treatment of NCDLB with donepezil was sometimes associated with an increase in Parkinsonian features [109]. However, a large body of subsequent research indicates that donepezil reduces neurocognitive symptoms in patients with NCDLB without worsening Parkinsonian features [110–120], and 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 [121].

When compared to other acetylcholinesterase inhibitors including Galantamine and Rivastigmine for use with patients diagnosed with PD and NCDLB, donepezil has performed well, improving cognition [122], but with fewer side effects [123]. PD and NCDLB patients treated with donepezil demonstrated significant improvements in cognition and behavior which disappeared when donepezil was withdrawn, and later showed restoration of treatment gains upon recommencement of donepezil [124]. In patients with NCDLB, long-term administration of donepezil at 10 mg/day has been shown to improve cognitive function for up to 52 weeks without increasing the risk of Parkinsonian features or other clinically significant safety events [125, 126].

4.1 Donepezil for symptom relief of constipation

Conventional treatments for constipation have proven ineffective in older patients in residential settings, especially for patients with neurocognitive disorders [12]. Recalling that 95% of the innervation of the MP and CSMP in the ENS is cholinergic [64], it is interesting to note that donepezil has been shown to reduce ANS symptoms including constipation in nongeriatric affective patients [127]. Donepezil increases cholinergically mediated bowel contractions as much as 477% in patients suffering from severe intestinal dysmotility [128]. 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 [69]. Donepezil is a specific, reversible AChE inhibitor [129, 130]. Donepezil also interacts independently with neuronal nicotinic ACh receptors [131]. Donepezil's dual action has made it a long-standing choice for countering cholinergic impairment [69, 124, 131].

4.2 A hypothetical model for symptom relief of cholinergic α-synuclein pathology in the ENS

On the basis of substantial research a) linking constipation in patients with NCDLB and PD to α-synucleopathology-based impairment of cholinergic function in the MP and CSMP in the ENS, b) demonstrating that the use of the donepezil as

[2] Rare, potentially dangerous side effects of cholinergic agonists include rhabdomyolysis and neuroleptic malignant syndrome (NMS) [100–106].

a cholinergic agonist mitigates cholinergic impairment in α-synuclein pathology patients, and c) showing that the use of the donepezil increases bowel motility in non-geriatric patients with gastric immotility, it was postulated that the use of donepezil might counter α-synuclein pathological impairment of the MP and CSMP in patients with NCDLB and PD, leading to increased bowel motility and a consequent reduction in the symptom of constipation.

PD patients and NCDLB patients with significant Parkinsonian features are frequently prescribed L-dopa agents like carbidopa-levodopa (known also by the brand name Sinemet) to preserve balance, gait, and other basic motor functions [31, 76]. Carbidopa-Levodopa's potential side effects include constipation [77]. Accordingly, it was postulated that the use of donepezil might have specific benefit in reducing constipation in patients with PD and NCDLB receiving L-dopa agents like carbidopa-levodopa.

To test these hypotheses, in a series of case studies donepezil was prescribed to four PD and NCDLB patients at different stages of disease progression, each suffering from constipation, obstipation, and/or impaction. Discussion of other diagnoses, symptoms, or treatments is limited, in order to make the case studies as brief as possible, while maintaining focus on donepezil's potential for reducing constipation, obstipation, and impaction.

5. Four case studies: methods

5.1 Case study #1

Mr. A. was a non-Hispanic white male 50–55 years of age. He had been diagnosed with PD. His presenting symptoms included depression, transient hand tremor, cognitive interference resulting in permanent disability work status, lower back pain, insomnia, and significant constipation, with frequency of bowel movements about once a week. For treatment of his Parkinsonian symptoms, the patient had been treated for 2 years with carbidopa-levodopa (Sinemet) and pramipexole (Mirapex) (both dopamine agonists). He had also been prescribed acetaminophen/oxycodone (Percoset) for back pain, and dronabinol (Marinol) for pain and insomnia. For constipation, he had been advised to use over the counter (OTC) products including stewed prunes, prune juice, psyllium (fiber), and Senokot laxative/stool softener. None of the OTC remedies had produced any reduction in the symptom of constipation.

Donepezil was prescribed at a starting dose of 5 mg per day. Within 2 weeks, the patient reported that his frequency of bowel movements had increased to every other day. After 4 weeks, the frequency of bowel movements had increased to once a day. There was no increase in Parkinsonian features or other clinically significant symptoms, nor was there emergence of new symptoms.

5.2 Case study #2

Ms. B. was a non-Hispanic white female 65–70 years of age. She had not yet received a neurocognitive or Parkinsonian diagnosis, but had been diagnosed with late-life onset of acute anxiety and depression without suicidal ideation, in addition to standing diagnoses of hypertension, hypothyroid, and possible sleep apnea. For several years she had received prescriptive Spironolactone 25 mg HS (as a diuretic), Levothyroxine 75 mcg HS (for hypothyroid), and most recently Lorazepam 1 mg PRN (for anxiety). Her presenting symptoms included cognitive interference (short-term memory loss and difficulty word-finding), agitation, panic attacks,

dysphoria, insomnia (onset, median, and terminal waking), restless sleep (which her spouse described as talking and flailing in her sleep), and constipation (of approximately 5 years). At intake, the patient reported that the frequency of bowel movements was approximately twice a week. She had tried a variety of OTC and dietary remedies, all of which had been ineffective. The patient was administered the MMSE [94], the Quick Dementia Rating Scale (QDRS) [132] and the Lewy Body Composite Risk Score (LBCRS) [133]. Her scores indicated mild cognitive impairment (MCI) and suggested neurocognitive impairment consistent with that found in patients with Lewy body disorders. In combination, the symptoms of MCI, late-life onset depression, and sleep disturbance (possible REM sleep behavior disorder or RSBD and/or REM sleep without atonia, or RSWA) [105] are considered prodromal for NCDLB. A neurological evaluation and a sleep study were ordered in order to gather confirmatory evidence. The neurological assessment confirmed MCI, and an MRI showed reduced cerebral (white matter) volume. RSBD/RSWA was confirmed by the sleep study.

Donepezil was prescribed at a starting dose of 5 mg per day. Within 3 weeks the patient reported that her frequency of bowel movements had increased to about every other day. After 5 weeks, she reported daily bowel movements. There was no exacerbation of Parkinsonian features or other clinically significant symptoms.

