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LETTER TO THE EDITOR

Secondary parkinsonism associated with tetrabenazine: A case report

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Dear Editor,

Tardive dyskinesia is a hyperkinetic movement disorder that usually emerges as a late complication of chronic dopamine D2 receptor antagonism. It typically presents with repetitive orofacial movements and is a common late-onset adverse effect of antipsychotic medications. Its pathophysiology involves postsynaptic dopamine receptor supersensitivity and dopaminergic imbalance (1).

Tetrabenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor, reduces synaptic dopamine release and is commonly used in the management of tardive dyskinesia. However, it may also induce depression, anxiety, or secondary parkinsonism, particularly in elderly or psychiatrically vulnerable individuals (2).

Here, we describe a rare case of tetrabenazine-induced secondary parkinsonism in an elderly woman with prior short-term antipsychotic exposure.

CASE REPORT

A 71-year-old woman was referred from the psychiatry outpatient clinic to the neurology outpatient clinic because of involuntary perioral movements, including jaw clenching and lip pursing, which worsened during speech. According to the available history, the symptoms emerged approximately two months after initiation of low-dose olanzapine (2.5 mg/day), risperidone (1 mg/day), and alprazolam (2.5 mg/day), prescribed in an outpatient psychiatric setting for bereavement-related anxiety and behavioral symptoms. A formal diagnosis of complicated grief was not established. Antipsychotics were prescribed empirically at low doses and introduced sequentially over a short period before referral. These medications were subsequently discontinued, and the patient was referred for neurological evaluation.

Her medical history included type 2 diabetes mellitus and hypertension. Current medications included insulin, sitagliptin/metformin, gliclazide, verapamil, and acetylsalicylic acid. She had no prior history of chronic psychiatric illness, long-term antipsychotic use, or exposure to other dopamine receptor-blocking agents such as metoclopramide. The recent two-month course of antipsychotic therapy represented her first exposure to antipsychotic medication. There was no history of extrapyramidal symptoms or tardive dyskinesia.

At the initial neurological examination, no bradykinesia, rigidity, or postural instability was detected, and the phenomenology of the movement disorder had not yet been fully characterized. Although the clinical picture was dominated by perioral hyperkinetic movements, an early

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extrapyramidal syndrome related to recent dopamine receptor-blocking agent exposure was considered in the differential diagnosis. In this context, biperiden (2 mg twice daily) was initiated empirically. However, as the movements were subsequently recognized to be predominantly hyperkinetic and consistent with a tardive-type orofacial dyskinesia, and because no clinical benefit was observed, biperiden was discontinued after three weeks.

Approximately one month after the initial neurology evaluation, tetrabenazine was initiated at 25 mg twice daily for persistent involuntary movements. Partial symptomatic improvement was observed; however, depressive symptoms subsequently emerged, prompting the addition of sertraline (50 mg/day). Several weeks later, the tetrabenazine dose was reduced to 12.5 mg twice daily because of adverse effects. Lorazepam (1 mg/day) was introduced for accompanying anxiety symptoms.

Following the later emergence of generalized bradykinesia and jaw tremor, tetrabenazine was gradually reduced to 6.25 mg three times daily. Levodopa/benserazide (100/25 mg three times daily) was initiated as both a diagnostic and symptomatic trial to differentiate drug-induced parkinsonism from an underlying neurodegenerative parkinsonian disorder. The patient demonstrated minimal clinical improvement in parkinsonian features with levodopa. Treatment was continued temporarily during ongoing clinical evaluation and medication adjustments. Tetrabenazine was not immediately discontinued because of persistent hyperkinetic symptoms.

Cranial magnetic resonance imaging (MRI) was unremarkable. Dopamine transporter imaging (DaTSCAN) demonstrated normal presynaptic dopaminergic transporter activity, supporting a diagnosis of drug-induced secondary parkinsonism.

Several months later, tetrabenazine was discontinued because of supply limitations, while levodopa/benserazide was continued. During follow-up, psychiatric treatment adjustments were made by the psychiatry team in response to persistent and evolving depressive and anxiety symptoms. Treatment decisions, including initiation of sertraline and lorazepam, were based on clinical psychiatric assessment rather than standardized rating scales. At one stage, the regimen included clomipramine (25 mg three times daily), sertraline (50 mg/day), venlafaxine (225 mg/day), and alprazolam (1 mg/day), which were introduced sequentially rather than as part of a single planned combination. Given the patient's advanced age and cardiovascular comorbidities, such regimens required careful monitoring because of potential safety concerns and drug interactions.

During later follow-up, tetrabenazine was reinitiated at 25 mg/day.

At the most recent follow-up, involuntary movements had mildly worsened, whereas neuropsychiatric status remained stable. She continued treatment with tetrabenazine (6.25 mg three times daily), sertraline, and lorazepam, with doses adjusted as clinically indicated.

