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Atypical Presentation of Duloxetine-Induced Parkinsonism in an Adult Female with Chronic Depression: Observation from Brain Perfusion Scintigraphy

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Abstract

Drug-induced parkinsonism (DIP) refers to parkinsonian symptoms that emerge after initiating or adjusting certain medications. Although DIP has been frequently associated with selective serotonin reuptake inhibitors, cases related to serotonin–norepinephrine reuptake inhibitors are uncommon, especially those with progressive features. We describe a 52-year-old woman with major depressive disorder, fibromyalgia, and rheumatoid arthritis who developed orofacial and limb tremors one month after starting duloxetine (30 mg/day). Her symptoms continued to worsen—spreading to the distal limbs and accompanied by dysphagia and speech difficulties—even after the medication was discontinued. Brain perfusion scintigraphy showed no interval change in her preexisting bilateral prefrontal hypoperfusion and preserved dopamine transporter binding in the striata and basal ganglia. These imaging findings supported a diagnosis of DIP rather than primary neurodegenerative parkinsonism, highlighting duloxetine's potential to trigger persistent, progressive parkinsonism and the value of brain scintigraphy in evaluating suspected DIP.

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Key Messages

- Duloxetine is related to extrapyramidal symptoms; the mechanism remains unclear.
- Atypical parkinsonism continued and progressed after duloxetine withdrawal.
- Preserved DAT binding on TRODAT-1 supported drug-induced parkinsonism.
- Functional SPECT helped distinguish DIP from neurodegenerative disease.

Introduction

Drug-induced parkinsonism (DIP) manifests with resting tremor, rigidity, akinesia, or bradykinesia after initiating medications that interfere with dopaminergic pathways [1]. Because it often mimics idiopathic Parkinson's disease, dopamine transporter imaging is essential for differentiation [1]. Duloxetine, an SNRI used for depression, anxiety, and pain, inhibits serotonin and norepinephrine reuptake and indirectly enhances prefrontal dopamine [2,3]. Although generally well tolerated, rare effects include serotonin syndrome, cycloplegia, and extrapyramidal symptoms such as DIP [4,5]. Duloxetine-induced parkinsonism is extremely rare, with only eight reported cases, including our case [6-10]. We report a progressive case occurring one month after duloxetine initiation, evaluated using brain perfusion scintigraphy.

Case History

A 52-year-old woman had medical histories including fibromyalgia, major depressive disorder, rheumatoid arthritis (RA), and a prior sleeve gastrectomy for severe weight-related health issues. She is on corticosteroids for RA management and has multiple drug allergies. She presented with involuntary tremors of the tongue, lips, and limbs, which began one month after taking 30 mg of duloxetine (Cymbalta) to manage her musculoskeletal pain and depressive symptoms. Despite discontinuing the medication, her symptoms persisted and progressively worsened, extending to her fingers and toes. She also developed dysphagia, characterized by frequent aspiration episodes, along with speech difficulties affecting clarity. Additionally, the patient reported muscle cramps during sleep and progressive numbness in her hands and feet, more pronounced in the right hand.

The patient exhibited resting tremors and involuntary movements affecting the orofacial region and limbs. Lip tremors, blepharospasms, and mandibular tremors were obvious when asked to perform facial movements such as pouting and raising of eyebrows. There were bilateral hand and arm tremors at rest, with increased severity on the right-hand during fist clenching and alternating supination-pronation. Head tremors, grimacing, and increased blinking appeared during shoulder elevation as well.

The patient underwent brain scintigraphy with SPECT/CT 30 minutes after an intravenous injection of 30 mCi Tc-99m ethyl cysteine dimer (ECD). Statistical imaging analysis using the Easy Z-score Imaging System (eZIS) before and after duloxetine both showed hypoperfusion of the bilateral prefrontal regions and the anterior cingulate cortex (ACC; Figure 1, 3A). However, further decrease in perfusion developed after administration of duloxetine, particularly in the left ACC, which might indicate an underlying mechanism (Figure 2, 3B). Another tool for dopamine reuptake transporter (DAT) binding, 99m Tc-TRODAT-1 SPECT, showed preserved in the bilateral striata, caudate nuclei, and putamen, suggesting intact dopaminergic nigrostriatal pathways (Figure 4). A comprehensive laboratory workup was conducted to exclude secondary causes of her dyskinetic symptoms, but no notable abnormalities were identified.