5.3 Case study #3

Mr. C. was a non-Hispanic white male 65–70 years of age recently diagnosed with Major Depressive Disorder, with history of cervical vertebral fusions C5–C7. His presenting symptoms included cognitive interference (short-term memory loss and difficulty word-finding), panic attacks, appetite suppression, generalized anxiety, frequent migraine headaches, feeling off balance, dysphoria, insomnia (onset, median and terminal waking), restless sleep (which his spouse described as yelling and striking out in his sleep), and constipation (for about 4 years). OTC and dietary treatments had not been effective for reducing the symptom of constipation. To treat his anxiety and depression, the patient had recently been prescribed Paroxetine HCl (Paxil) 30 mg daily, and for his panic and anxiety, clonazepam (Klonopin) 0.5 mg PRN. The patient was administered the MMSE, the QDRS and the LBCRS. His scores indicated mild cognitive impairment (MCI) and suggested neurocognitive impairment consistent with that found in patients with Lewy body disorders. The patient soon began to complain of increasing difficulties with balance, gait, and weakness. His depression increased, and he began to report suicidal ideation. He stated that his appetite suppression and constipation had both increased. During the same time frame, the patient's cognitive impairment escalated rapidly. The combination of symptoms including MCI, rapid cognitive changes, balance/gait impairment, late-life onset depression and anxiety, weakness, appetite suppression, constipation, and sleep disturbance (possible REM sleep behavior disorder or RSBD and/or REM sleep without atonia, or RSWA) is consistent with the diagnosis of NCDLB. A neurological evaluation and a sleep study were ordered. Although an MRI was unrevealing, the neurological assessment was confirmatory for MCI. The sleep study confirmed the diagnosis of RSBD/RSWA.

Paroxetine is known to have anticholinergic properties [134], so its use was discontinued. Sertraline 100 mg per day was prescribed, and within weeks was increased to 200 mg per day. The PRN dosage of Clonazepam was increased to 0.75 mg. Abilify (aripiprazole) 1 mg per day was added to address the patient's intractable depression. Topiramate 75 mg HS was prescribed for the migraine headaches. To address the sleep disturbance, melatonin 6 mg and Mirtazapine 30 mg were prescribed for use at bedtime. It was hoped that mirtazapine might

potentiate the effects of the Sertraline, while reducing restlessness in bed. The patient reported reductions in depression. However, there appeared to be no reduction in RSBD/RSWA. To address the patient's rapidly advancing cognitive impairment, Memantine was prescribed 10 mg morning and at night, which produced significant cognitive improvement. To address the balance issues, tremor, gait disturbance, and general weakness, carbidopa-levodopa (Sinemet) 25/100 mg was prescribed three times a day, soon producing improvement in motor function. However, during the same time period, the symptom of constipation intensified. The patient reported that the frequency of bowel movements had fallen to less than once per week. OTC and dietary remedies had not produced any improvement. During this time frame, the patient became impacted twice, and each time had to be treated in the emergency room using bowel voiding medications intended for colonoscopies or bowel surgical procedures.

Donepezil was prescribed at a starting dose of 2.5 mg per day. The patient reported that during the first 2 weeks, his bowel movement frequency had increased to once every other day. After 4 weeks, he reported that the frequency of his bowel movements had increased to once a day. There was no change in the frequency of bowel movements for the next 3 months, but the patient expressed concern that his appetite and bowel production were not adequate. In an effort to achieve further symptom improvement, the dosage of donepezil was increased to 5 mg per day. Within days, there were improvements in appetite, volume of dietary intake, and bowel output. There was no increase in Parkinsonian features or other clinically significant symptoms.

Following the increase in donepezil to 5 mg daily, the patient and his spouse described significant improvement in his cognitive functioning, including word finding and short-term memory. The patient was again administered the MMSE, the QDRS and the LBCRS. His scores had improved significantly on all three instruments, suggesting overall recovery of cognitive function.

5.4 Case study #4

Mr. D. was a non-Hispanic white male 75–80 years of age. He had recently been diagnosed with PD and Major Depressive Disorder, with history of hypercholesterolemia, arteriosclerosis, lower back surgery, coronary artery stent replacement, small bowel obstruction, peripheral vascular disease, and chronic lower back pain. His presenting symptoms included cognitive interference (short-term memory loss and difficulty with word-finding), generalized anxiety, blunted affect, appetite suppression, depression, passive suicidal ideation, lower back pain, weakness, hand tremor, motor retardation, difficulties with balance, tottering or shuffling gait, sleep disturbance (onset, median and terminal waking), and constipation. At intake, he reported the frequency of bowel movements at approximately twice a week. OTC and dietary treatments had not been effective in reducing his constipation. The patient stated that for several years, he had experienced difficulties with balance. He sought referral to an orthopedist, and ultimately underwent surgery. The patient reported that subsequent to the surgery, he experienced chronic lower back pain, which was significant enough to interfere with routine activities. He ceased routine physical exercise, reported increasing weakness over the past few months, lost confidence in his coordination, leading him to give up driving, and stated that his hand tremor had evolved to the extent that his handwriting was no longer legible. He described a deepening depression and the emergence of suicidal ideation. There was no report or evidence of symptoms consistent with RSBD or RSWA. However, the patient reported that the his constipation had increased and remained unresponsive to OTC or dietary remedies.

The patient was administered the MMSE, the QDRS and the LBCRS. His scores suggested mild cognitive impairment (MCI) and neurocognitive impairment consistent with that found in patients with Lewy body disorders. The combination of symptoms including cognitive impairment, blunt affect, anxiety, late-life onset depression, motor retardation, hand tremor, handwriting changes, lower back pain, weakness, impaired/shuffling gait, difficulties with balance, sleep disturbance, appetite suppression, and constipation is consistent with the diagnosis of NCDLB. A neurological evaluation and a sleep study were ordered. The neurological assessment confirmed the diagnosis of MCI, and an MRI indicated reduced cerebral (white matter) volume. The sleep study confirmed the diagnosis of RSBD/RSWA.

Donepezil was prescribed at a starting dosage of 5 mg per day. After 2 weeks, the patient reported that the frequency of his bowel movements had increased to about every other day. Within 3 weeks, he reported that he was having bowel movements every day. He also reported that his appetite had significantly increased. There was no exacerbation of Parkinsonian features or other clinically significant symptoms.

6. Results

6.1 Case study initial results

In each of the four patients in the case studies, the use of donepezil significantly reduced the symptom of constipation within a few weeks, without increasing Parkinsonian features or other clinically significant symptoms. There was also significant reduction of constipation for each of the two patients prescribed carbidopa-levodopa. In addition, when the patient whose NCDLB symptom progression was most advanced was readministered the MMSE, the QDRS and the LBCRS, he scored higher on all three tests, indicating improvements in overall cognitive functioning, word finding, and short-term memory.

6.2 Case study six-month follow-up

The symptom status of the four patients was reviewed 6 months later. The two patients in case studies #1 and #2 showed no symptom change. The two patients in case studies #3 and #4 each showed evidence of Lewy body symptom progression, including increased cognitive interference (short-term memory loss and difficulty with word-finding), generalized anxiety, dysphoric mood, blunted affect, appetite suppression, passive suicidal ideation, sleep disturbance (onset, median and terminal waking, REM sleep behavior disorder or RSBD and/or REM sleep without atonia, or RSWA), and Parkinsonian features (motor retardation, joint and muscle pain, reduced range of motion, diminished strength and coordination, increased tremor, gait disturbances, and difficulties with balance). Constipation, however, had not increased for any of the patients, nor was there evidence of new symptom emergence. Coincident with the 6 month symptom review, the patient in case study #3 had his dosage of donepezil doubled, from 5 to 10 mg orally administered daily, with the intention of mitigating his neurocognitive symptom progression.

