

Worsening Choreoathetosis in Huntington's Disease with Fluoxetine, Lisdexamfetamine, and Melatonin: A Case Report

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ABSTRACT

Cognitive, affective, and sleep disturbances can be found in patients with Huntington's disease (HD), and medications used to treat these HD-related sequela can also impact HD-related movement disorders. We present the case of a 52-year-old Caucasian man with previously undiagnosed HD who exhibited significant choreoathetoid movements that improved with discontinuation of fluoxetine and lisdexamfetamine upon hospital admission. Following diagnosis of HD through genetic testing, he was administered 5mg of oral melatonin on two consecutive evenings, which resulted in worsening choreoathetosis. We calculated Naranjo adverse event scores of 5, 5, and 2 for fluoxetine, lisdexamfetamine, and melatonin, respectively, based on our assessment, review of outpatient medical records, and available literature. We review the literature surrounding these possible adverse drug events and their mechanisms regarding dopaminergic modulation in early-middle stages of HD. Our report indicates that caution should be exercised when initiating psychostimulants, fluoxetine, and melatonin in patients with early-middle stage HD. Screening for HD might be warranted for patients who develop choreoathetosis after initiation of the aforementioned medications. We recommend ascertaining baseline level of chorea before initiating these medications in patients with known HD and closely monitoring for exacerbation during therapy.

KEYWORDS: Fluoxetine, antidepressant, psychostimulant, amphetamine, melatonin, Huntington's disease, chorea, and dopamine

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease and is diagnosed in part by determining the number of cytosine-adenine-guanine (CAG) trinucleotide repeats located within the huntingtin (*HTT*) gene on chromosome four.[1] HD is often characterized by affective and cognitive symptoms, in early and middle stages, in addition to progressive chorea, which might be replaced by bradykinesia, rigidity, and dystonia in late stages.[2,3] The degree of chorea is associated with fluctuations in dopamine (DA) release and DA receptor sensitivity and might follow a biphasic model over the course of the disease.[4] Though cognitive, psychiatric, and sleep disturbances are common in HD,[5–7] clinical trials evaluating medications have been challenging due to the rarity of disease and high drop-out rates.[8] Therefore, while antidepressants and psychostimulants have been recommended for affective symptoms, the effects of these medications are not well understood.[9] Pharmacotherapy for insomnia in HD is even less studied. As antidepressants, psychostimulants, and melatonin can alter dopaminergic regulation, it is plausible they could alter the chorea phenotype when used in patients with HD.[10–13] We describe a male patient with previously undiagnosed HD who presented with significant choreoathetoid movements that significantly improved upon discontinuation of fluoxetine and lisdexamfetamine at hospital admission. The patient's chorea additionally worsened after a two-day trial of melatonin during hospitalization. This report is the second to describe worsening chorea in a patient with HD following fluoxetine and psychostimulant use and is the first following melatonin use.[13,14]

CASE REPORT

A 52-year-old Caucasian male presented with police to the emergency room after allegedly becoming increasingly disruptive, physically intrusive, and assaulting staff at his assisted living facility. He was admitted to the neurobehavioral medicine inpatient unit for further evaluation. Past psychiatric history was significant for two psychiatric hospitalizations within the past 3.5 years in the context of personality change, neurocognitive dysfunction, and mild movement abnormalities. During previous admissions, frontotemporal or progressive cortical dementia was suspected but not confirmed, and magnetic resonance

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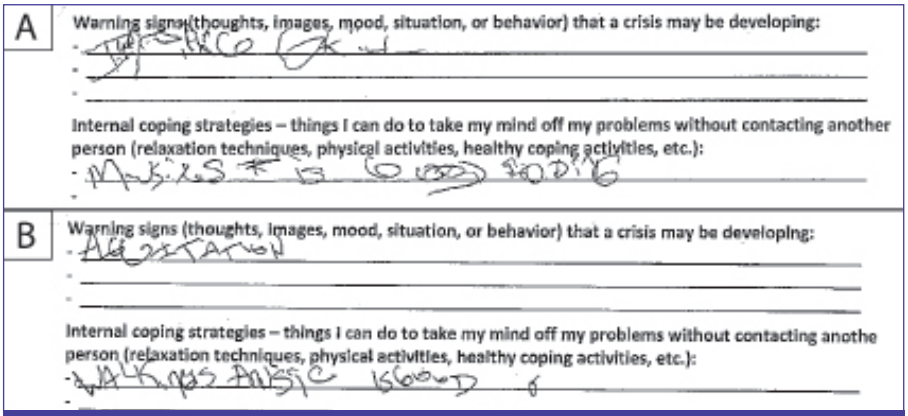