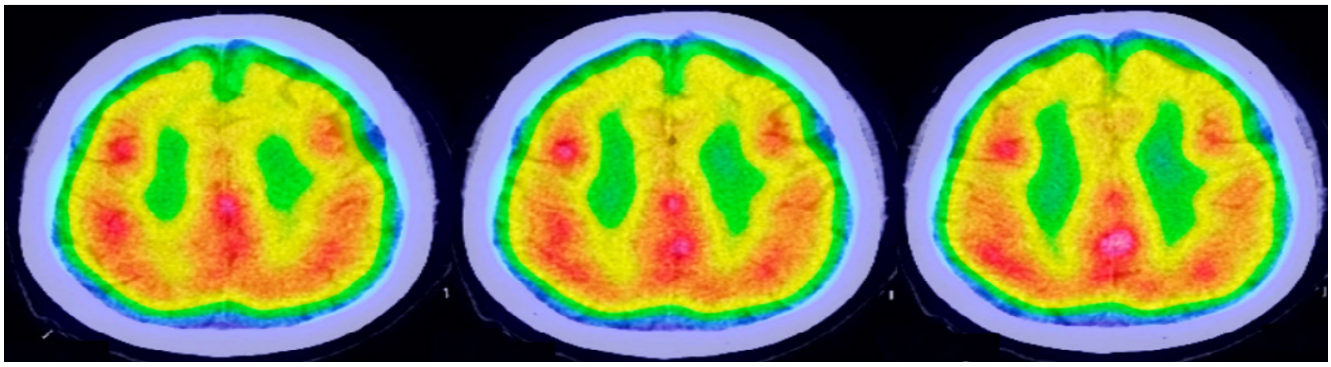

Figure 1: Transverse brain SPECT/CT taken in 2023, before initiating duloxetine

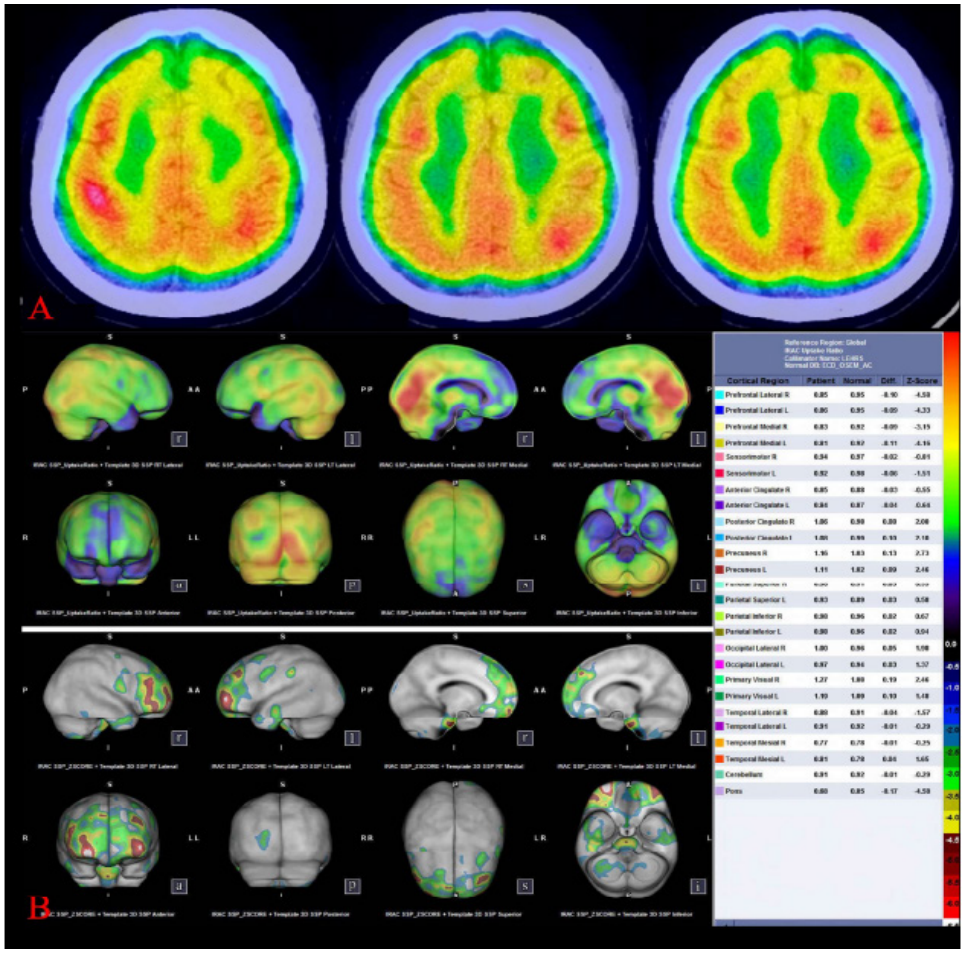