6.3 Case study twelve-month follow-up

Twelve months after the initial findings had been reported, the symptom status of the four patients was again reviewed. During the interval between the 6 month and 12 month reviews, there was no apparent progression of Lewy body symptoms

in any of the four patients. At 6 months, the patient in case study #3 had his dosage of donepezil doubled (from 5 to 10 mg orally administered daily) to address the progression of neurocognitive symptoms. At 12 months, he demonstrated reduced cognitive interference (short-term memory loss and difficulty with word-finding), which appeared to be associated with the increase in his dosage of donepezil. No other symptom changes were evident in that patient. In the remaining three patients, no symptom progression or change was apparent. None of the patients exhibited new symptoms, or any increase in the symptoms of constipation, obstipation, or impaction.

6.4 Case study eighteen-month follow-up

At 18 months, the symptom status of each of the four patients in the case studies was again reviewed. There was no apparent progression of Lewy body symptoms in any of the four patients between the 12 month and 18 month reviews. In the patient in case study #3, whose Lewy body symptoms had progressed at 6 months, doubling the dosage of donepezil (from 5 to 10 mg orally administered daily) continued to be associated with reduced cognitive interference (short-term memory loss and difficulty with word-finding). No other symptom changes were evident in that patient. In the remaining three patients, no symptom progression or change was apparent. None of the patients exhibited new symptoms, or any increase in the symptoms of constipation, obstipation, or impaction.

7. Summary, discussion, and conclusions

One of the consequences of greater worldwide longevity has been an upsurge in the number of older adults living with neurocognitive disease [1, 2]. Currently, over 50 million people in the world have neurocognitive diseases, almost 20 million of which have Parkinson's Disease (PD) or Neurocognitive Disorder with Lewy Bodies (NCDLB). The overall number of people in the world with neurocognitive disease is expected to exceed 131.5 million by year 2050, with about 43 million of those attributable to PC or NCDLB [1, 2, 4, 5].

In 2015, the global cost of providing treatment and long-term care to people with neurocognitive disease was about $818 billion. That figure is expected to exceed $4 trillion by year 2050 [2–4]. The cost of providing treatment and long-term care to patients with PD and NCDLB exceeds one third of the total global expense, because Lewy body diseases like PD and NCDLB encompass a large and varied number of cognitive, motor, and autonomic symptoms [8]. Lewy bodies are abnormal intracellular aggregations of α-synuclein protein [9] that can affect any neurotransmitter pathway in any one or all of the ANS, CNS, PNS, or ENS.

Gastric slowing due to α-synucleopathology is an almost universal feature of PD and NCDLB, but is often not a focus of treatment [18]. As the symptoms of constipation, obstipation, and impaction progress, they negatively impact mobility, sleep, cognition, and mood, increasing the cost of care and debilitating or dramatically reducing the quality of life for patients [11–17]. From a phylogenetic perspective, the central nervous system and all its higher cortical functions exist solely in service of the alimentary canal. The impact that constipation, obstipation, and impaction have on the quality of life cannot be overstated.

When constipation, obstipation, and impaction are addressed for patients with α-synucleopathology, conventional over-the-counter treatments are usually recommended, even though research has shown that such treatments are ineffective for patients with PD and NCDLB [12]. Such treatment suggests unawareness that

constipation is considered a common feature of α-synucleopathology, likely prodromal for Lewy body (α-synuclein) pathology, often manifesting years before other α-synucleopathology [17, 21, 37, 54–57]; and that in constellation with late-life onset depression, cognitive impairment, and RBD/RSWA, constipation may be a reliable biomarker for α-synucleopathology [18, 24, 25, 29, 30].

In this chapter, a description was given of α-synucleopathology in the Lewy body diseases PD and NCDLB, and its symptomatic manifestations in the ENS. Explanation was made for the specific mechanisms through which α-synucleopathology interferes with gastric motility, as well as the specific mechanisms through which specific medications can address α-synucleopathology in the ENS. It was hypothesized that α-synuclein pathological impairment of the MP and CSMP in patients with NCDLB and PD might be mitigated with the use of the AchEI donepezil, which has demonstrated effectiveness for boosting cholinergic activity, and mitigating symptoms of α-synucleopathology in patients with PD and NCDLB. The expected outcomes included reduction of the symptoms of constipation, obstipation, and impaction. It was also hypothesized that donepezil might have specific benefit for reducing constipation in PD and NCDLB patients for whom L-dopa agents like carbidopa-levodopa are prescribed.

A series of case studies was then presented, in which four patients at varying levels of disease progression with PD and NCDLB were orally administered donepezil in daily doses varying from 5 to 10 mg. Results indicated that the use of donepezil was associated with significant reduction in the symptoms of constipation, obstipation and/or impaction. Although there had been progression of cognitive interference, movement disorders, and other Lewy body pathology in two of the patients (case studies #3 and #4), symptom reduction for constipation, obstipation and/or impaction for all four patients was consistent over time, assessed at intervals of two, four and 6 weeks, and later, at intervals of 6, 12, and 18 months [135–137].

The findings support the hypothesis donepezil might reduce α-synuclein pathological impairment of the MP and CSMP in patients with NCDLB and PD, increasing bowel motility and reducing the symptom of constipation. The findings also support the hypothesis that donepezil might have specific benefit in reducing constipation in PD and NCDLB patients for whom L-dopa agents like carbidopa-levodopa are prescribed. It appears that donepezil achieves such symptom reduction through its "dual action:" in part, specifically and reversibly limiting the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase [129, 130]; and in part, by independently facilitating neuronal nicotinic acetylcholine receptors [131]. The combined effect of these two mechanisms is to effectively increase acetylcholine levels and mitigate the symptoms of cholinergic impairment [128].

The reduction of constipation, obstipation, and impaction without exacerbation or emergence of other symptoms in all four patients over an 18 month period suggests that donepezil might be efficacious for treating these symptoms over an extended time frame, including its use for patients simultaneously taking carbidopa-levodopa. The findings are also consistent with previous research demonstrating that donepezil is effective for slowing or reversing cognitive symptom progression in Lewy body disorders, including short-term memory loss, difficulty with word-finding, hallucinations, and cognitive interference [107, 110–123]. To increase our understanding of α-synucleopathology and its role in PD and NCDLB, the symptoms of constipation, obstipation, and impaction, and effective medical interventions, further research is suggested, including longitudinal case studies, as well as large data set analyses using larger numbers of subjects matched for diagnosis, age, gender, and other variables.

