mhc
MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Adverse outcomes of abrupt switch and discontinuation of acetylcholinesterase inhibitors in dementia with Lewy bodies: Case report and literature review

Tristyn L. Greiman[1]
Brittani N. Dear[2]
G. Lucy Wilkening, PharmD[3]

How to cite: Greiman TL, Dear BN, Wilkening GL. Adverse outcomes of abrupt switch and discontinuation of acetylcholinesterase inhibitors in dementia with Lewy bodies: Case report and literature review. Ment Health Clin [Internet]. 2019;9(5):309-14. DOI: 10.9740/mhc.2019.09.309.

Abstract

Due to the well-defined risks of abrupt discontinuation of certain psychiatric medications, such as withdrawal and worsening symptoms, guideline recommendations describe evidence-based strategies for tapering some psychiatric medications, such as antidepressants. Despite widespread use of acetylcholinesterase inhibitor (ACHEI) therapy in the management of dementia, guideline recommendations for discontinuation of these therapies are very inconsistent. Specifically, studies and evidence-based recommendations for discontinuing ACHEIs in patients with dementia with Lewy bodies (DLB) are severely lacking. This deficit is problematic in that emerging reports suggest several adverse outcomes, such as worsening cognition and behavioral symptoms, are associated with abrupt switching and discontinuation of ACHEI therapy in this population. A case of rapid cognitive and functional decline following both abrupt switch and discontinuation of donepezil in a patient diagnosed with DLB is presented. A literature review of outcomes following changes in ACHEI therapy in DLB is also presented.

Keywords: acetylcholinesterase inhibitors, dementia, medication discontinuation syndrome, donepezil, dementia with Lewy bodies

[1] PharmD Candidate, University of the Incarnate Word Feik School of Pharmacy, San Antonio, Texas, ORCID: https://orcid.org/0000-0002-4320-4359; [2] PharmD Candidate, University of the Incarnate Word Feik School of Pharmacy, San Antonio, Texas, ORCID: https://orcid.org/0000-0002-8041-6537; [3] (Corresponding author) Assistant Professor, Department of Pharmacy Practice, University of the Incarnate Word Feik School of Pharmacy, San Antonio, Texas, g.lucy.wilkening@gmail.com, ORCID: https://orcid.org/0000-0002-2247-1466

Disclosures: The authors have no actual or potential conflicts of interest to report in relation to this publication.

Introduction

Abrupt discontinuation of psychiatric medications, including antidepressants, antipsychotics, benzodiazepines, and mood stabilizers, has been commonly associated with myriad adverse effects, such as rebound symptoms and withdrawal.[1] Consequently, best practice recommendations in psychiatry often include specific guidelines for tapering medications safely, such as the National Institute for Health and Care Excellence[2] guidelines for antidepressant therapy. Recommendations for the appropriate discontinuation of acetylcholinesterase inhibitors (ACHEIs), however, are far less defined. The ACHEIs, which include the medications donepezil, rivastigmine, and galantamine, work by increasing the relative availability of acetylcholine in neuronal synapses by inhibiting the degradation enzyme acetylcholinesterase.[3] The neurotransmitter acetylcholine plays a role in cognitive symptoms, agitation, anxiety, and hallucinations, and concentrations are thought to be decreased in patients with major neurocognitive disorders or dementia.[3,4]

Major neurocognitive disorders is the significant cognitive decline from a previous level of performance in at least

one of the following: complex attention, executive function, learning and memory, language, motor function, and social cognition.[5] Available medications generally target symptom control as no evidence demonstrates that any medication prevents or slows neurodegeneration.[6] There are several types of major neurocognitive disorders, including Alzheimer dementia (AD), dementia with Lewy bodies (DLB), frontotemporal dementia, Parkinson disease with dementia (PDD), and vascular dementia.[5] Specifically, DLB is caused by α–synuclein accumulation throughout most areas of the brain as well as general dopaminergic neuronal loss.[7] The dopaminergic component of DLB sets it apart from AD, which is not associated with the same level of Parkinsonian symptoms.[7]

