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Severe parkinsonism caused by brexpiprazole: A case report

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Antipsychotic medications commonly cause drug-induced parkinsonism (DIP) due to dopamine receptor antagonism, with a higher likelihood in female and elderly patients [1]. Atypical antipsychotics have a lower rate of DIP and other extrapyramidal symptoms (EPS) than typical antipsychotics due to a lower affinity for dopamine D2 receptors and a higher affinity for other non-dopaminergic receptors [1,2]. A subtype of atypical antipsychotics are the dopamine partial agonists, which may confer an even lower risk of DIP/EPS [2]. Aripiprazole was the first agent of this class used in clinical practice, which despite its lower risk category can still cause DIP [1]. Older adults may have a greater risk of developing DIP on this drug [3].

A newer dopamine partial agonist, brexpiprazole, gained approval in the US for the treatment of schizophrenia and as an adjunctive treatment for depression in 2015. Compared to aripiprazole, brexpiprazole is more potent at serotonergic and adrenergic receptors and has less intrinsic activity at the D2 receptor. It is considered to have a more favorable risk of EPS than its predecessor, which has thus far been supported by clinical studies [4]. However, the majority of these have focused on younger patients, with one exception [5]. We report a case of an elderly woman who developed severe parkinsonism after starting brexpiprazole.

The patient is a 71-year-old woman with severe anxiety/depression since adolescence, without psychosis, and longstanding essential tremor involving the hands. Three years' prior, a movement disorders neurologist at another institution documented an action tremor of the hands with mild persistence at rest, but no leg tremors, bradykinesia or rigidity. In the 2 years before our evaluation, she developed worsening rest tremor, with spread to the jaw and legs. She endorsed talking during sleep without other dream enactment behaviors, and constipation in the setting of opiate treatment for osteoarthritis. Olfaction was normal, and there were no cognitive symptoms. Pertinent medications included duloxetine, alprazolam, and symptomatic treatments for gastroesophageal reflux, but no dopamine antagonists for gastrointestinal symptoms. Notably, she had tried aripiprazole for depression/anxiety during the past 2 years, but specific timing and duration of use were unclear. There was no other prior antipsychotic use.

At that initial visit, her examination revealed mild parkinsonism including asymmetric bradykinesia and rigidity, bilateral hand tremor with similar severity at rest and with maintenance of posture, and bilateral leg tremor. She was started on low-dose carbidopa/levodopa, but reported progressive worsening of tremor, cramping of her feet, and weakness after two weeks of treatment. The levodopa dose was gradually increased to 900 mg per day, but symptoms continued to worsen. Two months after her initial visit she experienced a more rapid and profound worsening of tremor, marked decline in mobility with gait freezing episodes, anterocollis, and a sense of restlessness. A dopamine transporter scan was normal.

She was brought back to the clinic for evaluation, and her parkinsonism had clearly worsened (see video). She had more constant and higher amplitude rest tremors of both hands, legs, and jaw. She also had severe anterocollis, increased bradykinesia bilaterally, and severe shuffling of gait. At that time, history was obtained that her psychiatrist had started brexpiprazole 1 mg daily as an adjunctive treatment for depression/anxiety around the time of our initial evaluation. The dose had been increased to 2 mg daily two months after that evaluation, coinciding with the drastic worsening of her parkinsonism. She was rapidly weaned off of brexpiprazole and noticed improvement within a month. Examination seven months after brexpiprazole discontinuation showed marked improvement in posture, gait, and mobility, though had mild residual rest tremor. Despite improvement, the persistence of parkinsonism prompted continued concern for underlying Parkinson's disease, but dopamine transporter imaging was again normal.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.11.013.

Differentiating between Parkinson's disease and DIP can be difficult. In this case, persistence of rest tremor more than six months after drug withdrawal and the change in tremor quality prior to initiation of brexpiprazole would suggest underlying Parkinson's disease, though previous treatment with aripiprazole could have also initially induced her parkinsonism. While not FDA approved for this purpose, dopamine transporter imaging can be used to help differentiate between DIP or a neurodegenerative parkinsonism, with a sensitivity of around 85% [1]. Our patient's two normal studies separated by over eight months argue against neurodegenerative parkinsonism. Regardless, this case demonstrates that brexpiprazole can contribute to parkinsonism based on the onset of severe parkinsonian symptoms after its initiation, worsening after the dose increase, and improvement after discontinuation. While the risk of DIP with brexpiprazole is thought to be lower than other atypical antipsychotics, its safety has not been as extensively studied in older patients such as ours. Physicians should consider the possibility of

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parkinsonism when treating elderly patients with brexpiprazole.

Ethics

This manuscript did not require IRB approval. Informed patient consent for video publication in print and online forms was obtained. Both authors contributed to clinical care of the patient and writing of the manuscript, and have approved the manuscript in its final form. The authors have no declarations of interest relevant to this activity. Dr. Jackowiak reports no additional financial disclosures. Dr. Chou receives research support from the National Institutes of Health (NS091856-01, NS10061102, NS107158), participates as a site-PI in clinical trials sponsored by the Parkinson Study Group (STEADY-PD III, SURE-PD3, NILO-PD) receives royalties from UpToDate and Springer Publishing and served as a consultant for Accordant and Boston Scientific.

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Eric M. Jackowiak*, Kelvin L. Chou
Department of Neurology, University of Michigan, Ann Arbor, MI, USA
E-mail address: ejackowi@med.umich.edu (E.M. Jackowiak).

* Corresponding author. 2301 Commonwealth Blvd. Suite 1022, Ann Arbor, MI, 48105, USA.