8. Declarations

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Written consent was provided by each of the four patients described in the case studies to release the clinical information contained therein. Patient identifiers have been kept to a minimum. This paper was written according to the Ethical Principles of the American Psychological Association. Charles M. Lepkowsky, PhD, is the sole author of this work, including its conception and design; the acquisition, analysis, and interpretation of data; drafting, writing, and editing; and final approval of the version published; and accepts accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

There are no competing interests involved in the research reported or the writing of this chapter.

Author details

Charles M. Lepkowsky
Independent Practice, Solvang, CA, USA

*Address all correspondence to: clepkowsky@gmail.com

References

[1] World Health Organization. Life expectancy: Global Health Observatory Data [Internet]. 2018. Available from: http://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends/en/ [Accessed 2018-07-08]

[2] US Census Bureau. An Aging World: 2015 [Internet]. 2016. Available from: https://www.census.gov/content/dam/Census/library/publications/2016/demo/p95-16-1.pdf [Accessed 2018-07-08]

[3] Alzheimer's Disease International. World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends [Internet]. 2016. Available from: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf [Accessed 2018-07-08]

[4] Kowal S, Dall T, Chakrabarti R, Storm M, Jain A. The current and projected economic burden of Parkinson's disease in the United States. Movement Disorders. 2013;**28**(3):311-318. DOI: 10.1002/mds.25292

[5] Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013;**80**(19):1778-1783. DOI: 10.1212/WNL.0b013e31828726f5

[6] U.S. Centers for Medicare and Medicaid Services. Hospice Center [Internet]. 2015. Available from: http://www.cms.gov/Medicare/MedicareFee-for-Service-Payment/Hospice/Medicare_Hospice_Data.html.[Accessed 2016-07-12]

[7] U.S. Burden of Disease Collaborators. The state of U.S. health, 1990-2010: Burden of diseases, injuries, and risk factors. JAMA. 2013;**310**(6):591-608. DOI: 10.1001/jama.2013.13805

[8] Lepkowsky CM. Neurocognitive disorder with Lewy bodies: Evidence-based diagnosis and treatment. Practice Innovations. 2016;**1**(4):234-242. DOI: 10.1037/pri0000031

[9] Taguchi K, Watanabe Y, Tsujimura A, Tanaka M. Brain region-dependent differential expression of alpha-synuclein. The Journal of Comparative Neurology. 2015;**524**(6):1236-1258. DOI: 10.1002/cne.23901. [Accessed 2018-07-08]

[10] Sanjari MH, Zare-Shahabadi A, Rahmani F, Rezaei N. Neurotransmission systems in Parkinson's disease. Reviews in the Neurosciences. 2017;**28**(5):509-536. DOI: 10.1515/revneuro-2016-0068

[11] Gonera E, Van't Hof M, Berger H, van Weel C, Horstink M. Symptoms and duration of the prodromal phase in Parkinson's disease. Movement Disorders. 1997;**12**(6):871-876. DOI: 10.1002/mds.870120607

[12] Phillips C, Polakoff D, Maue S, Mauch R. Assessment of constipation management in long-term care patients. Journal of the American Medical Directors Association. 2001;**2**(4):149-154. PMID: 12812571

[13] Klockgether T. Parkinson's disease: Clinical aspects. Cell and Tissue Research. 2004;**318**(1):115-120. DOI: 10.1007/s00441-004-0975-6

[14] Chaudhuri K, Healy D, Schapira A. Non-motor symptoms of Parkinson's disease: Diagnosis and management. Lancet Neurology. 2006;**5**(3):235-245. DOI: 10.1016/S1474-4422(06)70373-8

[15] Winter Y, von Campenhausen S, Brozova H, Skoupa J, Reese J, Bötzel K, et al. Costs of Parkinson's disease in Eastern Europe: A Czech cohort study. Parkinsonism & Related Disorders.

2010;**16**(1):51-56. DOI: 10.1016/j.parkreldis.2009.07.005

[16] Wasner G, Deuschl G. Pains in Parkinson disease—Many syndromes under one umbrella. Nature Reviews. Neurology. 2012;**8**(5):284-294. DOI: 10.1038/nrneurol.2012.54

[17] Rossi M, Merello M, Perez-Lloret S. Management of constipation in Parkinson's disease. Expert Opinion on Pharmacotherapy. 2014;**16**(4):547-557. DOI: 10.1517/14656566.2015.997211

[18] Lepkowsky CM. Donepezil for Lewy body constipation: Four case studies. Activitas Nervosa Superior. 2017;**59**(1):19-27. DOI: 10.1007/s41470-017-0004-1

[19] Scott D, Roy S. α-Synuclein inhibits intersynaptic vesicle mobility and maintains recycling-pool homeostasis. The Journal of Neuroscience. 2012;**32**(30):10129-10135. DOI: 10.1523/JNEUROSCI.0535-12.2012

[20] Larson M, Sherman M, Greimel S, Kuskowski M, Schneider J, Bennett D, et al. Soluble α-synuclein is a novel modulator of Alzheimer's disease pathophysiology. The Journal of Neuroscience. 2012;**32**(30):10253-10266. DOI: 10.1523/JNEUROSCI.0581-12.2012

[21] Donaghy P, McKeith I. The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis. Alzheimer's Research & Therapy. 2014;**6**(4):46. DOI: 10.1186/alzrt274. [Internet]. Available from: https://alzres.biomedcentral.com/articles/10.1186/alzrt274 [Accessed 2016-06-13]

[22] McKeith I, Dickson D, Lowe J, Emre M, O'Brien J, Feldman H, et al. Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. Neurology. 2005;**65**(12):1863-1872. DOI: 10.1212/01.wnl.0000187889.17253.b1

[23] McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Journal of Alzheimer's Disease. 2006;**9**(3 Suppl):417-423. PMID: 16914880

[24] McCarter SJ, St Louis EK, Boeve BF. REM sleep behavior disorder and REM sleep without Atonia as an early manifestation of degenerative neurological disease. Current Neurology and Neuroscience Reports. 2012;**12**(2):182-192. DOI: 10.1007/s11910-012-0253-z

[25] Allan LM, Ballard CG, Allen J, Murray A, Davidson AW, McKeith I, et al. Autonomic dysfunction in dementia. Journal of Neurology, Neurosurgery, and Psychiatry. 2007;**78**(7):671-677. DOI: 10.1136/jnnp.2006.102343

[26] Cersosimo M. Gastrointestinal biopsies for the diagnosis of alpha-synuclein pathology in Parkinson's disease. Gastroenterology Research and Practice. 2015: Article ID 476041. DOI: 10.1155/2015/476041 [. Accessed 2016-06-17]

