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CASE REPORT

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Suspected donepezil toxicity: A case report

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Abstract

Donepezil toxicity can present similarly to beta-blocker overdose and colitis. Symptoms include confusion, diaphoresis, and bradycardia. In patients with suspected medication-related toxicities, it is important to consider all possible causative agents in the active medication list.

KEYWORDS

beta-blocker, Donepezil, toxicity

1 | INTRODUCTION

Donepezil is an acetylcholinesterase inhibitor (AChEI) that prevents the breakdown of acetylcholine, a neurotransmitter, which is depleted in patients with Alzheimer's disease and dementia.[1] There are few reports showcasing donepezil toxicity in the literature and even less that display a coinciding beta-blocker toxicity.[2-8] This case highlights symptoms representative of a donepezil toxicity and risks that may occur even at the manufacturer's recommended doses.

The American Geriatrics Society's Beer's list recognizes donepezil as a high-risk medication in older adults due to increased rates of orthostatic hypotension and bradycardia within this population.[9] Some common (>10%) adverse reactions of donepezil include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. Other less common (1%-10%) adverse effects are insomnia, emesis, gastritis, hypertension, syncope, bradycardia, chills, generalized coldness, pain, dizziness, abnormal gait, confusion, fatigue, diaphoresis, abdominal pain, bloating, and constipation and were reported to occur more often in females of advancing age.[10] Toxicity symptoms reported in other case reports included: nausea, vomiting, confusion, somnolence, diaphoresis and bradycardia with greater prominence at higher donepezil doses.[2-8] In addition, postmarketing data have revealed hyperglycemia and hypothermia reported in less than 1% of patients.[10] One of the dose-related signs of toxicity in animals was lower body surface temperature.

Like donepezil toxicity, altered mental status and bradycardia commonly occur with beta-blocker toxicity. Hypothermia can occur with both agents; however, it is less prevalent in beta-blocker toxicity. Other effects seen with beta-blocker toxicity include hypotension, respiratory depression, seizure, hypoglycemia, and bronchospasm.[11,12] When AChEIs are co-administered with heart rate-lowering agents like beta-blockers, a theoretical risk of enhanced bradycardia exists.[12] Beta-blockers lower the heart rate by blocking beta-1 receptors and impeding the action of epinephrine and norepinephrine.[13] AChEIs increase acetylcholine at the synapses and affect the parasympathetic innervation of the heart, resulting in decreased sinoatrial- and atrioventricular node conduction and decreased heart rate.[14]

2 | CASE HISTORY

A 96-year-old female patient presented to the emergency department when her son reported she was difficult to awaken, diaphoretic and had an altered mental status compared to baseline. On the day of admission, the patient awoke in her usual state of health, able to converse, and ambulate, but prior to dinner, her son noted the patient was lethargic and unable to ambulate to the bathroom. The family also reported that the patient had been suffering from intermittent diarrhea and abdominal pain the past several months but was otherwise in her normal state of health. During a geriatric appointment three months prior, diarrhea and postprandial discomfort were noted with a possible relation to her donepezil dose, but the medical team chose to continue her donepezil as prescribed and monitor her symptoms. The patient's heart rate at this visit was 64 beats per minute (BPM) and weight was 99 pounds (45 kg).

The patient's history was notable for arteriosclerotic heart disease, chronic renal impairment, dementia, gastroesophageal reflux disease, hyperlipidemia, hypertension, and sensorineural hearing loss. Home medications included aspirin 81 mg daily, atorvastatin 40 mg nightly, donepezil 10 mg daily, esomeprazole 40 mg daily, and metoprolol succinate 50 mg nightly. Donepezil was prescribed two years ago, with the last dose change being one year ago from 5 mg to 10 mg daily and no metoprolol dose changes were made within the past two years. Her last metoprolol and donepezil doses were presumed to be given the evening and morning prior to admission, respectively.

