In the Balance: A Case of Neuroleptic Malignant Syndrome When Donepezil Is Added to Maintenance Haloperidol Decanoate

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Abstract

Objective: To report the development of neuroleptic malignant syndrome (NMS) after donepezil was added to maintenance haloperidol. **Case Summary:** An East Asian female in her mid-50s with a 25-year history of schizophrenia was prescribed fluvoxamine 150 mg daily, haloperidol decanoate 200 mg intramuscularly every 4 weeks, and benztropine 0.5 mg twice daily. Donepezil 5 mg daily was initiated for the treatment of possible dementia and 2 days later she appeared pale, displayed malaise, reported emesis, but was afebrile. The following day she was notably changed in behavior, withdrawn with a blunted affect. Decreased appetite, hyperthermia (temperatures 99.2–101°F), tachycardia, drooling, and slow, stiff movements with a creatine phosphokinase level of 1413 units/L (normal 26–192 units/L) were noted, and the patient was transferred to a medical hospital for treatment of suspected NMS. Symptoms improved with antipsychotic discontinuation, intravenous fluids, bromocriptine, and dantrolene. Five days after the adverse reaction the creatine phosphokinase significantly improved and she was noted to be more alert and responsive. **Discussion:** A literature search revealed 9 case reports of cholinesterase inhibitors causing NMS reactions either alone or, more commonly, when used in combination with antipsychotics. In this case, it was probable (Drug Interaction Probability Scale Score 6) the interaction between donepezil and haloperidol decanoate contributed to NMS. **Conclusions:** Use of cholinesterase inhibitors with antipsychotic medications may create an imbalance in acetylcholine and dopamine, which can precipitate the onset of NMS in susceptible individuals. These agents should be used cautiously in combination with careful monitoring for NMS.

Keywords

adverse drug reactions, antipsychotics, cholinergics, drug interactions, drug-related problems, drug safety, interactions, neuroleptics, pharmacodynamics

Introduction

The incidence of neuroleptic malignant syndrome (NMS) is estimated to be between 0.01% and 0.02% among those prescribed antipsychotics.¹ Individuals who develop NMS have usually been exposed to an antipsychotic within the 72 hours preceding symptom onset. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* diagnostic features of NMS commonly include hyperthermia (>100.4°F or >38°C), generalized rigidity, changes in mental status, autonomic activation or instability, diaphoresis, as well as other symptoms and laboratory findings (Table 1). Serotonin syndrome and NMS may have a similar clinical presentation with mental status changes, autonomic nervous system disturbances, neurologic manifestations, and hyperthermia, which can make it difficult to distinguish between these 2 adverse drug reactions. Elevations in creatine kinase, liver function tests, and white blood cell count, along with low serum iron levels, can help

differentiate NMS from serotonin syndrome in those taking antidepressants and antipsychotic medications.²

Risk factors for NMS may include agitation, exhaustion, dehydration, iron deficiency, and prior history of NMS.^{1,3} High-potency antipsychotics are associated with a greater risk compared with low-potency antipsychotics or atypical antipsychotics. Other risk factors may include parenteral administration, rapid titration, and high doses of dopamine antagonists. Once NMS is identified and the offending medication is discontinued, most individuals will recover in

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Table 1. DSM-5 NMS Diagnostic Features.¹

Common Clinical Characteristics	Other Possible Abnormalities
Hyperthermia (>100.4°F or >38°C)	Leukocytosis
Generalized rigidity	Metabolic acidosis
Creatine kinase elevation	Hypoxia
Mental status changes	Decreased serum iron
Autonomic activation or instability	Catecholamine elevations
Diaphoresis	Electroencephalogram generalized slowing
Tachypnea or respiratory distress	
Urinary incontinence	
Pallor	

7 to 10 days; however, the duration can be prolonged with long-acting antipsychotics.