[27] Funabe S, Takao M, Saito Y, Hatsuta H, Sugiyama M, Ito S, et al. Neuropathologic analysis of Lewy-related α-synucleinopathy in olfactory mucosa. Neuropathology. 2013;**33**(1):47-58. DOI: 10.1111/j.1440-1789.2012.01329.x

[28] Landy KM, Salmon DP, Galasko D, Filoteo JV, Festa EK, Heindel WC, et al. Motion discrimination in dementia with Lewy bodies and Alzheimer disease. Neurology. 2015;**85**(16):1376-1382. DOI: 10.1212/WNL.0000000000002028

[29] Kosaka K, Oyanagi S, Matsushita M, Hori A. Presenile dementia with Alzheimer-, Pick- and Lewy-body changes. Acta Neuropathologica. 1976;**36**(3):221-233. . PMID: 188300. DOI: 10.1007/BF00685366

[30] Ferman TJ, Smith GE, Kantarci K, Boeve BF, Pankratz VS, Dickson DW, et al. Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. Neurology. 2013;**81**(23):2032-2038. DOI: 10.1212/01.wnl.0000436942.55281.47

[31] Molloy S, McKeith IG, O'Brien JT, Burn DJ. The role of levodopa in the management of dementia with Lewy bodies. Journal of Neurology, Neurosurgery, and Psychiatry. 2005;**76**(9):1200-1203. DOI: 10.1136/jnnp.2004.052332

[32] Schenck C, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: A 16-year update on a previously reported series. Sleep Medicine;**14**(8):744-748. DOI: 10.1016/j.sleep.2012.10.009

[33] Coune PG, Craveiro M, Gaugler MN, Mlynárik V, Schneider BL, Aebischer P, et al. An in vivo ultrahigh field 14.1 T (1) H-MRS study on 6-OHDA and α-synuclein-based rat models of Parkinson's disease: GABA as an early disease marker. NMR in Biomedicine. 2013;**26**(1):43-50. DOI: 10.1002/nbm.2817.

[34] Kupsky WJ, Grimes MM, Sweeting J, Bertsch R, Cote LJ. Parkinson's disease and megacolon: Concentric hyaline inclusions (Lewy bodies) in enteric ganglion cells. Neurology. 1987;**37**(7):1253-1255. PMID: 3037441

[35] Shankle WR, Landing BH, Ang SM, Chui H, Villarreal-Engelhardt G, Zarow C. Studies of the enteric nervous system in Alzheimer disease and other dementias of the elderly: Enteric neurons in Alzheimer disease. Modern Pathology. 1993;**6**(1):10-14. PMID: 8426853

[36] Braak H, Braak E. Pathoanatomy of Parkinson's disease. Journal of Neurology. 2000;**247**(Supplement 2):ii3-ii10. DOI: 10.1007/PL00007758

[37] Abbott R, Webster R, Petrovitch H, Tanner C, Davis D, Masaki K, et al. Bowel movement frequency in late-life and incidental Lewy bodies. Movement Disorders. 2007;**2**(11):1581-1586. DOI: 10.1002/mds.21560

[38] Lebouvier T, Chaumette T, Paillusson S, Duyckaerts C, Bruley des Varannes S, Neunlist M, et al. The second brain and Parkinson's disease. The European Journal of Neuroscience. 2009;**30**(5):735-741. DOI: 10.1111/j.1460-9568.2009.06873.x

[39] Beach T, Adler C, Sue L, Vedders L, Lue L, White C, et al. Multi-organ distribution of phosphorylated α-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathologica. 2010;**119**(6):689-702. DOI: 10.1007/s00401-010-0664-3

[40] Lebouvier T, Neunlist M, Bruley d, Varannes S, Coron E, Drouard A, et al. Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms. PLoS One. 2010;**5**(9):e12728. DOI: 10.1371/journal.pone.0012728

[41] Gold A, Turkalp Z, Munoz D. Enteric alpha-synuclein expression is increased in Parkinson's disease but not Alzheimer's disease. Movement Disorders. 2013;**28**(2):237-241. DOI: 10.1002/mds.25298

[42] Semar S, Klotz M, Letiembre M, Van Ginneken C, Braun A, Jost V, et al. Changes of the enteric nervous system in amyloid-β protein precursor transgenic mice correlate with disease progression. Journal of Alzheimer's Disease. 2013;**36**(1):7-20. DOI: 10.3233/JAD-120511

[43] Gelpi E, Navarro-Otano J, Tolosa E, Gaig C, Compta Y, Rey M, et al. Multiple organ involvement by alpha-synuclein

pathology in Lewy body disorders. Movement Disorders. 2014;**29**(8):1010-1018. DOI: 10.1002/mds.25776

[44] Corbillé A, Neunlist M, Derkinderen P. Cross-linking for the analysis of α-synuclein in the enteric nervous system. Journal of Neurochemistry. 2016;**139**(5):839-847. DOI: 10.1111/jnc.13845

[45] Jost W, Schimrigk K. Constipation in Parkinson's disease. Klinische Wochenschrift. 1991;**69**(20):906-909. Available from: https://link.springer.com/article/10.1007/BF01798536 [Accessed 2016-01-04]

[46] Tanaka Y, Kato T, Nishida H, Yamada M, Koumura A, Sakurai T, et al. Is there a delayed gastric emptying of patients with early-stage, untreated Parkinson's disease? An analysis using the 13C-acetate breath test. Journal of Neurology. 2011;**258**(3):421-426. DOI: 10.1007/s00415-010-5769-z

[47] Kaye J, Gage H, Kimber A, Storey L, Trend P. Excess burden of constipation in Parkinson's disease: A pilot study. Movement Disorders. 2006;**21**(8):1270-1273. DOI: 10.1002/mds.20942

[48] Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, MacPhee G, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. Movement Disorders. 2007;**22**(11):1623-1629. DOI: 10.1002/mds.21586

[49] Langston J. The Parkinson's complex: Parkinsonism is just the tip of the iceberg. Annals of Neurology. 2006;**59**(4):591-596. DOI: 10.1002/ana.20834

[50] Dickson DW, Fujishiro H, Delle Donne A, Menke J, Ahmed Z, Klos KJ, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. Acta Neuropathologica. 2008;**115**(4):437-444. DOI: 10.1007/s00401-008-0345-7.

[51] Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurology. 2015;**14**(6):625-639. DOI: 10.1016/S1474-4422(15)00007-1.