Dementia, including DLB, is progressive and terminal, and symptoms frequently require pharmacologic intervention. The AChEIs are Food and Drug Administration-approved for treatment of AD and, although not approved for treatment of DLB due to lack of large, well-powered studies, are often utilized to help manage cognitive, behavioral, and psychiatric symptoms of DLB.[6,8,9] For other types of dementia, such as vascular dementia and frontotemporal dementia, AChEIs are not routinely recommended as first-line pharmacotherapy.[8,10]

Approximately 21% of patients with end-stage dementia are prescribed an AChEI at the time of hospice enrollment, half of whom are prescribed donepezil specifically.[11] Abrupt discontinuation of these agents due to cardiovascular or gastrointestinal side effects, lack of efficacy, or family preference in end-of-life treatment is common although potentially detrimental.[12] Cases of substantial decline in cognition and behavioral symptoms along with a marked deterioration in Mini-Mental State Examination scores, a 30-point questionnaire used to measure cognitive impairment, have been reported following abrupt donepezil discontinuation in patients with PDD and DLB.[12] A PubMed literature search was conducted and identified several publications detailing adverse outcomes associated with abrupt discontinuation and switching of AChEI therapy in patients with DLB. Presented below is a review of this literature along with a case of an elderly female with DLB who experienced rapid cognitive and physical mobility decline following both abrupt switch of AChEI therapy and subsequent discontinuation. Patient and caregiver consent was obtained preceding publication of this report.

Case Report

This case outlines the events of an 83-year-old white female with a medical history of major depression, chronic kidney disease, hypertension, peripheral neuropathy, and DLB, which were well managed in the outpatient setting by a psychiatrist, psychiatric pharmacist, and primary care provider. Her medications at the time of these events included amlodipine 10 mg orally once daily, clonazepam 0.25 mg orally once daily as needed at night for anxiety and insomnia, gabapentin 300 mg orally 3 times daily, and losartan 100 mg orally once daily. The patient was diagnosed with unspecified dementia during hospitalization following knee replacement surgery. Three months after diagnosis, donepezil 10 mg once daily was initiated by outpatient psychiatry, after which the patient and family reported marked improvements in mobility and cognition. At 10 months, neurology confirmed a diagnosis of DLB through neuroimaging and switched donepezil to rivastigmine 4.6 mg/24-hour patch. Following this transition, her overall clinical picture began to deteriorate within days, including increased confusion, anxiety, visual hallucinations (VH), and decreased physical mobility. The patch was switched back to donepezil at month 12, resulting in improved sleep, mood, and mobility within days.

All medications were continued with good tolerability and response until month 18 when she began experiencing chronic diarrhea following high-dose amoxicillin treatment from a dental appointment. The patient was hospitalized during month 20 for 1 week for recurrent *Clostridium difficile* infection, at which time she experienced moderate decline in psychiatric health, including decreased sleep, increased confusion, a fall, and increased frequency of VH. Home medications were continued during her hospitalization, and psychiatric symptoms trended toward baseline as her infection responded to antibiotic therapy. The patient was discharged from the hospital to a step-down rehabilitation facility. During her 3-week stay in the rehabilitation facility, mental status exams demonstrated stepwise improvements in short-term memory, sleep, energy, and mood. Mobility continued to improve throughout the course of rehabilitation treatment; however, the patient continued to experience an increase in the intensity and frequency of VH. This was thought to be related to continued stay outside the home. The psychiatric team recommended placement back in the home with 24-hour care and 1:1 observation.