FIGURE 1. Patient's handwriting sample—A) At hospital admission while taking fluoxetine and lisdexamfetamine; B) At hospital discharge after the discontinuation of fluoxetine and lisdexamfetamine

imaging (MRI) showed generalized cerebral atrophy. During the current hospitalization, he demonstrated significant choreoathetoid movements, dysarthria, and moderately disorganized thought process on admission. Neurology was consulted due to suspected HD, and a HD deoxyribonucleic acid (DNA) sequence was ordered. Additionally, physical therapy utilizing strengthening exercises, a walker, and weights placed on all four extremities to control involuntary movements was initiated, which only resulted in mild improvement.

His medications at admission included fluoxetine 60mg daily, clonazepam 0.5mg twice daily, olanzapine 7.5mg nightly, lisdexamfetamine 40mg daily, and fluconazole 200mg weekly for onychomycosis. Lisdexamfetamine and fluconazole were discontinued on Hospital Day 1 due to lack of strong indication and potential for drug–drug interactions. Fluoxetine was reduced to 40mg daily starting on Hospital Day 1, reduced to 20mg daily on Hospital Day 3, and was discontinued on Hospital Day 8 due to suspected contribution to movement disorder. Clonazepam was reduced to 0.5mg at bedtime on Hospital Day 4, reduced to 0.25mg at bedtime on Hospital Day 8, and discontinued on Hospital Day 12 to reduce fall risk. He demonstrated gradual improvement of choreoathetoid movements over a one-week period, resulting in the ability to ambulate without the assistance of arm weights, leg weights, and a weighted walker. Despite remarkable improvement, the patient still experienced mild choreoathetoid movements, speech spasticity, and behavioral disinhibition. Results from the HD DNA sequence returned positive (45 CAG repeats) on Hospital Day 8 and a formal diagnosis of HD was made. On Hospital Day 21, oral melatonin 5mg was initiated nightly for new onset insomnia. Following two nights of melatonin, increased choreoathetoid movements were observed by nursing staff, leading to melatonin discontinuation. Movements returned to baseline one day following discontinuation of melatonin. The patient was discharged, on olanzapine 10mg nightly, to a group home on Hospital Day 27 with significantly improved choreoathetoid movements, ability to ambulate, and handwriting (Figure 1).

Following discharge, the patient's past three years of outpatient medical records were reviewed independently by three authors of this article (CH, IM, and RM). These records revealed that three years prior to the previously described hospitalization, fluoxetine had been titrated from 20mg to 60mg daily over a three-month period and continued until admission. During fluoxetine titration, the patient experienced significant decrease in coordination, falls, and increased hyperactivity. Two years prior to the previously described hospitalization, lisdexamfetamine was initiated and titrated both upward and downward, in which he experienced worsening chorea and psychomotor agitation at higher doses. There was no documentation that the patient had previously taken melatonin. Finally, genetic testing revealed the patient to be a cytochrome P450 (CYP) 2D6 poor metabolizer, though no other CYP450 test results were available.

DISCUSSION

The reported patient presented with HD-related chorea that initially was exacerbated by fluoxetine, worsened with addition of lisdexamfetamine, and significantly improved after discontinuation of both medications at hospital admission. These findings were supported per review of the patients past three years of outpatient medical records. As the patient had attended an outpatient psychiatric clinic on approximately a monthly basis, documentation of worsening or improvement of movement-related side effects were clearly documented. Unfortunately, due to an absence of an HD diagnosis at the time, and desires to aggressively treat the patient's apathy and depressive symptoms, fluoxetine and lisdexamfetamine were likely overlooked for causing choreoathetosis exacerbation. In light of this patient's CYP 2D6 poor metabolizer status, it would also be expected that his plasma concentrations of fluoxetine and lisdexamfetamine would be elevated compared to a CYP 2D6 extensive (normal) metabolizer. Additionally, because fluconazole is a CYP 2C9 inhibitor, it is plausible that it further increased fluoxetine concentration, a CYP 2C9 and 2D6 substrate.[15] These CYP450 pharmacokinetic interactions likely increased his risk for movement-related adverse events. At first glance, the slow and progressive improvement of choreoathetosis after both drugs were discontinued could be best explained by the discontinuation of fluoxetine, which has an elimination half-life of 4 to 6 days for the parent drug and 4 to 16 days for the active metabolite, norfluoxetine, after chronic administration.[12] However, a previous case report of psychostimulant-induced chorea described symptoms that persisted up to 72 hours after drug discontinuation, and in the context of our patient being a CYP 2D6 poor metabolizer, delayed lisdexamfetamine elimination should also be considered.[16]