[52] Visanji N, Marras C. The relevance of pre-motor symptoms in Parkinson's disease. Expert Review of Neurotherapeutics. 2015;**15**(10):1205-1217. DOI: 10.1586/14737175.2015.1083423

[53] Schulz J, Hausmann L, Hardy J. 199 years of Parkinson disease – What have we learned and what is the path to the future? Journal of Neurochemistry. 2016;**139**(S1):3-7. DOI: 10.1111/jnc.13733

[54] Pfeiffer R. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurology. 2003;**2**(2):107-116. PMID: 12849267

[55] Savica R, Carlin J, Grossardt B, Bower J, Ahlskog J, Maraganore D, et al. Medical records documentation of constipation preceding Parkinson disease: A case-control study. Neurology. 2009;**73**(21):1752-1758. DOI: 10.1212/WNL.0b013e3181c34af5

[56] Iranzo A, Gelpi E, Tolosa E, Molinuevo J, Serradell M, Gaig C, et al. Neuropathology of prodromal Lewy body disease. Movement Disorders. 2014;**29**(3):410-415. DOI: 10.1002/mds.25825

[57] Alzforum. International Dementia with Lewy Bodies Conference 2015 [Internet]. Available from: http://www.alzforum.org/print-series/554861. [Accessed 2016-01-03]

[58] Wakabayashi K, Takahashi H, Takeda S, Ohama E, Ikuta F. Lewy bodies in the enteric nervous system in Parkinson's disease. Archives of Histology and Cytology.

1989;**52**(Supplement P):191-194. [Internet] Available from: https://pdfs.semanticscholar.org/d2c8/68f7e2853ec299d7962dd75048ac239d3d48.pdf [Accessed 2016-03-15]

[59] Braaka H, de Vosb R, Bohlc J, Del Tredici K. Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. Neuroscience Letters. 2006;**396**(1):67-72. DOI: 10.1016/j.neulet.2005.11.012

[60] Hawkes C, Del Tredici K, Braak H. Parkinson's disease: A dual-hit hypothesis. Neuropathology and Applied Neurobiology. 2007;**33**(6):599-614. DOI: 10.1111/j.1365-2990.2007.00874.x

[61] Minguez-Castellanos A, Chamorro C, Escamilla-Sevilla F, Ortega-Moreno A, Rebollo A, Gomez-Rio M, et al. Do α-synuclein aggregates in autonomic plexuses predate Lewy body disorders? Neurology. 2007;**68**(23):2012-2018. DOI: 10.1212/01.wnl.0000264429.59379.d9

[62] Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T, et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neurologica Scandinavica. 2014;**128**(6):805-820. DOI: 10.1007/s00401-014-1343-6

[63] Gjerløff T, Fedorova T, Knudsen K, Munk O, Nahimi A, Jacobsen S, et al. Imaging acetylcholinesterase density in peripheral organs in Parkinson's disease with 11C-donepezil PET. Brain. 2015;**138**(3):653-663. DOI: 10.1093/brain/awu369

[64] Porter A, Wattchow D, Brookes S, Costa M. Cholinergic and nitrergic interneurones in the myenteric plexus of the human colon. Gut. 2002;**51**(1):70-75. DOI: 10.1136/gut.51.1.70

[65] McKeith I, Galasko D, Kosaka K, Perry E, Dickson D, Hansen L, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology. 1996;**47**(5):1113-1124. DOI: 10.1212/WNL.47.5.1113

[66] Smith WW, Jiang H, Pei Z, Tanaka Y, Morita H, Sawa A, et al. Endoplasmic reticulum stress and mitochondrial cell death pathways mediate A53T mutant alpha-synuclein-induced toxicity. Human Molecular Genetics. 2005;**14**(24):3801-3811. DOI: 10.1093/hmg/ddi396

[67] Cooper AA, Gitler AD, Cashikar A, Haynes CM, Hill KJ, Bhullar B, et al. Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models. Science. 2006;**313**(5785):324-328. DOI: 10.1126/science.1129462

[68] Devi L, Anandatheerthavarada HK. Mitochondrial trafficking of APP and alpha synuclein: Relevance to mitochondrial dysfunction in Alzheimer's and Parkinson's diseases. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2010;**1802**(1):11-19. DOI: 10.1016/j.bbadis.2009.07.007

[69] Parsons CG, Danysz W, Dekundy A, Pulte I. Memantine and cholinesterase inhibitors: Complementary mechanisms in the treatment of Alzheimer's disease. Neurotoxicity Research. 2013;**24**(3):358-369. DOI: 10.1007/s12640-013-9398-z], 10.1007/s12640-013-9398-z]

[70] Edwards L, Quigley E, Pfeiffer R. Gastrointestinal dysfunction in Parkinson's disease: Frequency and pathophysiology. Neurology. 1992;**42**(4):726-732. DOI: 10.1212/WNL.42.4.726

[71] Johanson J, Sonnenberg A, Koch T, McCarty D. Association of constipation with neurologic diseases. Digestive Diseases and Sciences. 1992;**37**(2):179-186. PMID: 1735333

[72] Winge K, Rasmussen D, Werdelin L. Constipation in neurological diseases. Journal of Neurology, Neurosurgery, and Psychiatry. 2003;**74**(1):13-19. DOI: 10.1136/jnnp.74.1.13

[73] Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. Journal of Neurochemistry. 2016;**139**(S1):318-324. DOI: 10.1111/jnc.13691

[74] Lebouvier T, Tasselli M, Paillusson S, Pouclet H, Neunlist M, Derkinderen P. Biopsable neural tissues: Toward new biomarkers for Parkinson's disease? Frontiers in Psychiatry. 2010;**1**:128. DOI: 10.3389/fpsyt.2010.00128. [Internet] Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2010.00128/full [Accessed 2016-01-14]

[75] Molloy S, McKeith I, O'Brien J, Burn D. The role of levodopa in the management of dementia with Lewy bodies. Journal of Neurology, Neurosurgery, and Psychiatry. 2005;**76**(9):200-1203. DOI: 10.1136/jnnp.2004.052332

[76] Lepkowsky CM. Medications linked to cognitive impairment in older adults. Practice Innovations. 2016;**1**(4):253-264. DOI: 10.1037/pri0000033

[77] Merck Pharmaceuticals: Product Information: Sinemet CR (carbidopa-levodopa). [Internet]. 2016. Available from: https://www.merck.com/product/usa/pi_circulars/s/sinemet/sinemet_pi.pdf [Accessed 2016-01-15]

[78] Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: A review and practical application. Aging Health. 2008;**4**(3):311-320. DOI: 10.2217/1745509X.4.3.311

[79] Campbell N, Boustani M, Limbil T, Ott C, Fox C, Maidment I, et al. The cognitive impact of anticholinergics: A clinical review. Clinical Interventions in Aging. 2009;**4**(1):225-233. PMID: 19554093 PMCID: PMC2697587

[80] Cai X, Campbell N, Khan B, Callahan C, Boustani M. Long-term anticholinergic use and the aging brain. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2013;**9**(4):377-385. DOI: 10.1016/j.jalz.2012.02.005

[81] Hutchinson M, Fazzini E. Cholinesterase inhibition in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry. 1996;**61**(3):324-325. PMID: 8795611 PMCID: PMC486563

[82] Tiraboschi P, Hansen L, Alford M, Sabbagh M, Schoos B, Masliah E, et al. Cholinergic dysfunction in diseases with Lewy bodies. Neurology. 2000;**54**(2):407-411. PMID: 10668703