2.1 | Differential diagnosis, investigations, and treatment

Upon initial observation, the patient was nonconversant and diaphoretic with abdominal tenderness and minimal response to stimulation. Vitals were notable for a 2 kg weight loss and a heart rate of 36 BPM; an electrocardiogram (ECG) revealed sinus bradycardia with nonspecific T wave abnormalities (see vitals in Table 1 and ECG in Figure 1). Baseline laboratories were pertinent for leukocytosis ($10.3x10^3$/L) with neutrophilic predominance, hyperglycemia (123 mg/dL) hypocarbia (20 mmol/L), and euthyroid (TSH = 0.72 μIU/mL). The patient was admitted to a general medicine floor for further workup of bradycardia and possible colitis.

TABLE 1 Initial ED Vitals

BP (mm Hg)	HR (bpm)	RR	Temp (˚F)	Wt (kg)	Height (cm)
140/52	36	11	96.8	43.1	145

Abbreviations: BP, blood pressure; HR, heart rate; RR, respiratory rate, Wt, weight.

On day one of the hospital admission, continuous telemetry was initiated, and metoprolol was held. Then, 500 mL of 5% dextrose with 0.9% saline was administered along with 2 g of magnesium and 10 mEq of potassium. A computed tomography scan was performed, and results were suggestive of colitis. Stool cultures were ordered, and the presumed colitis was empirically treated with intravenous (IV) ciprofloxacin and metronidazole. At approximately 0100 on day two, the patient's resting heart rate dropped from 40 BPM into the 30 s. In the event of a beta-blocker toxicity, a 3 mg IV injection of glucagon was administered, and the patient's heart rate temporarily increased to 82 BPM after 30 minutes. A glucagon infusion was then initiated at 2 mg/h for 2 hours. During this time, the heart rate ranged between 39 and 89 BPM (see Figure 2 for heart rate, temperature, and glucagon trends). Following this, a two-hour interruption in the glucagon infusion occurred due to the bag running out. Consequently, the heart rate decreased to 48 BPM and the patient also became hypothermic with an oral temperature of 90°F. The glucagon infusion was resumed at 3 mg/h, and the heart rate remained between 53 and 63 BPM over the course of the next 6.5 hours. The patient was still hypothermic at approximately 0800, so a warming blanket was applied with good effect. Throughout the afternoon, the patient became more alert and oriented, and the heart rate stabilized around 53 BPM. The glucagon infusion was stopped at 1500. After stopping the infusion on day two, the heart rate ranged between 58 BPM and 69 BPM throughout the day.

On the third day, the care team re-evaluated the patient's current medications and discontinued the home medication of donepezil, out of concern that it may have contributed to the patient's symptoms. Up to this point no doses of donepezil were given during the patient's stay. The heart rate on day three ranged from 58 to 70 BPM. The patient's white count also improved, shifting from 11.58 K/μL on day two to 7.05 K/μL on day three.

2.2 | Outcome and follow-up

On day four the heart rate ranged from 57 BPM while sleeping to 78 BPM while wake. The patient's mental status and overall health improved. On day five, the patient was re-started on her metoprolol succinate and donepezil at half dose, 25 mg nightly and 5 mg daily, respectively. The patient's median heart rate was 64 BPM (similar to her baseline heart rate) and the temperature stabilized at 97.3°F. On day six, the patient was discharged with plans to complete a seven-day course of antibiotics, continue reduced dose of metoprolol 25 mg nightly and further decrease donepezil to 2.5 mg daily. The patient was discharged on day six with two more days of antibiotic therapy (ciprofloxacin and metronidazole) and

