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## Atypical Antipsychotic-Induced Parkinsonism: A Patient Case with CYP Enzyme Implications

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### Abstract

**Objective:** To report a case of Parkinsonism potentially caused by neuroleptic medications. **Summary:** The case analyzed is that of a 57-year-old male patient referred to a pharmacotherapy service by a neurologist after organic causes of tremor had been ruled out. Iatrogenic cause was suspected and referral expectation was to identify the offending agent or agents and propose alternative therapy. **Conclusion:** This case illustrates iatrogenic risk associated with neuroleptic medications while illustrating mechanisms of drug interaction via CYP enzymes that can lead to iatrogenic disease.

**Abbreviations:** DIP = Drug-induced Parkinsonism; MTM = Medication Therapy Management; PD = Parkinson's Disease

**Keywords:** Drug-induced Parkinsonism, Parkinsonism, Neuroleptic Medication, Medication Therapy Management, Pharmacotherapy

### Introduction

Parkinson's Disease (PD) is currently the second most common neurodegenerative disease affecting our population today,<sup>1</sup> as many as 14/100,000 in the general population, and 160 cases per 100,000 in individuals age 65 or greater.<sup>2</sup> There are many proposed risk factors for PD, including high amounts of dairy consumption, exposure to pesticides, brain injury, over-exposure to vitamins and minerals, among others.<sup>2</sup> PD often presents itself in the form of resting tremor, dyskinesia, stiffness, and postural instability. The root cause of these symptoms is the same – a loss of dopamine in the CNS needed for neuronal firing. Parkinson's Disease cannot be reversed, however progression can be slowed by the use of anti-Parkinson's agents. Unfortunately, it is not uncommon for reversible causes of diminished dopamine to be misdiagnosed as Parkinson's Disease. This case study analyzes a case of Parkinsonism induced by neuroleptic medications. Drug-induced Parkinsonism (DIP) is the second leading contributor to Parkinson-like symptoms, second only to true Parkinson's Disease. Consideration of iatrogenic causes of Parkinson-like symptoms can have a life changing effect for patients in the form of returned mobility status, cessation of tremor, and improved quality of life.

### Setting

The practice setting is a multispecialty, tertiary care clinic located in Florida. The clinic offers pharmacist-provided MTM, including more advanced pharmacotherapy services to all patients in the clinic via referral from physicians and other providers with ordering privileges. The pharmacist pharmacotherapy service sees patients from more than 20 different departments and is considered a specialty service, similar to other specialty services within the clinic.

### Case Report

Our subject is a 57 year-old white male presented to his neurology physician because his wife noticed a considerable change in mental status. He had been seeing "demons" at church, had lost his ability to do simple math (seen by difficulty tipping), and had lost his general sense of direction, often getting lost while driving. Our patient's medical history includes bipolar depression, loss of memory, recent onset tremor, hyperlipidemia, and history of head trauma. Because many of these symptoms had recent, sudden onset, his wife was concerned. Neurologic exam revealed bradykinesia, mild nuchal rigidity, increased tone in upper limbs, slight tremor, and slight anterocollis, stooped gait with decreased arm swing. See Table 1 for a list of his medications at presentation.

Upon evaluation by his neurological provider, our patient was found to have an incipient neurodegenerative process, likely due to a distant history of head trauma. His mother also had a history of severe depression and early-onset Alzheimer's Disease; this indicates that his psychological and behavioral issues may have a genetic component. While an iatrogenic contribution to his memory loss, dyscalculia, and dysgraphesthesia were possible, organic causes were not the only concern of the provider at this time. His tremor, however, did not fit the traditional presentation of organic tremor. It was subtle, and varied in severity over time. The neurology provider suspected iatrogenic cause of tremor, and referred this patient to our service. Both prescription and over-the-counter medications were reviewed for adherence, and their side effect profiles assessed for possible iatrogenic cause (Table 2).

By analyzing his medications, their receptor binding activity, and effects on dopamine, we were able to identify recent changes in his medications that correlated well with his recent onset tremor (Table 2).

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**Topiramate.** Topiramate is a weak inducer of CYP3A4.<sup>11</sup> His total daily dose has recently decreased due to the dosing interval being changed from three times a day to two times a day.