[83] Francis P, Perry E. Cholinergic and other neurotransmitter mechanisms in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies. Movement Disorders. 2007;**22**(S17):S351-S357. DOI: 10.1002/mds.21683

[84] Bohnen N, Albin R. The cholinergic system and Parkinson disease. Behavioural Brain Research. 2011;**221**(2):564-573. DOI: 10.1016/j.bbr.2009.12.048

[85] Müller M, Bohnen N. Cholinergic dysfunction in Parkinson's disease. Current Neurology and Neuroscience Reports. 2013;**13**(9):377. DOI: 10.1007/s11910-013-0377-9

[86] Grothe M, Schuster C, Bauer F, Heinsen H, Prudlo J, Teipel S. Atrophy of the cholinergic basal forebrain in dementia with Lewy bodies and Alzheimer's disease dementia. Journal of Neurology. 2014;**261**(10):1939-1948. DOI: 10.1007/s00415-014-7439-z

[87] Hall H, Reyes S, Landeck N, Bye C, Leanza G, Double K, et al. Hippocampal Lewy pathology and cholinergic dysfunction are associated with dementia in Parkinson's disease. Brain. 2014;**137**(9):2493-2508. DOI: 10.1093/brain/awu193

[88] Perez-Lloret S, Barrantes F. Deficits in cholinergic neurotransmission and their clinical correlates in Parkinson's disease. Npj Parkinson's Disease. 2016;**2**,. Article number: 16001. DOI: 10.1038/npjparkd.2016.1

[89] Scharre D, Chang S, Nagaraja H, Park A, Adeli A, Agrawal P, et al. Paired studies comparing clinical profiles of Lewy body dementia with Alzheimer's and Parkinson's diseases. Journal of Alzheimer's Disease. 2016;**549**(3):995-1004. DOI: 10.3233/JAD-160384

[90] Watanabe H, Ieda T, Katayama T, Takeda A, Aiba I, Doyu M, et al. Cardiac (123)Imetaiodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: Comparison with Alzheimer's disease. Journal of Neurology, Neurosurgery, and Psychiatry. 2001;**70**(6):781-783. [Internet] available from: http://jnnp.bmj.com/ [Accessed on 2017-12-15]

[91] Perry E, Smith C, Court J, Perry R. Cholinergic nicotinic and muscarinic receptors in dementia of Alzheimer, Parkinson and Lewy body types. Journal of Neurology. 1990;**2**(3):149-158. PMID: 2175197

[92] McKeith IG. Spectrum of Parkinson's disease, Parkinson's dementia, and Lewy body dementia. Neurologic Clinics. 2000;**18**:865-902. PMID: 11072265

[93] Aarsland D, Hutchinson M, Larsen J. Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. International Journal of Geriatric Psychiatry. 2003;**18**(10):937-941. DOI: 10.1002/gps.949

[94] Folstein MF, Folstein SE, McHugh P. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;**12**(3):189-198. PMID: 1202204

[95] McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, et al. Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. Lancet. 2000;**356**(9247):2031-2036. DOI: 10.1016/S0140-6736(00)03399-7

[96] McKeith IG, Grace JB, Walker Z, Byrne EJ, Wilkinson D, Stevens T, et al. Rivastigmine in the treatment of dementia with Lewy bodies: Preliminary findings from an open trial. International Journal of Geriatric Psychiatry. 2000;**15**(5):387-392. PMID: 10822236

[97] Grace J, Daniel S, Stevens T, Shankar KK, Walker Z, Byrne EJ, et al. Long-term use of rivastigmine in patients with dementia with Lewy bodies: An open-label trial. International Psychogeriatrics. 2001;**13**(2):199-205. PMID: 11495394

[98] Bullock R, Cameron A. Rivastigmine for the treatment of dementia and visual hallucinations associated with Parkinson's disease: A case series. Current Medical Research and Opinion. 2002;**18**(5):258-264. DOI: 10.1185/030079902125000813

[99] Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. The New England Journal of Medicine. 2004;**351**(24):2509-2518. DOI: 10.1056/NEJMoa041470

[100] Bourke D, Druckenbrod RW. Possible association between donepezil and worsening Parkinson's disease. The Annals of Pharmacotherapy. 1998;**32**(5):610-611. DOI: 10.1345/aph.17355

[101] Babic T, Zurak N. Convulsions induced by donepezil. Journal of Neurology, Neurosurgery, and Psychiatry. 1999;**66**(3):410. PMID 1008455

[102] Hashimoto M, Imamura T, Tanimukai S, Kazui H, Mori E. Urinary incontinence: An unrecognized adverse effect with donepezil. Lancet. 2000;**356**(9229):568. DOI: 10.1016/S0140-6736(00)02588-5

[103] Onofrj M, Thomas A. Severe worsening of parkinsonism in Lewy body dementia due to donepezil. Neurology. 2003;**61**(10):1452. DOI: 10.1212/01.WNL.0000094201.80888.DA

[104] Rozzini L, Ghianda D, Trabucchi M, Padovani A. Severe worsening of parkinsonism in Lewy body dementia due to donepezil. Neurology. 2004;**63**(8):1543-1544. PMID: 15505196

[105] Iraqi A, Hughes T. An unusual case of nightmares with galantamine. Journal of the American Geriatrics Society. 2009;**57**(3):565. DOI: 10.1111/j.1532-5415.2009.02157.x

[106] News Medical: Health News and Information: Alzheimer's Drug Aricept (donepezil) Linked to Serious Side Effects. [1]. 2015. Available from: http://www.news-medical.net/news/20150121/Alzheimers-drug-Aricept-(donepezil)-linked-to-serious-side-effects.aspx. [Accessed: 2016-01-15]

[107] Fabbrini G, Barbanti P, Aurilia C, Pauletti C, Lenzi GL, Meco G. Donepezil in the treatment of hallucinations and delusions in Parkinson's disease. Neurological Sciences. 2002;**23**(1):41-43. DOI: 10.1007/s100720200022

[108] Bergman J, Lerner V. Successful use of donepezil for the treatment of psychotic symptoms in patients with Parkinson's disease. Clinical Neuropharmacology. 2002;**25**(2):107-110. PMID: 11981238

[109] Shea C, MacKnight C, Rockwood K. Donepezil for treatment of dementia with Lewy bodies: A case series of nine patients. International Psychogeriatrics. 1998;**10**(3):229-238. PMID: 9785144

[110] Aarsland D, Brønnick K, Karlsen K. Donepezil for dementia with Lewy bodies: A case study. International Journal of Geriatric Psychiatry. 1999;**14**(1):69-72. PMID: 10029938