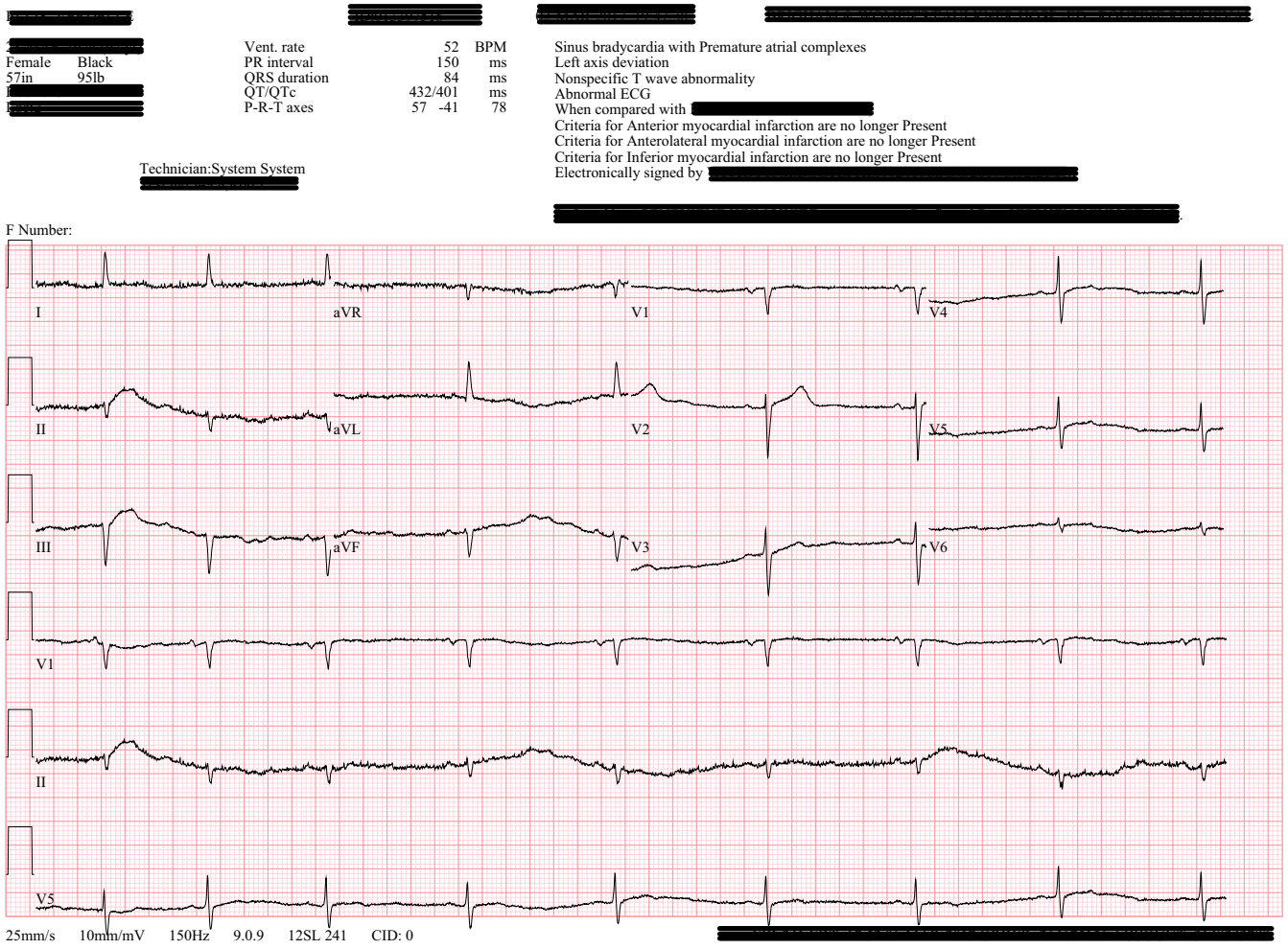

FIGURE 1 Electrocardiogram (ECG)

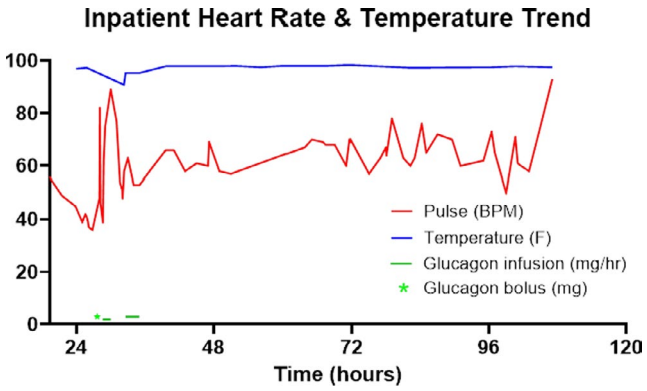

FIGURE 2 Displays a timeline of the patient's heart rate and temperature, along with the corresponding glucagon administration

complete resolution of her symptoms. Heart rate 10 days after discharge was 78 BPM and patient was back to her usual state of health. Six months later, the donepezil dose was increased back to 10 mg daily. One week after dose change, the patient had worsening abdominal pain and diarrhea and heart rate at office visit was 64 BPM.