**Quetiapine.** Quetiapine is a CYP3A4 substrate,<sup>9</sup> and acts in part as a prodrug converting dopamine affinity quetiapine to more 5-hydroxytryptophan affinity norquetiapine.<sup>10</sup> Since the inducing effects of topiramate were recently reduced (less doses given per day), but the quetiapine dose was not changed, the quetiapine was now likely being converted from the dopamine blocking compound more slowly, producing more dopamine inhibiting effects.<sup>9-10</sup> Quetiapine, an atypical antipsychotic, does have reports of causing DIP, although much less commonly than other agents.<sup>1</sup>

**Brexpiprazole.** Brexpiprazole is also a CYP3A4 substrate.<sup>6</sup> The brexpiprazole was initiated at the same time that the topiramate total daily dose was reduced; because of this, the brexpiprazole was not being cleared at the anticipated rate, and may have been accumulating. Brexpiprazole is also an atypical antipsychotic; it is a cousin of a common DIP-offender, aripiprazole.<sup>1</sup> Brexpiprazole has a history of reported Parkinsonism, and is a likely offender in our patient.<sup>14</sup>

**Divalproex.** Our patient was also taking divalproex, a weak inhibitor of CYP3A4.<sup>7</sup> This may also have been contributing to an accumulation of brexpiprazole.

**Lithium.** Lithium is not metabolized through the CYP450 system,<sup>8</sup> making interactions with the above medications highly unlikely. Additionally, no recent changes had been made to his lithium dose, making contributions of lithium to his recent tremor highly unlikely.

Multiple interventions were suggested by our service to reverse the effects of DIP:

- A trial discontinuation of one antipsychotic is warranted. Maximization of one agent should be considered before addition of another medication in this case.
- Since brexpiprazole is a possible major contributor, slowly taper off and discontinue.
- Quetiapine is not currently optimized to a maximum daily dose of 800 mg. If needed upon discontinuation of brexpiprazole, titrate dose slowly upward to 800 mg daily.
- Resolution of symptoms from DIP may take up to 18 months to resolve. If after this time symptoms have not subsided, consider alternative therapy to divalproex, to remove the CYP3A4 inhibition. Instead, consider alternative lamotrigine, which is metabolized by UGT.

At this time, the patient has not had a follow-up appointment with neurology for a final assessment of his case, so it is not yet possible to evaluate the effectiveness of this recommendation for alleviation of his symptoms. The patient is scheduled for 4/26/17 for return.

### Parkinsonism vs. Parkinson's Disease

Both Parkinson's Disease and Parkinsonism can cause tremors, stiffness, slow movement, and postural instability that are commonly associated with PD.<sup>3</sup> These symptoms are a result of a loss of dopamine, which is why the two disorders present similarly, often indistinguishable until severe progression of the disease has taken place. Because of the shared pathophysiology of the symptoms, there is not a diagnostic test that is helpful in differentiating between the two disorders (ex: Dopamine Transporter – DaT – Test).<sup>1</sup> The difference between these two presentations lies in the reason for the loss of dopamine.

Parkinson's Disease generally progresses slowly, and is commonly coupled with depression, loss of smell, cognitive decline, and/or gastric problems.<sup>4</sup> Parkinsonism, on the other hand, generally has a sudden onset, and can be associated with more severe symptoms such as falling, hallucinations, and dementia-like cognitive defects.<sup>3</sup> Our patient had these, including the hallucination of seeing demone in church. A patient experiencing Parkinsonism may not respond to traditional Levodopa therapy the way a PD patient would.<sup>5</sup> There are many different causes of Parkinsonism, including: drug-induced Parkinsonism, progressive supranuclear palsy, multiple-system atrophy, vascular Parkinsonism, dementia with Lewy bodies, and corticobasal degeneration.<sup>3</sup>

### Drug-Induced Parkinsonism

Drug-induced Parkinsonism (DIP) is the 2<sup>nd</sup> most common etiology of Parkinsonism, second only to Parkinson's Disease.<sup>3</sup> Some common classes of DIP culprits include typical antipsychotics, atypical antipsychotics, dopamine depleters, anti-emetics, and calcium channel blockers. Extrapyramidal symptoms are common among patients using antipsychotic medications because of their effects on dopamine receptors in the brain.<sup>1</sup> Although presentation of DIP generally occurs within weeks of beginning therapy with the offending antipsychotic, presentation months after initiation is not unlikely.

Many of the movement disorders seen in DIP are the same as PD, but may be more sudden and severe in nature. Fortunately, upon discontinuation of the offending agent, the movement disorders associated with DIP will usually subside. It is important to note, however, that restoration of normal dopamine levels can take up to 18 months, and therefore, it is not appropriate to consider treatment of the movement disorders for at least 18 months after discontinuation of the

anticipated offending agent.<sup>3</sup> It is also possible that the patients may have been in a preclinical state of PD, and the use of these medications simply unmasked the underlying disease; there is a chance that the effects may not subside once this point is reached, even upon discontinuation of the offending agent.<sup>1</sup> Only after adequate time has passed after discontinuation of any possible offending agents is it reasonable to consider the use of anti-PD medications.