[111] Samuel W, Caligiuri M, Galasko D, Lacro J, Marini M, McClure FS, et al. Better cognitive and psychopathologic response to donepezil in patients prospectively diagnosed as dementia with Lewy bodies: A preliminary study. International Journal of Geriatric Psychiatry. 2000;**15**(9):794-802. PMID: 10984725

[112] Rojas-Fernandez CH. Successful use of donepezil for the treatment of dementia with Lewy bodies. The Annals of Pharmacotherapy. 2001;**35**(2):202-205. DOI: 10.1345/aph.10192

[113] Aarsland D, Laake K, Larsen J, Janvin C. Donepezil for cognitive impairment in Parkinson's disease: A randomised controlled study. Journal of Neurology, Neurosurgery, and Psychiatry. 2002;**72**:708-712. DOI: 10.1136/jnnp.72.6.708

[114] Aarsland D, Mosimann UP, McKeith IG. Role of cholinesterase inhibitors in Parkinson's disease and dementia with Lewy bodies. Journal of Geriatric Psychiatry and Neurology. 2004;**17**(3):164-171. DOI: 10.1177/0891988704267463

[115] Leroi I, Brandt J, Reich SG, Lyketsos CG, Grill S, Thompson R, et al. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. International Journal of Geriatric Psychiatry. 2004;**19**(1):1-8. DOI: 10.1002/gps.993

[116] McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, et al. International psychogeriatric association expert meeting on DLB. Dementia with Lewy bodies. Lancet Neurology. 2004;**3**(1):19-28. PMID: 14693108

[117] Thomas AJ, Burn DJ, Rowan EN, Littlewood E, Newby J, Cousins D, et al. A comparison of the efficacy of donepezil in Parkinson's disease with dementia and dementia with Lewy bodies. International Journal of Geriatric Psychiatry. 2005;**20**(10):938-944. DOI: 10.1002/gps.1381

[118] Ravina B, Putt M, Siderow A, Farrar J, Gillespie M, Crawley A, et al. Donepezil for dementia in Parkinson's disease: A randomised, double blind, placebo controlled, crossover study. Journal of Neurology, Neurosurgery, and Psychiatry. 2005;**76**(7):934-939. DOI: 10.1136/jnnp.2004.050682

[119] Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, Matsukawa N, et al. Donepezil-DLB study investigators. Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: Results from a 52-week, open-label, multicenter extension study. Dementia and Geriatric Cognitive Disorders. 2013;**36**(3-4):229-241. DOI: 10.1159/000351672

[120] Ikeda M, Mori E, Matsuo K, Nakagawa M, Kosaka K. Donepezil for dementia with Lewy bodies: A randomized, placebo-controlled, confirmatory phase III trial. Alzheimer's Research & Therapy. 2015;**7**(1):4. DOI: 10.1186/s13195-014-0083-0

[121] Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. Cochrane Database of Systematic Reviews. 2012;(3):CD006504. DOI: 10.1002/14651858.CD006504.pub2

[122] Bosboom JL, Stoffers D, Wolters ECH. Cognitive dysfunction and dementia in Parkinson's disease. Journal of Neural Transmission (Vienna). 2004;**111**(10-11):1303-1315. DOI: 10.1007/s00702-004-0168-1

[123] Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database of Systematic Reviews. 2006;**1**:CD005593. DOI: 10.1002/14651858.CD005593

[124] Minett TSC, Thomas A, Wilkinson L, Daniel SL, Sanders J, Richardson J, et al. What happens when donepezil is suddenly withdrawn? An open label trial in dementia with Lewy bodies and Parkinson's disease with dementia. International Journal of Geriatric Psychiatry. 2003;**18**(11):988-993. DOI: 10.1002/gps.995

[125] Mori E, Iked M, Kosaka K. Donepezil for dementia with Lewy bodies: A randomized, placebo-controlled trial. Annals of Neurology. 2012;**72**(1):41-52. DOI: 10.1002/ana.23557

[126] Mori E, Ikeda M, Nagai R, Matsuo K, Nakagawa M, Kosaka K. Long-term donepezil use for dementia with Lewy bodies: Results from an open-label extension of phase III trial. Alzheimer's Research & Therapy. 2015;7(1):5. DOI: 10.1186/s13195-014-0081-2

[127] Jacobsen FM, Comas-Díaz L. Donepezil for psychotropic-induced memory loss. The Journal of Clinical Psychiatry. 1999;**60**(10):698-704. PMID: 10549687

[128] Broad J, Kung V, Boundouki G, Aziz Q, De Maeyer J, Knowles C, et al. Cholinergic interactions between donepezil and prucalopride in human colon: Potential to treat severe intestinal dysmotility. British Journal of

Pharmacology. 2013;**170**(6):1253-1261. DOI: 10.1111/bph.12397

[129] Davidsson P, Blennow K, Andreasen N, Eriksson B, Minthon L, Hesse C. Differential increase in cerebrospinal fluid-acetylcholinesterase after treatment with acetylcholinesterase inhibitors in patients with Alzheimer's disease. Neuroscience Letters. 2001;**300**(3):157-160. PMID: 11226635

[130] Wilkinson DG, Francis PT, Schwam E, Payne-Parrish J. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: The relationship between pharmacological effects and clinical efficacy. Drugs & Aging. 2004;**21**(7):453-478. PMID: 15132713

[131] Di Angelantonio S, Bernardi G, Mercuri NB. Donepezil modulates nicotinic receptors of substantia nigra dopaminergic neurons. British Journal of Pharmacology. 2004;**141**(4):644-652. DOI: 10.1038/sj.bjp.0705660

[132] Galvin J. The quick dementia rating system (QDRS): A rapid dementia staging tool. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2015;**1**(2):249-259. DOI: 10.1016/j.dadm.2015.03.003

[133] Galvin J. Improving the clinical detection of Lewy body dementia with the Lewy body composite risk score. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2015;**1**(3):316-324. DOI: 10.1016/j.dadm.2015.05.004

[134] Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, et al. Anticholinergic activity of 107 medications commonly used by older adults. Journal of the American Geriatrics Society. 2008;**56**(7):1333-1341. DOI: 10.1111/j.1532-5415.2008.01737.x

[135] Lepkowsky CM. Donepezil for Lewy body constipation: A six month follow-up. Journal of Molecular and Genetic Medicine. 2017;**11**(3). DOI: 10.4172/1747-0862.1000287

[136] Lepkowsky CM. Donepezil for constipation in Lewy body disease: A twelve month follow-up. Journal of Molecular and Genetic Medicine. 2018;**12**(1). DOI: 10.4172/1747-0862.1000337

[137] Lepkowsky CM. Donepezil for α-synuclein constipation: An 18 month follow-up. POJ Clinical Case Reports. 2018;**1**(1):1-4. Available from: https://proskolar.org/wp-content/uploads/2018/08/Donepezil-for-%CE%B1%E2%80%90synuclein-Constipation-An-18-Month-Follow-Up.pdf [Accessed 08/02/2018]