

# Drug-Induced Parkinsonism Frequently Missed

*Of 17 DIP patients seen by a neurologist, only 2 were correctly diagnosed, according to an informal study.*

BY KERRI WACHTER  
Senior Writer

WASHINGTON — Even neurologists are missing the diagnosis of drug-induced parkinsonism, according to an informal study of patients at one movement disorder clinic presented at the World Parkinson Congress.

Overall 8% (23 of 304 patients) of all cases of new patients with parkinsonian symptoms seen at the Emory University movement disorders clinic between January 2004 and January 2006 were diagnosed with drug-induced parkinsonism (DIP), said Dr. Stewart A. Factor, director of the movement disorders program at Emory University.

The age at diagnosis ranged between 49 and 97 years; the age at onset ranged between 48 and 96 years. Patients were predominantly female (73%). Records were available for 22 patients with DIP.

“Seventeen of the 22 patients had been seen previously by neurologists, and yet only 2 of them were diagnosed with drug-induced parkinsonism,” said Dr. Factor. Of these, 10 were misdiagnosed with Parkinson’s disease (PD) and were treated with antiparkinsonian drugs. Seven patients had no clear diagnosis.

DIP, defined by Dr. Factor to include tardive dyskinesia, is misdiagnosed frequently; it has been estimated variously

that only 1 in 16 cases and 2 in 12 patients with DIP are correctly diagnosed. “What I’m seeing is that even neurologists are missing this diagnosis.”

The older, conventional antipsychotic drugs have been most commonly associated with DIP. It has been assumed that the risk of DIP was reduced with the introduction of atypical antipsychotic drugs. However, Dr. Factor’s experience has been just the opposite. Only three patients in his clinic developed DIP in response to typical antipsychotics (haloperidol, trifluoperazine, and amoxapine). In contrast, 12 cases were caused by atypical antipsychotics (3 from risperidone, 6 from olanzapine, 1 from ziprasidone, and 2 from aripiprazole). Five cases were caused by metoclopramide and two were caused by drug combinations (metoclopramide/serpine, metoclopramide/ziprasidone).

In terms of clinical features, 11 patients had tardive dyskinesia (including 5 with respiratory dyskinesia), 2 had akathisia, 19 had tremor (17 with resting tremor and 2 with asymmetric tremor, alone or in combination), and 3 had akinetic rigidity. Clinically, 11 patients had psychiatric diagnoses—primarily mood disorders (9 patients)—and 6 patients had neurologic diagnoses (dementia, Huntington’s chorea, hydrocephalus). Of the 13 patients who stopped the drug and returned for follow-up, 12 showed an improvement

in symptoms within about 6 months. DIP has a subacute onset and all of the cardinal features of Parkinson’s disease—tremor, rigidity, bradykinesia, and abnormalities of posture, gait, and balance—can be seen. Akinetic rigidity (without tremor) is seen in more than half of patients with DIP. Drug-use history and tardive dyskinesia appear to be key to the differential diagnosis.

Several other factors can also help differentiate DIP from PD, including subacute onset, bilateral features, more postural tremor than resting tremor, and the presence of other extrapyramidal signs.

Among psychiatric patients, 90% of DIP cases have their onset in the first 3 months of drug use or within 3 months of a dosage increase. The condition may reverse spontaneously, though this is rare. The condition may also be chronic and progressive. Most importantly, withdrawal of the drug does not lead to immediate improvement of symptoms, typically taking up to 6 months to resolve.

Metoclopramide, an antiemetic drug used primarily for gastrointestinal disorders, has also been implicated in DIP. Though the drug is intended for short-term use (2-8 weeks), many patients are treated long term with this drug. “With chronic use, they develop drug-induced parkinsonism or tardive dyskinesia,” said Dr. Factor.

The prevalence of DIP among psychiatric patients on metoclopramide may be as great as 25%, according to estimates. