Understanding drug-induced parkinsonism
Separating pearls from oy-sters

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In 1817, James Parkinson described the shaking palsy now known as Parkinson disease (PD). Descriptions evolved until the term “parkinsonism” now refers to a syndrome characterized by the presence of tremor, rigidity, and bradykinesia in addition to loss of postural reflexes and freezing. The most common cause of parkinsonism is PD. However, in any parkinsonian patient, one must obtain a careful medical and medication history, as drug-induced parkinsonism (DIP) is often reversible, especially if the offending drug is discontinued early.

CASE SCENARIO
A 46-year-old man developed upper limb tremors 2 weeks after initiating perphenazine for mood disorder. Perphenazine was promptly changed to quetiapine, though his tremor persisted. He had a history of hypertension, hypercholesterolemia, and chronic nausea. His medications include verapamil, lovastatin, and metoclopramide. Motor, sensory, and cerebellar testing were normal. Although mildly stooped, he had normal gait and postural reflexes. Extrapyramidal examination revealed a mild chin tremor, moderate symmetric 3 to 4 Hz resting tremor of the upper and lower limbs, and faster frequency postural tremor of both arms. Finger tapping was moderately irregular bilaterally.

"PEARLS" FOR EVALUATING DIP
Many patients with DIP are often misdiagnosed with PD. While recognizing clues that suggest DIP is critical (see table 1A), identifying risk factors (table 1B)2 and offending agents is just as important (summarized in table 2).3 DIP falls under the category of secondary parkinsonism (due to drugs, toxins, structural lesions).4 Thus, early recognition may lead to a better prognosis.

The most common culprits are the neuroleptics with potent dopamine D2-receptor blocking actions, including haloperidol and perphenazine.1 If chronic neuroleptic drug use is required, the lowest effective dose or an atypical neuroleptic drug is preferred. In one study, clozapine was shown to significantly improve psychosis without worsening or causing motor symptoms of parkinsonism.5 However, clozapine can cause agranulocytosis, which requires regular monitoring of blood count.

Metoclopramide is used widely in patients with gastric motility disorders and it has a chemical structure similar to the neuroleptic drug chlorpromazine.1 The occurrence of parkinsonism secondary to chronic metoclopramide use had been well documented.1 Another neuroleptic, prochlorperazine, is frequently used to treat gastric motility disorder. It too has the potential to cause parkinsonism and can cause acute dystonia in the first 24 to 48 hours.1

Table 1

<table>
<thead>
<tr>
<th>Clues that might suggest DIP</th>
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<tbody>
<tr>
<td>Subacute bilateral onset and progression of symptoms</td>
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<tr>
<td>time-locked with medication intake</td>
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<tr>
<td>Early presence of postural tremor</td>
</tr>
<tr>
<td>Concurrent oral-buccal dyskinesias</td>
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<tr>
<td>Risk factors for development of DIP</td>
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<tr>
<td>High dose, high potency, piperazine side chain neuroleptics</td>
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<tr>
<td>Elderly</td>
</tr>
<tr>
<td>Female (female: male ratio 2:1)</td>
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<tr>
<td>Hereditary Parkinson disease</td>
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<tr>
<td>Preclinical parkinsonism</td>
</tr>
<tr>
<td>AIDS</td>
</tr>
<tr>
<td>Coexistence of tardive dyskinesia</td>
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</tbody>
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From Mayo Clinic Arizona, Scottsdale.

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patients have previously unnoticed, undiagnosed tremors.\textsuperscript{3} EPT can also be associated with endocrine dysfunction, particularly hyperthyroidism, hypoglycemia, and caffeine intake.\textsuperscript{3} Cerbellar tremor is a slow intention tremor (usually less than 5 Hz) and may be postural.\textsuperscript{7}

\textbf{Tests you do not want to miss.} Apart from identifying a potential offending agent, it is also a must to look for other secondary causes of parkinsonism. Wilson disease (WD) should be considered in patients with onset of movement disorder before age 50 years. It is critical not to miss the diagnosis of WD because it is usually treatable with drugs that chelate copper.\textsuperscript{3} Clinical manifestations may include hepatic, neurologic, psychiatric, and ophthalmologic abnormalities.\textsuperscript{8} The classic neurologic sign is a wing-beating proximal upper limb postural tremor, though parkinsonism can be seen. Screening tests include serum ceruloplasmin (normal >20 mg/dL), 24-hour urine copper (normal <100 pg/24 hours), and slit-lamp eye examination looking for copper deposits within the cornea around the iris (Kayser-Fleischer rings).\textsuperscript{3}

Hypothyroidism can present with subacute to chronic onset of symmetric parkinsonism. Serum TSH may be a useful screening test.

\textbf{MANAGING DIP} DIP may persist or remit slowly despite prompt discontinuation of the offending drug. Some patients may require medications temporarily to relieve symptoms.

\textbf{Pearls in choosing drugs.} Use of l-dopa or anticholinergic agents may be indicated and effective.\textsuperscript{3} Symptoms should eventually resolve if the parkinsonism was drug-induced.\textsuperscript{1} In our experience, levodopa and dopamine agonists can potentially improve most features of parkinsonism, though they may be less effective in alleviating severe neuroleptic-induced tremor.

\textbf{Avoiding the oyster.} Tetrabenazine has been used worldwide to alleviate hyperkinetic movements such as tardive dystonia and chorea, but it can worsen parkinsonism.\textsuperscript{3} Perhaps this can be explained best by its dopamine-depleting property. Beta-blockers like metoprolol have been regarded as mainstays of pharmacologic therapy for ET, but not for DIP.\textsuperscript{9} Similarly, primidone has been useful in reducing tremor in ET but not in DIP.\textsuperscript{9} Surgical procedures are available that effectively ameliorate tremor in ET that is refractory to medical management.\textsuperscript{9} Their potential effectiveness in DIP remains to be investigated.

Though our patient discontinued perphenazine, his persistent tremor probably was due to continued intake of metoclopramide. He experienced 50% improvement after discontinuing metoclopramide and being placed on 750 mg/day of levodopa.

\textbf{PEARSLS TO TAKE HOME} Prompt recognition of DIP is the key. The next step is discontinuation of the culprit. Most cases remit within 4 months after stopping the causative drugs.\textsuperscript{3} Rarely, parkinsonism can be persistent, unremitting, and disabling. In such cases, certain drugs may provide symptomatic relief. Finally, prevention remains the most important strategy.\textsuperscript{2}

\textbf{REFERENCES}

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