2.3 | Other case reports

After review of the literature, the following cases reported donepezil toxicities. A 79-year-old female patient presented with lethargy and vomiting after erroneously receiving a 50 mg dose of donepezil, rather than her prescribed 5 mg dose. Her vital signs included a blood pressure of 167/83 mm Hg, a heart rate of 56 BPM, and a respiratory rate of 16 breaths per minute. Her skin was pale and diaphoretic. The patient was treated with a total of 3 mg of atropine and returned to baseline by day two in the hospital.[2] Another case of an 84-year-old man that ingested a 35 mg dose of donepezil reported symptoms of nausea, vomiting, diarrhea, fatigue, excessive sweating, and disorientation. His vital signs included a blood pressure of 131/58 mm Hg, a heart rate of 50 BPM, and a respiratory rate of 16 breaths per minute. The patient's heart rate fluctuated between 50 and 60 BPM, and QTc prolongation was also reported. The patient received a dose of atropine 0.5 mg IV when his heart rate fell below 50 BPM. The patient's bradycardia and QTc prolongation resolved, and the patient returned home after six days in the hospital.[3] The

third donepezil case occurred in a 74-year-old female that took nine times her regular dose of donepezil (45 mg) and reported symptoms of nausea, vomiting, drowsiness, flushing, and diarrhea, but returned to baseline after stopping her donepezil dose and a day of home observation.[4]

Two cases of donepezil toxicity have also been reported at therapeutic doses. A 90-year-old man's dose of donepezil increased from 5 mg to 10 mg. The patient's body temperature was 96.8°F, blood pressure was 158/49 mm Hg, and heart rate was 36 BPM. An ECG revealed an advanced 2:1 atrioventricular block and QT prolongation. The patient's donepezil was discontinued and 30 mg of orciprenaline was administered. By the fifth day, the patient's ECG and other symptoms had normalized.[5] The second case involved an 87-year-old woman with a history of bradycardia, atrial fibrillation, and QT prolongation. Patient's home medications included cilostazol, amlodipine, spironolactone, warfarin, and donepezil. She was admitted to the hospital after a fall caused by syncope. Her temperature was 97.5°F, blood pressure was 115/63 mm Hg, heart rate was 40 BPM, and QT prolongation was reported. She also complained of nausea and vomiting. Orciprenaline 30 mg daily was administered to prevent progression of bradycardia. On the fifth day, the donepezil was discontinued, and her heart rate increased to 55 BPM. On day 18, the QT prolongation resolved.[6]

3 | DISCUSSION

Suitable management of donepezil overdose should include donepezil discontinuation and supportive care. IV atropine therapy at 1mg to 2 mg may be considered to reverse cholinergic effects, including bradycardia seen with donepezil toxicity.[7,10] Similarly, fluids and atropine may also be used to treat bradycardia due to beta-blocker overdose. If this is not effective, other treatment options for beta-blocker toxicity include IV glucagon, IV calcium salts, vasopressor therapy, high-dose insulin with glucose infusions, and lipid emulsion therapy.[11,15,16] As beta-blocker toxicity could have been on the differential for this case, glucagon was used. Glucagon exhibits positive inotropic and chronotropic effects on the heart through stimulation of glucagon receptors which increase cyclic-AMP in the sinoatrial node to increase heart rate.[17] Animal studies have shown that mice without glucagon receptors have naturally decreased heart rates and altered parasympathetic control compared to mice with glucagon receptors. When cats and dogs were exposed to glucagon, heart rates significantly increased from baseline by approximately 22 to 30%. These results suggest glucagon plays a key role in heart rate control independent of medication exposure. Thus, glucagon's transient increased effect on the patient's heart rate was likely due to its mechanism of action and not an antidotal effect for beta-blocker toxicity.[18]