Figure 2: Brain SPECT/CT taken in 2024, after duloxetine (A. transverse; B. 3D)

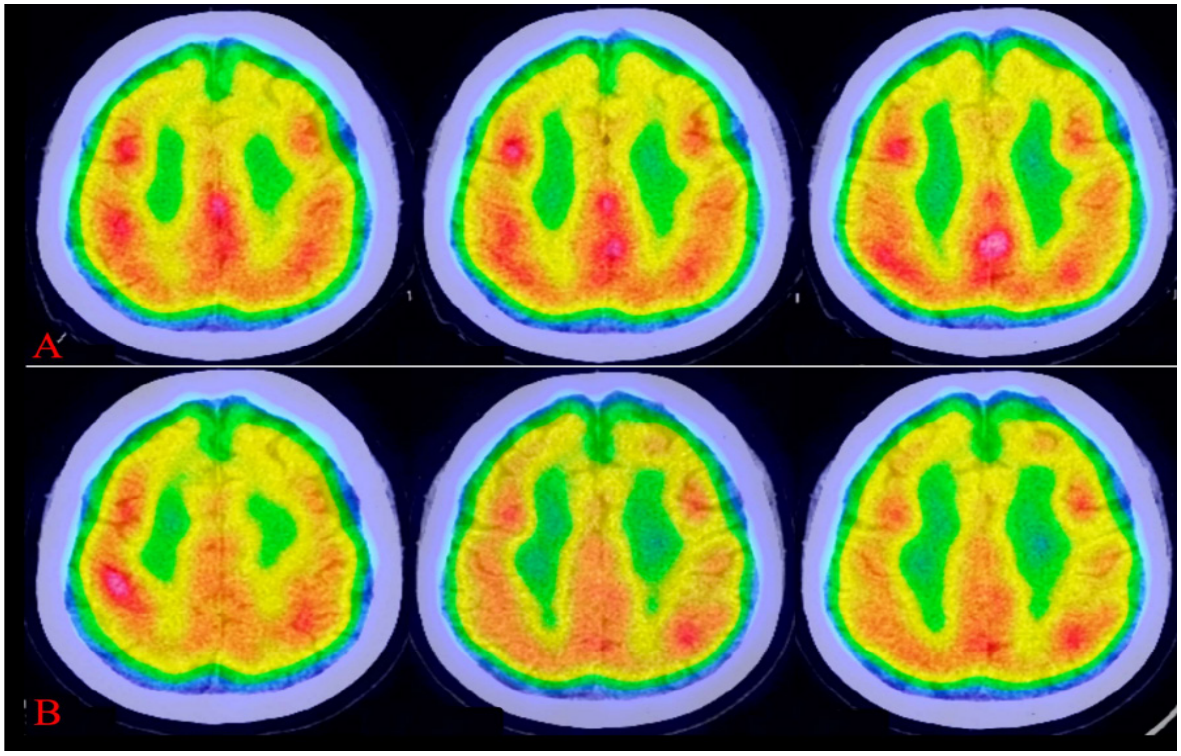

Figure 3: Comparison of brain SPECT/CT before and after duloxetine (A. Before; B. After)