We find it probable that worsening choreoathetosis occurred secondary to fluoxetine use (Naranjo[17] score=5) due to previous reports of this reaction, outpatient medical records documenting an exacerbation of symptoms within two months following fluoxetine initiation in the absence of a psychostimulant, worsened coordination, increased falls, hand-flapping, and psychomotor agitation upon dose increases of fluoxetine,

and marked improvement following drug discontinuation. Fluoxetine has previously been associated with a number of extrapyramidal movement disorders,[10] and the effects of antidepressants on HD-related chorea are unclear. In a large sample of prodromal HD subjects, an association was found between antidepressant use and motor symptom progression; however, there are a number of explanations for this, including worsening affective symptoms secondary to disease progression.[18] A randomized, double-blind trial of 30 nondepressed subjects with HD received fluoxetine 20mg/day or placebo, of which 12 subjects receiving fluoxetine completed the trial. A trend toward worsening resting chorea, eye movements, and maximum chorea occurred with fluoxetine compared to placebo.[19] Additionally, a patient with HD had an exacerbation of chorea after two weeks of fluoxetine 20 mg/day that abated after discontinuation.[14] Alternatively, a report of two patients with HD described improvement of choreiform movements after initiation of fluoxetine 20mg/day.[20] The causes for these contradictory responses to fluoxetine in these reports is uncertain, but this has also been reported with DA agonists and antagonists.[4,14,20] The variable response could be due to differences between HD progression between patients.[4]

We find it probable that lisdexamfetamine contributed to choreoathetosis (Naranjo score=5) in our patient, based previous reports of this reaction, previous medical records documenting exacerbation of symptoms after psychostimulant initiation, worsened chorea with dosage increases, improved coordination and psychomotor agitation upon dosage decreases, and marked improvement following drug discontinuation.[17] Several case reports have described young children who developed chorea or dyskinesia following consumption of psychostimulants.[13,16,21,22] These movement disorders either responded to dopaminergic blocking agents or resolved spontaneously within 12 to 72 hours with no pharmacologic intervention.[16,21,22] Another young child with attention-deficit/hyperactivity disorder demonstrated dysarthria, tremor, and increased extremity tone after four weeks of methylphenidate therapy.[13] These adverse events prompted HD DNA testing, where he was found to have 75 CAG repeats, confirming a diagnosis of HD.[13] Despite cases of chorea, dyskinesia, and potential unmasking HD in childhood, as well a dearth of evidence from clinical studies, psychostimulants have been recommended to treat apathy in HD.[9] Certainly this practice should only be conducted with significant caution and monitoring for worsening of movement-related symptoms.

TABLE 1. Using the Naranjo Adverse Drug Reaction Probability Scale, worsening choreoathetosis was deemed probable, probable, and possible for fluoxetine (F), lisdexamfetamine (L), and melatonin (M) use, respectively

QUESTIONS		F	L	M
1	Are there previous conclusive reports on this reaction? Yes (+1); No (0); Do not know or not done (0)	1	1	0
2	Did the adverse events appear after the suspected drug was given? Yes (+2); No (-1); Do not know or not done (0)	2	2	2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Yes (+1); No (0); Do not know or not done (0)	1	1	1
4	Did the adverse reaction appear when the drug was readministered? Yes (+2); No (-1); Do not know or not done (0)	0	0	0
5	Are there alternative causes that could have caused the reaction? Yes (-1); No (+2); Do not know or not done (0)	-1	-1	-1
6	Did the reaction reappear when a placebo was given? Yes (-1); No (+1); Do not know or not done (0)	0	0	0
7	Was the drug detected in any body fluid in toxic concentrations? Yes (+1); No (0); Do not know or not done (0)	0	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Yes (+1); No (0); Do not know or not done (0)	1	1	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Yes (+1); No (0); Do not know or not done (0)	0	0	0
10	Was the adverse event confirmed by any objective evidence? Yes (+1); No (0); Do not know or not done (0)	1	1	0
Final score	≥9=definite ADR; 5–8=probable ADR; 1–4=possible ADR; 0=doubtful ADR	5	5	2

ADR: adverse drug reaction

Later, during hospitalization, our patient experienced worsening of chorea after administration of a two-day trial of exogenous melatonin, which improved after melatonin discontinuation. As exogenous melatonin has not been studied in HD, was never previously utilized by our patient, nor been previously described to worsen chorea, it is possible (Naranjo score=2) that melatonin caused worsening choreoathetosis.[17] Indeed, HD rat model studies indicate that melatonin can act as a neuroprotectant in HD.[23,24] The fact that the choreatic movements increased rapidly after administration of melatonin and subsided after discontinuation of use suggests that melatonin might modulate the pharmacological response linked to motor alterations. Since the core of motor alterations in HD are apparently rooted in neurochemical changes in DA, effects of melatonin in dopaminergic signaling could impact this relationship. There exists a biphasic nature of DA in the behavioral pathology of HD. Early in the disease, increased DA signaling is associated with choreatic dysfunction, while later in the disease low DA signaling manifests

as akinesia.[24,25] To explain the overt appearance of choreatic movements in our patient, we need to identify the possible changes in the DA system after melatonin administration. While melatonin enhances DA release, this phenomenon was only evident in retina and not in striatum, a region clearly linked to motor behavior.[26] The short-term exposure to melatonin and subsequent rapid attenuation of the effects after discontinuation argue against irreversible neurotoxicological effects. Interestingly, a study done in rats identified an increase in DA receptor affinity with no changes in total receptor expression in striatum after exposure to melatonin.[11] This type of allosteric modification could explain the exacerbation of the motor deficits, as equivalent levels of DA will lead to enhanced postsynaptic response. Additionally, melatonin could also enhance DA synthesis because it has been demonstrated to increase levels and activity of tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis.[27] Thus, the combined effect of increased DA synthesis and enhanced DA receptor affinity possibly contributed to the worsening chorea seen in our patient.

Limitations. There are several limitations to this case report. First, we retrospectively reviewed outpatient clinic notes to correlate previous medication trials with movement disorder symptoms. While these notes were detailed and well documented, there could have been omissions in documentation, and no specific movement disorder severity scales were available. Second, the Naranjo Adverse Drug Reaction Probably Scale was not designed to assess multiple medication contributions to a specific adverse event.[17] In this context, and in our case, medications are to be scored individually and the drug with the highest Naranjo score is most likely the causative agent for the adverse event.[17] Fluoxetine and lisdexamfetamine had the same Naranjo score in our case, and we believe both contributed equally to the adverse event. Third, due to cognitive deficits, the patient had poor memory of his responses to medications prior to admission. Fourth, we did not perform therapeutic drug monitoring in this patient. Serum concentrations of fluoxetine, norfluoxetine, lisdexamfetamine, and dextroamphetamine obtained at hospital admission could have provided useful data when considering the aforementioned drug–drug interactions and CYP 2D6 poor metabolizer phenotype. Due to these limitations, we cannot establish causality of adverse events reported. Limitations notwithstanding, the patient was ultimately grateful for the care he received by our inpatient service and for his robust improvements in ambulation and coordination at hospital discharge.

CONCLUSION

Our case is the second to describe worsened choreoathetoid movements with fluoxetine and psychostimulants in HD, and the first with melatonin. These observations are objectified by our patient's marked improvements in movement and handwriting assessments (Figure 1). We calculated Naranjo adverse event scores of 5, 5, and 2 for fluoxetine, lisdexamfetamine, and melatonin, respectively, based on several years of this individual's outpatient medical records and current available literature (Table 1). Due to physiological and biochemical changes associated with HD progression, these medications could have different effects depending on HD staging. Melatonin has shown to be neuroprotective in toxicological and genetic models of HD, but it has not been studied in humans. However, if these neuroprotective effects hold true, there might be a possible use of melatonin in the late akinetic stages of HD. Fluoxetine and lisdexamfetamine appear to have worsened this patient's chorea, likely due to their dopaminergic effects and presumed increased serum concentrations caused by this patient's status as a CYP 2D6 poor metabolizer and other drug–drug interactions. Based on this, it might be prudent to use caution when initiating psychostimulants, fluoxetine, or melatonin in patients with known early-to-middle stage HD. Also, individuals who present with new or worsened choreoathetoid movements following administration of lisdexamfetamine, fluoxetine, or melatonin who have not been diagnosed with HD and have an unclear family history of HD might benefit from genetic testing to assess for presence of HD. We suggest vigilant monitoring for changes in motor function and frequent reassessment of medications over time in an attempt to account for fluctuations in dopaminergic activity and DA receptor sensitivity in the later stages of HD. Randomized withdrawal trials with melatonin, antidepressant, and/or psychostimulant in patients with HD that assess for changes in chorea would likely be worthwhile. Placebo-controlled crossover trials could also be utilized to further determine if our observations are generalizable.

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