The altered pharmacodynamics of aging can cause up to a 17% decrease in clearance of donepezil in older adults and result in higher serum levels of donepezil.[9] While the bradycardic effects may have been compounded by metoprolol, the hypotension, hypoglycemia, and respiratory depression commonly seen in beta-blocker toxicity were not observed in this case. This patient had multiple cholinergic symptoms including abdominal pain, diaphoresis, diarrhea, emesis, nausea, and salivation, along with hyperglycemia, which are unique to donepezil toxicity (Figure 3). Additionally, the patient's bradycardia and other symptoms started to resolve approximately 70 hours after the last donepezil dose, which coincides with donepezil's half-life.[10] Alternatively, metoprolol's half-life ranges from 3 to 7 hours.[19]

Donepezil should be used with caution in older adult patients, especially those with multiple medications and comorbidities. Donepezil is recorded on the Beer's Criteria list due to the increased risk of orthostatic hypotension, syncope, and bradycardia that can occur when used in older adults.[9] In addition, the medication is metabolized in the liver and hepatic impairment increases with age due to decrease in liver volume and hepatic blood flow.[6] Finally, low-weight patients (<55 kg; similar to this patient) may experience more nausea, vomiting, and weight loss than other patients taking donepezil.[10] For this reason, the Canadian labeling of donepezil recommends a maximum dose of 5 mg once daily instead of the United States labeling of up to 10 mg twice daily in older adult women (≥ 85 years old) with low body weight (<55 kg).[20] The patient experienced a four-pound weight loss and had complained of stomach discomfort in the two months prior to admission. The weight loss and potential decrease in nutrition may have resulted in an increase in serum concentrations of donepezil as this medication has a large volume of distribution and is 96% protein bound.[10] Though the patient's donepezil dose had not changed in the last year, the bradycardia and other side effects may have not manifested until these pharmacokinetic changes occurred.

Other than a purely medication driven event, the patient's presentation and improvement may also be somewhat explained by presumed colitis and antibiotic treatment. The patient had mild leukocytosis, abdominal pain, bloating, diarrhea, fatigue, hyperglycemia, and altered mental status. However, other common symptoms of colitis including fever, chills, and dehydration were absent in our patient, making it difficult to fully explain the symptoms with one diagnosis (Figure 3).[21]

The only way to be certain the signs and symptoms were part of a donepezil toxicity would be to complete a thorough toxicology screen of metoprolol and donepezil serum concentrations in the patient's blood. Unfortunately, these toxicity screens can be expensive and are not the standard of care for a suspected overdose with either of these medications. A reasonable alternative to toxicology information is the use of the Naranjo Adverse Drug Reaction Probability