The patient was discharged home at month 21 with 24-hour care given continued improvements in mobility and functioning. At home, VH began to decrease in intensity and frequency. One week after returning home, the patient's primary care provider changed. At her first appointment with the new provider, donepezil 10 mg was discontinued without taper due to the provider's concerns that the VH were an adverse effect of AChEI therapy. In the 5 weeks following this medication change, she experienced a sharp decline in cognition, mobility, and mood. At month 22, the patient's family

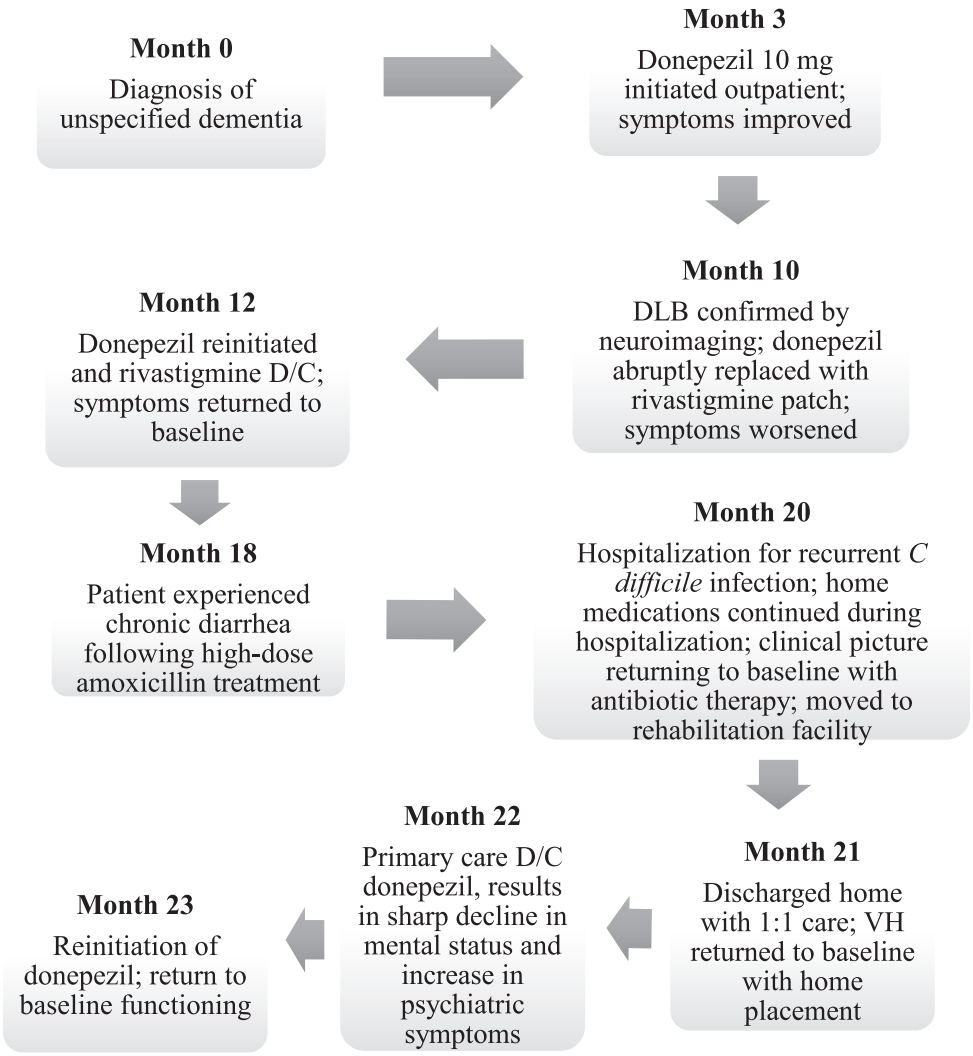

FIGURE: Timeline of case report events (D/C = discontinuation; DLB = dementia with Lewy bodies; VH = visual hallucinations)

