



Acute akathisia following initiation of opicapone: A case report

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A 76-year-old man with an approximately 12-year history of tremor-predominant Parkinson disease (PD) was prescribed the catechol-O-methyltransferase (COMT) inhibitor opicapone at a dose of 50 mg once daily to address wearing off of his carbidopa/levodopa. His other antiparkinsonian medications included carbidopa/levodopa extended release 48.75/195 mg 7 capsules daily, ropinirole extended release 2 mg daily, and rasagiline 0.5 mg daily; total levodopa equivalent daily dose (including opicapone) was 1115 mg. He had never taken any other COMT inhibitor. He took two doses of opicapone, but on the third day after initiation, he began experiencing a constellation of symptoms including a feeling of inner restlessness, sense of impending doom, paresthesia in both legs which he described as “bubbles underneath the skin”, difficulty catching his breath, and dry mouth. He was seen initially in a local Emergency Department and given lorazepam, after which his symptoms abated.

However, his symptoms reappeared several hours later, prompting presentation to the University of Colorado Hospital. There, he was tachypneic with a respiratory rate of 30 breaths per minute but otherwise normal vital signs; he appeared anxious and restless, frequently turning over in the bed and moaning in discomfort. Laboratory evaluation including complete blood count, metabolic panel, hepatic function, creatine kinase, and toxicology screen, as well as MRI of the brain, were unrevealing.

Given his restlessness and sense of dysphoria, we were concerned that he was experiencing acute akathisia. Opicapone was discontinued. He was given lorazepam 0.5 mg intravenously, which initially improved his symptoms though resulted in delirium. Propranolol 10 mg orally caused bradycardia. Trihexyphenidyl 1 mg orally every eight hours resulted in substantial improvement in his restlessness and discomfort, and he was subsequently discharged home. Carbidopa/levodopa extended release was increased to 8 capsules daily of 48.75/195 mg each, but his other antiparkinsonian medications were unchanged; total levodopa equivalent daily dose upon discharge was 870 mg. In the subsequent weeks, trihexyphenidyl was weaned and discontinued, without re-emergence of akathisia.

Akathisia is a neuropsychiatric syndrome comprised of both subjective and objective psychomotor restlessness. The latter includes excessive movements such as fidgety movements of the legs, rocking

from foot to foot, pacing, or an inability to sit or stand still [1]. Although exposure to dopamine receptor-blocking agents is the most common cause, akathisia has been described in PD patients, regardless of prior treatment with levodopa. Prior studies have suggested that the prevalence of akathisia in idiopathic PD may be as high as 45 % [2]. In about half of cases, akathisia symptoms may be related to timing of anti-parkinsonian drugs, though it is not clear if the association is with “on” times or wearing off [2,3].

Akathisia following initiation of COMT-inhibitors has rarely been reported [4]. The pathophysiology, as with other non-motor fluctuations, likely involves an excessive dopaminergic state, though modulation of other non-dopaminergic neurotransmitters has been postulated as well [5]. The differential diagnosis includes other syndromes commonly seen in PD patients, including restless leg syndrome, levodopa-induced dyskinesia, and anxiety [6]. In our case, we particularly considered respiratory dyskinesia given the patient’s subjective shortness of breath and tachypnea on exam. However, the other signs of discomfort including pacing and turning in bed were more suggestive of akathisia. Our patient had no prior history of cognitive impairment nor psychiatric disease that might have suggested an alternate diagnosis.

Treatment of akathisia primarily involves reduction or withdrawal of any offending agents. Addition of an anti-akathisia agent may also be considered. Beta blockers (such as propranolol), anticholinergics (such as trihexyphenidyl or benztropine), and the 5-HT_{2A} antagonist mirtazapine are often considered first-line [7]. Other treatment options include benzodiazepines, amantadine, or clonidine. Anticholinergics are often favored for parkinsonian patients, despite a lack of high-quality evidence supporting this approach [7].

In summary, this case of akathisia induced by the addition of the COMT inhibitor opicapone was successfully treated by cessation of the offending medication and ultimately by the anticholinergic drug trihexyphenidyl. Although there is a paucity of similar events reported, given the severity of symptoms, as indicated by multiple Emergency Department visits and hospital admission, it is important for physicians to be aware of this potential adverse effect.

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2. Ethical compliance statement

The authors confirm that approval of an institutional review board was not required for this work. Verbal and written informed consent were obtained from the patient. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

CRediT authorship contribution statement

Alexander J. Baumgartner: Conceptualization, Investigation, Resources, Writing – original draft. **Michelle Adkins:** Resources, Writing – review & editing. **Jacquelyn Bainbridge:** Resources, Writing – review & editing, Supervision. **Maureen A. Leehey:** Conceptualization, Investigation, Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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