The pathophysiology of NMS is thought to involve central and peripheral dopamine blockade. In addition to the dopaminergic system, serotonergic and cholinergic mechanisms are also believed to contribute. The neurotransmitters dopamine and acetylcholine have a reciprocal relationship. Dopaminergic neurons have postsynaptic connections with cholinergic neurons. The presence of dopamine inhibits the release of acetylcholine from postsynaptic cholinergic neurons. When antipsychotics are present, dopamine is not able to suppress acetylcholine release due to D2 receptor blockade. In turn, acetylcholine may become overly active (in the striatum this can lead to Parkinsonism and dystonia), which can be compensated with use of anticholinergic agents such as benztropine. However, when a cholinesterase inhibitor such as donepezil is used, the enzyme that degrades acetylcholine, acetylcholinesterase, is inhibited leading to a buildup of acetylcholine. This imbalance between dopamine and acetylcholine is thought to be one of the mechanisms that may contribute to the development of NMS.^{2,4}

Case Report

An East Asian female in her mid-50s residing at an inpatient psychiatric hospital for approximately 1 year with a diagnosis of schizophrenia developed NMS after initiation of donepezil. Three weeks preceding the onset of the adverse reaction, oral haloperidol 10 mg at bedtime, which had been prescribed over the past 8 months, was subsequently tapered and discontinued over the course of a week and haloperidol decanoate injection 200 mg q 4 weeks was continued after the haloperidol serum level was found to be 30.6 ng/mL (usual therapeutic range 3-15 ng/mL). The haloperidol serum level was obtained due to the drug-drug interaction with fluvoxamine, extrapyramidal symptoms, severe cognitive impairment, and to evaluate the continued need for oral haloperidol. Due to improvement in extrapyramidal symptoms after the taper of oral haloperidol, benztropine was then

reduced from 1 mg twice daily to 0.5 mg twice daily, approximately 2 weeks prior to the NMS reaction. A diagnosis of possible dementia was added with a Mini Mental State Exam score of 2 as severe cognitive symptoms persisted despite medication changes. She was uncooperative with a full neuropsychiatric workup for dementia due to the severity of her mental illness. Medications prescribed at the time of the adverse event were fluvoxamine 150 mg daily (same dose for the previous 9 months) for obsessive-compulsive disorder, haloperidol decanoate injection 200 mg intramuscularly every 4 weeks (continuous injections at the same dose for 10 months with the most recent injection administered 3 days prior to the adverse event), and benztropine 0.5 mg twice daily. Donepezil 5 mg daily was initiated 3 days prior to the NMS reaction for the treatment of possible dementia.

The day prior to NMS onset, she appeared pale, displayed malaise, and reported one episode of emesis. Temperatures were obtained and she was afebrile with temperatures not exceeding 98°F. The following day she was reported to be noticeably changed in behavior, withdrawn with a blunted affect. Decreased oral intake of food, drooling, and slow stiff movements were noted. Vital signs that morning were temperature 99.2°F, pulse 106 bpm (usual baseline pulse 70-80 bpm), blood pressure 134/84 mm Hg (usual baseline blood pressure around 110/70 mm Hg), and respiratory rate 18 breaths per minute. The temperature and pulse were rechecked 20 minutes later, and the temperature was 101°F with a pulse of 106 bpm. A stat creatine phosphokinase was ordered due to suspicion of NMS, and the level was significantly elevated at 1413 units/L (normal 26-192 units/L).

The patient was transferred to a local medical hospital with a creatine phosphokinase 1452 units/L, tachycardia, and hypertension (blood pressure 149/89 mm Hg) noted at the time of admission. NMS was suspected, and she was started on intravenous fluids, bromocriptine, and dantrolene. Haloperidol decanoate injections were discontinued; however, fluvoxamine, benztropine, and donepezil were continued. The following day dantrolene was discontinued as NMS symptoms were improved although rhabdomyolysis continued with downward trend in creatine phosphokinase of 907 units/L. It was difficult to assess her for rigidity due to resistance and unwillingness to have arms moved passively. Five days after the adverse reaction she was noted to be more alert, responded to questioning, and the creatine phosphokinase continued to decrease with a level of 383 units/L so bromocriptine was discontinued.

On return to the psychiatric hospital 5 days after the NMS reaction, there was no rigidity noted on the physical exam and all vitals were within normal limits except some residual mild tachycardia with pulse of 100 bpm. Medications on return to the psychiatric hospital included benztropine 0.5 mg daily, donepezil 5 mg daily, and fluvoxamine 150 mg daily. Lorazepam and diphenhydramine were also prescribed on an as needed basis for anxiety. Haloperidol decanoate was not

restarted and remained discontinued. Benztropine was discontinued 10 days after onset of NMS as the rigidity was no longer present and was no longer needed. Approximately 4 weeks after the adverse event, oral aripiprazole 5 mg daily was initiated and titrated up to 30 mg daily for symptoms of psychosis without return of NMS. The reinitiation of antipsychotic was delayed a month to minimize the risk of NMS recurrence due to prior haloperidol decanoate use and its associated long elimination half-life of 21 days.