reported a significant rise in VH accompanied with distress and difficulty redirecting from hallucinations, increased confusion, refusal of medications and food, progressive worsening of mobility to the point of requiring a motorized walker, and worsening sleep secondary to anxiety. On exam, the patient appeared anxious, demonstrated significant difficulties with word finding, and displayed increased confusion. The family requested pharmacologic intervention for VH. Changes to home routine, including new in-home care providers, were ordered as a nonpharmacologic means of managing symptoms, and donepezil 5 mg was restarted at the follow-up psychiatric appointment 1 month later. The family reported to the psychiatric pharmacist 3 days later that the patient assisted the caregivers in household activities for 2 days, attended her library group, and walked 1 mile. At the next visit 4 weeks later, the patient demonstrated significant improvements including verbal participation, responsiveness, improved recall, lessened frequency and distress from VH, and ambulation with a cane. Donepezil therapy was increased to 10 mg, and the patient returned to her baseline level of functioning. An abbreviated timeline of events can be found in the Figure.

Literature Review

A PubMed literature search was conducted in October 2018 using the medical subject heading (MeSH) terms *cholinesterase inhibitors* and *delirium; cholinesterase inhibitors* and *substance withdrawal syndrome;* and *cholinesterase inhibitors* and *withholding treatment*. A Google®

TABLE: Literature review summary organized by intervention

Study	Design/ Intervention	No. Patients	Disease State	Medication	Outcomes
Minett et al[12] (2003)	Open label trial Initiation D/C Re-initiation	19	DLB PDD	Donepezil	Improved symptoms on initiation, worsening symptoms on D/C, resolution of symptoms on re-initiation
Singh and Dudley[14] (2003)	Case series D/C Re-initiation	2	DLB AD	Donepezil	Worsening symptoms on D/C, improved symptoms on re-initiation
Shega et al[15] (2009)	Survey D/C	152	Hospice-defined dementia	Donepezil Rivastigmine Galantamine	Approximately 30% of hospice medical directors reported observation of worsening symptoms on D/C
Bhanji and Gauthier[16] (2005)	Case series Switch	3	DLB	Donepezil Galantamine	Worsening symptoms on switching, 2/3 re-initiated with improved symptoms
Pakrasi et al[17] (2006)	Open-label trial Taper	16	DLB PDD	Donepezil	All but 1 patient tolerated D/C

AD = Alzheimer dementia; D/C = discontinuation; DLB = dementia with Lewy bodies; PDD = Parkinson disease with dementia.

(Mountain View, CA) search of the terms *cholinesterase discontinuation Lewy body dementia* and *stopping cholinesterase inhibitors* was also performed. References of included publications were reviewed for relevance. The search revealed a case series, an open-label trial, and a survey-based research paper that discussed abrupt AChEI discontinuation; 1 case series that outlined the effects of switching AChEI therapy; and an open-label trial that evaluated AChEI gradual taper. Included publications were reviewed for inclusion of patients with DLB, medication utilized, and method of AChEI discontinuation. Results are summarized in the Table.

Discussion

A comprehensive review of practice guidelines[13] for discontinuing AChEI therapy in AD was recently published, recommending an individualized approach to managing therapy given the lack of consistency in available literature. Evidence-based recommendations for discontinuing AChEI therapy in DLB are further limited. In 1 case series,[14] donepezil was discontinued in an 81-year-old female with a history of DLB. The patient experienced rapidly changing mood, increased agitation and crying, and trouble sleeping 5-6 days after cessation, and symptoms resolved upon re-initiation of the medication. In the same series, donepezil was discontinued in a 59-year-old female with a history of AD and vascular dementia, resulting in severe agitation and worsened sleep and concentration. Unlike the case involving the patient with DLB, donepezil was not rechallenged, and withdrawal symptoms resolved after 2 weeks, suggesting that discontinuation of AChEIs may be better tolerated in certain types of dementia. One open-label trial[12] assessed the effects of donepezil treatment, abrupt withdrawal, and recommencement in 8 and 11 patients with DLB and PDD, respectively. Marked average worsening of Mini-Mental State Examination scores were seen upon abrupt discontinuation in both groups. All patients returned to prediscontinuation functioning after medication re-initiation. Last, a survey-based study[15] of 152 hospice medical directors found that 80% of respondents encouraged the discontinuation of donepezil in hospice care; however, 30% of respondents reported rapid decline in cognitive functioning and emergence of challenging behaviors upon AChEI discontinuation.