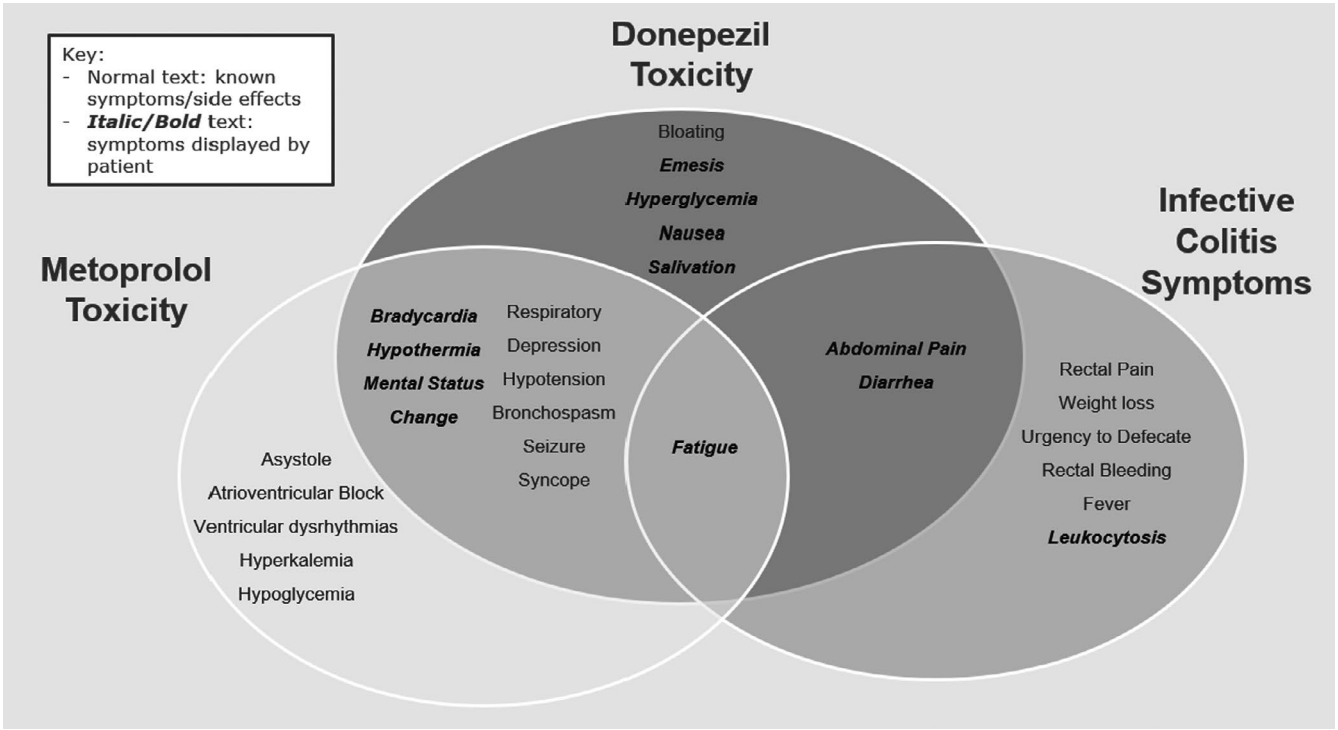

FIGURE 3 Displays symptoms unique to donepezil and metoprolol toxicities along with colitis and those that overlap. Bold symptoms represent those that the patient experienced.[10,11,21]

TABLE 2 Naranjo Adverse Drug Reaction Probability Scale. The total score is categorized into one of four categories: ≥ 9 indicates definite adverse drug reaction (ADR), 5-8 indicates probable ADR, 1-4 indicates possible ADR, and 0 indicates doubtful ADR

Question	Yes	No	Do Not Know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected medicine was administered?	+2	-1	0
Did the adverse reaction improve when the medicine was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the medicine was re-administered?	+2	-1	0
Are there alternate causes (other than the medicine) that could solely have caused the reaction?	-1	+2	0
Was the medicine detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar medicines in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Scale (Table 2). After the adverse event occurred, an evaluation was conducted using the Naranjo Scale and resulted in a +6, indicating donepezil was a probable cause of the patient's symptoms. While the score is compelling, it is important to note the Naranjo scale has not been validated to detect complex interactions involving more than one medication or disease state.[22]

4 | CONCLUSION

All recent and active medications should be assessed as contributing factors when a patient presents with abnormal symptoms and possible medication toxicities. In this specific case, it is even more important to complete a differential diagnosis when drugs and diseases have overlapping

symptoms, as donepezil's cholinergic symptoms present similarly to a beta-blocker overdose and colitis. The symptoms of emesis, nausea, salivation, and hyperglycemia were likely linked to donepezil toxicity and not due to other factors. In addition, the patient's bradycardia, hypothermia, mental status change, fatigue, abdominal pain, and diarrhea may also be linked to donepezil toxicity but overlap with metoprolol toxicity and infective colitis symptoms. Understanding the unique symptoms of each possible offending agent can help providers optimize therapy, withdraw potentially offending agents, and discontinue unnecessary treatment.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

CG: Performed chart review of patient case and wrote the manuscript with support from authors 2 and 3. Nicholas Pugliese, PharmD: Supported author 1 in writing of manuscript, figure development, and curating background and discussion of the manuscript. Gretchen Stern, PharmD, BCPS: Conceived idea of manuscript and reviewed manuscript. All authors discussed the conclusions and contributed to the final manuscript.

RESEARCH AND ETHICS AND PATIENT CONSENT

Consent was not required per institution protocol and waived per the Institutional Review Board at Brigham and Women's Hospital in Boston, Massachusetts.

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