DISCUSSION

This case provides several clinically relevant insights. First, it highlights that even short-term, low-dose exposure to dopamine receptor-blocking agents in elderly patients may predispose to the development of tardive-type orofacial dyskinesia or related hyperkinetic syndromes. Second, it demonstrates the potential for sequential and overlapping drug-induced movement disorders, with initial hyperkinetic symptoms followed by hypokinetic features during VMAT2 inhibitor therapy. Third, it underscores the vulnerability of elderly patients to neuropsychiatric and motor adverse effects in the context of psychotropic polypharmacy. Finally, this case emphasizes the importance of individualized treatment strategies and close interdisciplinary collaboration in managing complex movement disorders accompanied by comorbid psychiatric symptoms.

Tardive dyskinesia is a well-recognized adverse effect of chronic dopamine D2 blockade. Its pathophysiology involves postsynaptic receptor upregulation and hypersensitivity, leading to involuntary orofacial movements (1). Tetrabenazine, a reversible VMAT2 inhibitor, depletes presynaptic dopamine by inhibiting vesicular uptake, thereby reducing hyperkinetic symptoms. However, because of its relatively short half-life (4-8 h), abrupt discontinuation or inadequate titration may result in fluctuating dopaminergic activity and symptom recurrence. In our patient, symptom recurrence following drug discontinuation may reflect a pharmacodynamic rebound phenomenon; however, this interpretation should be made cautiously, as concurrent medication changes and the absence of standardized objective measures limit causal inference. Additionally, VMAT2 inhibition may affect other monoamines, including serotonin and gamma-aminobutyric acid (GABA), contributing to neuropsychiatric adverse effects such as depression and anxiety (3). This underscores the importance of concurrent psychiatric monitoring and the potential

need for adjunctive treatment with selective serotonin reuptake inhibitors or benzodiazepines, as demonstrated in this case.

Secondary parkinsonism resulting from pharmacological dopamine depletion must be distinguished from idiopathic Parkinson's disease. In this case, the limited clinical response to levodopa, together with normal DaTSCAN findings and the temporal association with tetrabenazine exposure, supported a diagnosis of drug-induced secondary parkinsonism. In a cohort of 526 patients, Jankovic et al. (4) reported that 28.5% of patients with hyperkinetic disorders developed parkinsonism during tetrabenazine treatment. Reported risk factors include advanced age, prior dopamine antagonist exposure, and individual susceptibility (5).

Newer VMAT2 inhibitors such as deutetrabenazine and valbenazine offer improved pharmacokinetic profiles. Deutetrabenazine, through deuterium substitution, exhibits a prolonged half-life and reduced peak-to-trough fluctuations, while valbenazine offers once-daily dosing with selective VMAT2 inhibition and minimal off-target receptor binding. These pharmacological advantages may reduce the risk of neuropsychiatric side effects and drug-induced parkinsonism, particularly in elderly populations. In this context, the adverse effects observed in our patient during tetrabenazine therapy might have been mitigated through the use of newer VMAT2 inhibitors (6-9).

Differentiating tardive dyskinesia from drug-induced parkinsonism is clinically important, as these conditions differ in pathophysiology, phenomenology, and management. Tardive dyskinesia typically presents with hyperkinetic, non-rhythmic choreiform, athetoid, or stereotyped movements, particularly in the orofacial region, whereas drug-induced parkinsonism manifests with hypokinetic features such as bradykinesia, rigidity, and rhythmic tremor. In this case, the initial presentation of isolated orofacial hyperkinetic movements without parkinsonian signs suggested a tardive-type process, whereas the later emergence of generalized bradykinesia and jaw tremor during tetrabenazine therapy supported secondary drug-induced parkinsonism (10).

The diagnosis of tardive dyskinesia in this case should be interpreted cautiously, given the relatively short duration and low dose of antipsychotic exposure. Alternative drug-induced movement disorders were considered in the differential diagnosis, including acute drug-induced dyskinesia and withdrawal-emergent dyskinesia (11). Acute dyskinesias typically occur shortly after drug initiation and are often transient, whereas withdrawal-emergent dyskinesia usually develops following dose reduction or discontinuation and tends to resolve within weeks. In contrast, the movements in our patient were predominantly stereotyped and orofacial in distribution and persisted beyond discontinuation of dopamine receptor-blocking agents, favoring a tardive-type process. Therefore, a cautious interpretation as a probable or early tardive syndrome appears most appropriate.

An important limitation of this case is the presence of extensive psychotropic polypharmacy. The concurrent use of multiple agents may have influenced both motor and neuropsychiatric symptoms through complex dopaminergic and non-dopaminergic interactions. Consequently, clinical changes cannot be attributed with certainty to a single agent. Additionally, the absence of standardized psychiatric rating scales represents a limitation, as symptom severity and treatment response were assessed primarily on the basis of clinical judgment.

In conclusion, tetrabenazine is an effective treatment for hyperkinetic movement disorders but may induce reversible secondary parkinsonism, particularly in elderly patients with prior dopamine antagonist exposure. This case highlights the importance of careful medication selection, close monitoring, and individualized management strategies. It also underscores the need to consider diagnostic complexity and potential confounding factors in patients receiving multiple psychotropic medications.

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