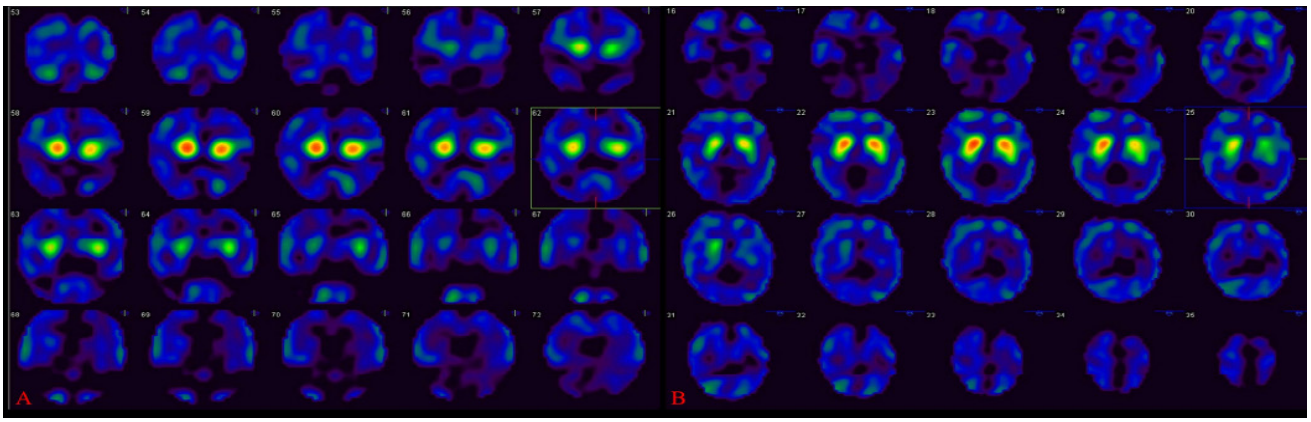

Figure 4: Tc-99m TRODAT-1 SPECT images revealing normal uptake in the bilateral basal ganglia (A. coronal; B. transverse)

Discussion

This is the case of a 52-year-old woman diagnosed with progressive duloxetine-induced parkinsonism, revealing increased hypoperfusion in the left ACC and prefrontal cortex after duloxetine treatment, visualized through SPECT/CT and preserved DAT binding. The only role of perfusion is in demonstrating the prefrontal hypoperfusion in this patient with depression. These findings support a drug-induced etiology rather than primary neurodegenerative parkinsonism. To date, eight cases of SNRI-related parkinsonism have been reported, including the present case. A literature review covering publications from 1995 to 2015 identified four cases of SNRI-induced parkinsonism, none of which were associated with duloxetine [6,7]. Three additional cases of duloxetine-induced parkinsonism were reported in 2015, 2022, and 2025, respectively, with symptoms that gradually resolved following duloxetine cessation [8-10].

DIP is the most common form of nondegenerative parkinsonism, often caused by typical antipsychotics and

other dopamine-2 (D2) receptor antagonists through postsynaptic receptor hypersensitivity from prolonged receptor blockade [11]. Although serotonergic antidepressants such as SSRIs and SNRIs do not directly block postsynaptic D2 receptors, various forms of EPS, including parkinsonism, dystonia, and akathisia, have been reported in association with their use [6,7,9-11]. The precise mechanism remains unclear; however, the widely accepted hypothesis suggests that increased serotonin release in the raphe nucleus, which has dense interconnections with the dopamine-rich substantia nigra, can suppress dopaminergic transmission, thereby mimic the effects of dopamine-blocking agents and lead to movement disorders [12].