Discussion

Based on the signs and symptoms at the time of the adverse event and the timeline of medication changes, it seems the most likely cause of NMS is the combination of donepezil and haloperidol. In addition, the dose reduction of benztropine 2 weeks prior to the NMS event may have also contributed to the imbalance of dopamine and acetylcholine. She did not have any concerns or medical history that would have indicated an infectious, metabolic, or other etiology for the event. The creatine kinase was more than 4 times the upper limit of normal and is commonly seen in cases of NMS. The Drug Interaction Probability Scale (DIPS) score was 6, indicating a probable interaction between the precipitant drug (donepezil) and the object drug (haloperidol) contributing to the adverse event.⁵ The DIPS uses a series of questions to estimate the probability of a drug interaction-induced adverse event. The DIPS score of 6 was obtained as there are previous reports of this interaction in humans, the interaction is consistent with the known interactive properties of the precipitant and object drug, the event is consistent with the known time course of the interaction, an alternative cause for the event was not found, and the interaction was confirmed by objective evidence (other than drug concentrations).

The haloperidol level was found to be supratherapeutic prior to the event; however, the oral haloperidol was subsequently tapered and discontinued 2 weeks prior to the NMS reaction, and she had been prescribed the same dose of haloperidol decanoate consistently for 10 months. A pharmacokinetic interaction does exist between haloperidol and fluvoxamine. Haloperidol is a major substrate of CYP 2D6 and 3A4 and minor substrate of CYP 1A2. Fluvoxamine is a strong inhibitor of 1A2 and a weak inhibitor of both 2D6 and 3A4. Dose-dependent inhibition of haloperidol metabolism has been described with 150 mg of fluvoxamine resulting in 160% increase in haloperidol levels.⁶ It is unlikely that the NMS reaction was precipitated by the increased serum haloperidol level since the oral haloperidol had been discontinued 2 weeks prior to the reaction (elimination half-life 18 hours) and the haloperidol level had likely declined significantly after its discontinuation despite the interaction with fluvoxamine, although a subsequent level was not obtained. In addition, both haloperidol decanoate and

fluvoxamine had been prescribed for several months at the same dose prior to the NMS reaction.

The dose of benztropine had been decreased from 1 mg twice daily to 0.5 mg twice daily 2 weeks prior to the adverse event, and the only recent change in the medication regimen had been the initiation of oral donepezil 5 mg daily 3 days prior to the development of NMS. Most cases of NMS develop within the first week after drug initiation. Around the time donepezil was started, she was also noted to be experiencing nausea and vomiting and had poor oral intake of food, which are not symptoms of NMS; however, it is known that dehydration may also increase the risk of NMS and therefore may have been a contributing factor. Cholinesterase inhibitors such as donepezil are well known for contributing to gastrointestinal side effects.

The generalizability of this case is limited in that it is an isolated single report with treatment of NMS at an outside facility; however, there have been other previously reported events of cholinesterase inhibitors such as donepezil causing NMS reactions either alone or, more commonly, when used in combination with typical or atypical antipsychotics (Table 2).⁷⁻¹⁴ It is thought that use of cholinesterase inhibitors with antipsychotics can create an imbalance between dopamine and acetylcholine, which may precipitate the development of NMS. One case report described development of NMS in a patient on olanzapine and donepezil. This patient had been treated with olanzapine for 10 years without adverse effects. Fatigue, progressive weakness, confusion, lethargy, and severe muscle stiffness was noted 1 week after initiation of donepezil.⁷ Another report detailed a case in which olanzapine was added on to rivastigmine therapy followed by NMS presentation. However, after the last increase of olanzapine, the rivastigmine dose was also increased shortly thereafter, making it difficult to determine if NMS was caused by olanzapine, rivastigmine, or by the combination of the agents.⁹ Two cases noted NMS-like reaction in patients who had been discontinued from antipsychotic medications and initiated on donepezil. Within 5 to 8 days of starting donepezil, both patients displayed lethargy, rigidity, diaphoresis, fluctuating blood pressure, and elevated creatine kinase.¹¹ In most of these cases, the presentation of NMS with the addition of the cholinesterase inhibitor is similar to antipsychotic-induced NMS; however, some cases noted no temperature elevation or less severe muscle rigidity than the “lead pipe” rigidity that is generally characteristic of NMS.^{7,10,11} In this case report, the presentation was similar to what would typically be expected in antipsychotic-induced NMS with the development of severe muscle rigidity and fever.