Sudden changes in AChEI therapy may also present risks to patients with DLB as demonstrated in the case series[16] of 3 elderly males with DLB who were abruptly switched from donepezil to galantamine. Upon switching, the most common adverse events reported were increased agitation, delirium, and worsening concentration and sleep. Two patients improved upon reinitiating donepezil; the third patient did not restart donepezil but experienced some symptom control with the addition of trazodone and quetiapine. Similar outcomes were observed in the presented case[17] with abrupt switch to rivastigmine, which resulted in worsening cognition, increased VH, impaired sleep, and anxiety. The adverse effects seen after the abrupt discontinuation of donepezil in these cases were delayed, which may be related to the long half-life of donepezil. Future studies assessing the implications of AChEI cross-tapers may be warranted and should be designed keeping the pharmacokinetic differences of AChEIs in mind.

Controlled tapering of ACHEI therapy has shown promising results for safe ACHEI discontinuation in a study of 16 patients with PDD and DLB.[17] An open-label trial[17] reviewed the safety of a gradual 5 mg per month taper of donepezil in 7 and 9 patients with DLB and PDD, respectively. Only 1 patient was unable to tolerate discontinuation. Overall, discontinuation of therapy was largely successful with minimal relapse in symptoms. One study[18] of patients with AD has suggested that delusions and hallucinations may occur more frequently upon discontinuation in patients with such symptoms at baseline. This finding may correspond with findings in this report as DLB is inherently associated with sleep and memory impairment, VH, and fluctuating alertness. The methods of these studies suggest that patients with AD may tolerate a quicker tapering schedule than patients with DLB or PDD, warranting additional studies to evaluate the differences among types of dementia and ACHEIs tapers.

There is currently no evidence that ACHEIs delay disease progression or reverse any dementia processes. Given this and the terminal nature of dementia, transition to palliative care presents difficulties for patients and caregivers, including decisions about medication therapy. Although abrupt cessation of ACHEIs is frequently recommended by palliative medical providers, several reports[12,14,15] have demonstrated this practice to be problematic, particularly in DLB. Recommendations for appropriate ACHEI discontinuation in DLB are needed given the impact these therapeutic changes may have on patient quality of life and administration of alternative medication therapies. For example, in 1 case presented,[16] a patient with DLB was initiated on quetiapine for rebound symptom control following donepezil discontinuation despite the known increase in all-cause mortality associated with the use of antipsychotics in dementia-related psychosis. A better understanding of proper ACHEI discontinuation practices could mitigate these rebound adverse effects and potentially minimize utilization of harmful alternative medications.

Conclusion

Dementia of all types is a neurologically degenerative disease that currently has no cure. The ACHEIs are frequently utilized for symptom control, but there is a significant lack of literature available to guide clinical use. Reports indicate that abrupt switching and discontinuation of ACHEI therapy can lead to worsening psychiatric and motor symptoms in patients with DLB. Large, prospective trials are needed to determine optimal strategies for discontinuing and switching ACHEI therapy in patients with DLB and ultimately assist clinicians with therapeutic decision making.