Our patient exhibited clinical features consistent with parkinsonism, as assessed by the Extrapyramidal Symptom Rating Scale (ESRS), and fulfilled the clinical diagnostic criteria for DIP proposed by Shin and Chung [14,1]. Preserved DAT binding on TRODAT SPECT further supports this diagnosis, differentiating it from idiopathic PD, where asymmetric or posterior putamen-predominant DAT reduction is typically observed [1,15]. Even in early PD, TRODAT SPECT imaging can reveal significant reductions in DAT uptake due to substantial dopaminergic neurodegeneration [16]. Meanwhile, drugs associated with DIP affect pri marily postsynaptic dopamine receptors and have negligible affinity for DAT, which may explain the normal findings in this case. Importantly, the patient was not taking any medications known to interact with duloxetine or induce parkinsonian-like symptoms, as outlined in the pharmacovigilance review by Doloto et al. (2024), minimizing the likelihood of confounding drug–drug interactions as a cause of her presentation [17]. There was an inconsistency result between TRODAT SPECT and perfusion SPECT. Normal basal ganglia on TRODAT scintigraphy suggests it to be DIP. Our case demonstrates the complementary diagnostic value of functional imaging for identifying the etiology of symptoms that might otherwise be missed through standard assessments alone. TRODAT SPECT proved valuable not only for distinguishing drug-induced parkinsonism (DIP) from Parkinson's disease (PD) but also for identifying subclinical neurodegeneration and clarifying parkinsonian presentations of uncertain etiology [9,22]. In our patient, preserved DAT alongside a clinical history of antidepressant exposure supports the diagnosis of DIP rather than an underlying lesion or neurodegenerative process (Table 1).

Conclusion

To our knowledge, this is the first reported case of duloxetine-induced DIP with persisting and gradually worsening of parkinsonian symptoms after discontinuation of duloxetine. This case highlights the potential for duloxetine to cause persistent parkinsonism, distinguishing it from previously reported cases where symptoms resolved after discontinuation and underscores the need for increased clinician awareness regarding the neurological risks associated with SNRIs. Utilizing brain SPECT/CT is a valuable diagnostic tool for distinguishing DIP from PD and elucidating its possible predispositions and underlying pathophysiological mechanisms.

Table 1: Clinical profiles from our case and previously published cases at our institution involving atypical Parkinsonian syndromes assessed with TRODAT SPECT

	Age/Sex	Diagnosis	Diagnostic Tool	Treatment
Our case	52/F	DIP	ECD SPECT-CT (positive), TRODAT SPECT (negative)	Conventional physical rehabilitation
Wei et al. (2017) [23]	36/F	Holmes tremor secondary to artery of Percheron infarction	MRI, ECD-SPECT, TRODAT SPECT (positive)	Conventional physical rehabilitation

He et al. (2018) [24]	34/F	Dentato-rubro-thalamo-cortical tract hypoperfusion with cerebellar and contralateral cerebral dysfunction	MRI, ECD-SPECT (positive), TRODAT SPECT (negative)	Conventional physical rehabilitation
Kuo & Chang (2018) [25]	90/F	Post-stroke perioral tremor (rabbit syndrome)	ECD SPECT-CT (positive)	Conventional physical rehabilitation
Ho et al. (2019) [26]	37/F	Prodromal postpartum parkinsonism	TRODAT SPECT (positive)	Medication (Carbidopa/Levodopa)
Chen et al. (2021) [27]	50/M	Hemorrhagic stroke with asymmetrical cogwheel rigidity	TRODAT SPECT (positive)	Medication (Pramipexole)
Hung et al. (2021) [28]	67/M	PD with PISA syndrome	X-ray, ECD-SPECT, TRODAT SPECT (positive)	Conventional physical rehabilitation

DIP: Drug-induced parkinsonism, PD: Parkinson's Disease; MRI: Magnetic Resonance Imaging; SPECT: Single-photon Emission Computed Tomography; M: Month; W: Week

Conclusion

To our knowledge, this is the first reported case of duloxetine-induced DIP with persisting and gradually worsening of parkinsonian symptoms after discontinuation of duloxetine. This case highlights the potential for duloxetine to cause persistent parkinsonism, distinguishing it from previously reported cases where symptoms resolved after discontinuation and underscores the need for increased clinician awareness regarding the neurological risks associated with SNRIs. Utilizing brain SPECT/CT is a valuable diagnostic tool for distinguishing DIP from PD and elucidating its possible predispositions and underlying pathophysiological mechanisms.

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