The patient had been prescribed haloperidol, benztropine, and fluvoxamine at stable doses for quite some time aside from the taper and discontinuation of oral haloperidol and dose reduction of benztropine 2 weeks prior to the reaction. The only recent addition to the regimen was donepezil.

Table 2. Neuroleptic Malignant Syndrome (NMS) Case Reports.

Demographic Characteristics	Agent and Regimen	Effect on Ch System	Effect on DA System	Regimen Change Post-NMS Symptoms
78-Year-old male with unspecified dementia and schizoaffective disorder ⁷	Donepezil 5 mg daily × 6 days Olanzapine 10 mg × 10 years	↑	↓	Donepezil and olanzapine discontinued
66-Year-old female with Alzheimer's and vascular dementia with psychosis and behavioral symptoms ⁸	Donepezil 10 mg daily × 1 year Olanzapine 15 mg × 10 days Chlorpromazine × 2.5 days	↑	↓ ↓	Olanzapine and chlorpromazine discontinued
58-Year-old male with Down syndrome and Alzheimer-type dementia ⁹	Rivastigmine 3 mg twice daily × 2 years, increased to 6 mg twice daily × 6 weeks Olanzapine 2.5 mg × 4 months	↑	↓	Olanzapine discontinued
66-Year-old female with a 36-year history of schizophrenia ¹⁰	Donepezil daily <3 weeks Olanzapine × 1 year Haloperidol <3 weeks	↑	↓ ↓	NMS reoccurred with haloperidol + olanzapine and benztropine 1 week later. Donepezil was not reported to be discontinued. ^a
Male with Parkinson's disease with cognitive impairment and psychosis ¹¹	Donepezil 5 mg daily × 8 days Levodopa + decarboxylase inhibitor × 4 years—dose recently decreased Entacapone Quetiapine recent trial discontinued	↑	↑ ↑ ↓	Donepezil discontinued
Male with depression, Parkinsonian symptoms and mild cognitive deficits ¹¹	Donepezil 5 mg daily × 4 days Levodopa/carbidopa × 10 weeks Olanzapine 2.5 mg discontinued 4 days prior to symptom onset	↑	↑ ↓	Donepezil discontinued
71-Year-old female with Lewy body dementia with psychosis and behavioral disturbance ¹²	Donepezil 3 mg daily × 2 days prior then increase to 5 mg with symptom onset same day Risperidone trial discontinued 12 days prior to symptom onset	↑	↓	Donepezil discontinued
73-Year-old male with Alzheimer's disease and vascular dementia ¹³	Donepezil 5 mg daily × 1 year 4 months Maprotiline 20 mg daily × 2 years	↑ ↓		Donepezil and maprotiline were discontinued
68-Year-old male with suspected Alzheimer's dementia and symptoms of psychosis ¹⁴	Donepezil 5 mg daily × 6 weeks Bromperidol 12 mg × 1 year	↑	↓	Donepezil and bromperidol were discontinued

Abbreviations: Ch, cholinergic activity; DA, dopaminergic activity.

^aSubsequent rechallenge with olanzapine without donepezil 2 days after prior discontinuation caused fever spike and elevated white blood cells. Later rechallenge with haloperidol + quetiapine without donepezil or olanzapine without return of NMS symptoms.

The episode of NMS resolved with the discontinuation of haloperidol decanoate and use of intravenous fluids, bromocriptine, and dantrolene despite the continuation of donepezil at the same dose.

Conclusions

Use of cholinesterase inhibitors with antipsychotic medications may create an imbalance in acetylcholine and dopamine, which can precipitate the onset of NMS in susceptible

individuals. In this case, the patient was prescribed haloperidol decanoate at the same dose for 10 months, and the onset of NMS occurred 3 days after initiating treatment with the cholinesterase inhibitor donepezil. The combination of cholinesterase inhibitors and antipsychotic medications should be used cautiously, and careful monitoring for signs and symptoms of NMS should be considered particularly during the first week after initiation of a cholinesterase inhibitor or antipsychotic to ensure early detection.

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