References

1. Joffe RT. Discontinuing treatment for psychiatric disorders. J Psychiatry Neurosci. 2006;31(1):11-2. PubMed PMID: 16496030.
2. National Institute for Health and Care Excellence. Depression in adults: recognition and management (NICE Guideline 90) [cited 2018 Nov 2]. Available from: https://www.nice.org.uk/guidance/cg90/resources/depression-in-adults-recognition-and-management-pdf-975742638037
3. Lleó A. Current therapeutic options for Alzheimer's disease. Curr Genomics. 2007;8(8):550-8. DOI: 10.2174/138920207783769549. PubMed PMID: 19415128.
4. Neef D, Walling AD. Dementia with Lewy bodies: an emerging disease. Am Fam Physician. 2006;73(7):1223-9. PubMed PMID: 16623209.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Washington: American Psychiatric Association; 2013.
6. Szigeti K, Hafeez MU. Exploring the role of donepezil in dementia with Lewy bodies. Drugs Today (Barc). 2015;51(10):579-90. DOI: 10.1358/dot.2015.51.10.2389166. PubMed PMID: 26583300.
7. Beyer K, Domingo-Sàbat M, Ariza A. Molecular pathology of Lewy body diseases. Int J Mol Sci. 2009;10(3):724-45. DOI: 10.3390/ijms10030724. PubMed PMID: 19399218; PubMed Central PMCID: PMC2671999.
8. Cunningham EL, McGuinness B, Herron B, Passmore AP. Dementia. Ulster Med J. 2015;84(2):79-87. PubMed PMID: 26170481.
9. Mori E, Ikeda M, Kosaka K. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann Neurol. 2012;72(1):41-52. DOI: 10.1002/ana.23557. PubMed PMID: 22829268; PubMed Central PMCID: PMC3504981.
10. Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry. 2007;15(1):84-7. DOI: 10.1097/01.JGP.0000231744.69631.33. PubMed PMID: 17194818.
11. Weschules DJ, Maxwell TL, Shega JW. Acetylcholinesterase inhibitor and N-methyl-D-aspartic acid receptor antagonist use among hospice enrollees with a primary diagnosis of dementia. J Palliat Med. 2008;11(5):738-45. DOI: 10.1089/jpm.2007.0125. PubMed PMID: 18588406.
12. Minett T, Thomas A, Wilkinson LM, 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. Int J Geriatr Psychiatry. 2003;18(11):988-93. DOI: 10.1002/gps.995. PubMed PMID: 14618549.
13. Renn BN, Asghar-Ali AA, Thielke S, Catic A, Martini SR, Mitchell BG, et al. A systematic review of practice guidelines and recommendations for discontinuation of cholinesterase inhibitors in dementia. Am J Geriatr Psychiatry. 2018;26(2):134-47. DOI: 10.1016/j.jagp.2017.09.027. PubMed PMID: 29167065; PubMed Central PMCID: PMC5817050.
14. Singh S, Dudley C. Discontinuation syndrome following donepezil cessation. Int J Geriatr Psychiatry. 2003;18(4):282-4. DOI: 10.1002/gps.811. PubMed PMID: 12673601.
15. Shega JW, Ellner L, Lau DT, Maxwell TL. Cholinesterase inhibitor and N-methyl-D-aspartic acid receptor antagonist use in older adults with end-stage dementia: a survey of hospice medical directors. J Palliat Med. 2009;12(9):779-83. DOI: 10.1089/jpm.

2009.0059. PubMed PMID: 19622011; PubMed Central PMCID: PMC2988459.
16. Bhanji NH, Gauthier S. Emergent complications following donepezil switchover to galantamine in three cases of dementia with Lewy bodies. J Neuropsychiatry Clin Neurosci. 2005;17(4):552-5. DOI: 10.1176/jnp.17.4.552. PubMed PMID: 16387998.
17. Pakrasi S, Thomas A, Mosimann UP, Cousins DA, Lett D, Burn DJ, et al. Cholinesterase inhibitors in advanced dementia with Lewy bodies: increase or stop? Int J Geriatr Psychiatry. 2006;21(8):719-21. DOI: 10.1002/gps.1547. PubMed PMID: 16858742.
18. Herrmann N, O'Regan J, Ruthirakuhan M, Kiss A, Eryavec G, Williams E, et al. A randomized placebo-controlled discontinuation study of cholinesterase inhibitors in institutionalized patients with moderate to severe Alzheimer disease. J Am Med Dir Assoc. 2016;17(2):142-7. DOI: 10.1016/j.jamda.2015.08.019. PubMed PMID: 26482056.