### Discussion

This patient was referred to our service by his neurologist within our healthcare system. Generally, when a patient is referred to our service, it is after evaluation by a diagnostic provider who deems deeper evaluation of medication therapy to be a necessity for the patient and after other diagnostic testing is negative.

As noted in the patient case, DIP is an issue suffered by thousands of patients annually. Through collaborative practices and thorough evaluation, healthcare teams can work together to eliminate misdiagnoses like these and improve the quality of life of thousands of patients every year.

There is an expansive role for pharmacists in the realm of Medication Therapy Management. Complicated patients present to health care providers every day, and there is no provider better equipped with the knowledge or resources to resolve complicated medication related problems (MRPs) than a practicing clinical pharmacist due to their extensive training in pharmacology, biochemistry, pathophysiology of medicine, and pharmacotherapy.

### Case Summary

The patient presented with tremor thought to be iatrogenic in nature, as evaluated by his neurologist. Upon evaluation by our service, he was found to have three possible contributing components to his symptoms: recent increase in dosing interval and lower dose of topiramate, an inducer of CYP3A4; recent initiation of brexpiprazole, a CYP3A4 substrate and likely offender of his DIP; and quetiapine, an agent unlikely to cause DIP, although cases have been reported. His quetiapine use was longstanding and no recent changes had occurred. The recommendation by our service was to discontinue the recently initiated brexpiprazole, and titrate the quetiapine dose up as necessary, not to exceed a maximum daily dose of 800 mg.

### Conclusion

By raising awareness of Drug-induced Parkinsonism and other causes possible causes of Parkinsonism, health care providers can avoid unnecessary reductions in quality of life for sufferers and avoid unnecessary therapies. Consideration of possible iatrogenic causes of Parkinson-like symptoms is important to eliminate possible misdiagnoses of PD, unnecessary treatment,

and suffering for patients. This can be accomplished by collaborating as an interdisciplinary health care team, keeping the patient at the center of all decision-making, and considering all possible causes before reaching a definitive diagnosis such as Parkinson's Disease. This includes analysis of pharmacokinetics, pharmacogenomics testing results, side effect profiles of all medications, and simplified treatment regimens for patients to improve patient treatment outcomes and quality of life.

**Disclosure:** The authors have no conflicts of interest to report.

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**Table 1: Medications at the Time of Pharmacotherapy Visit**

Medication	Dose	Time/frequency	Indication
Brexiprazole	1 mg	1 tab PO Daily	Depression
Cholecalciferol (Vitamin D3)	2000 IU	1 tab PO Daily	Vitamin D Deficiency
Divalproex sodium	250 mg	3 tabs PO BID daily	Bipolar Depression
Esomeprazole	40 mg	1 cap PO daily	GERD
Fluticasone nasal spray	50 mcg	1 puff nasally daily	Allergic Rhinitis
Levothyroxine	112 mcg	1 tab PO daily	Hypothyroidism
Lisinopril	10 mg	1 tab PO daily	HTN
Lithium Carbonate	300 mg	2 tabs PO daily	Bipolar Disorder
Botox	-	As directed every 12 weeks	Migraines
Phenylephrine	10 mg	1 tab PO BID	Congestion
Quetiapine	600 mg	2 tabs PO daily	Anti-psych
Simvastatin	40 mg	1 tab PO daily	HLD
Topiramate	200 mg	1 tab PO daily	Migraines
<b>OTC Medications</b>			
Excedrin Migraine	-	2 tabs PO PRN	Headache
Aspirin	81 mg	1 tab PO daily	Antiplatelet
Multivitamin	-	1 PO daily	General health

**Table 2: Rationale for Iatrogenic Presentation<sup>6-11</sup>**

Drug	Recent Change	CYP 450 Activity	Dopamine Receptor Activity	Occurrence of Pseudo-parkinsonism	Net Effect
Brexiprazole	Added	3A4 substrate	D2 partial agonist	Uncommon; usually within 2 weeks of initiation	Direct decrease in dopamine activity
Divalproex Sodium	No change	Weak inhibitor 3A4	-	Uncommon	Increased exposure to neuroleptic agents → Indirect decrease in dopamine activity
Quetiapine	No change	3A4 substrate	D1 antagonist D2 antagonist	~6%	Direct decrease in dopamine activity
Topiramate	Decreased daily dose and dosing interval	Weak inducer 3A4	-	Not reported	Increased exposure to neuroleptic agents → Indirect decrease in dopamine activity

DA = dopamine, D1 = dopamine 1 receptor, D2 = dopamine 2 receptor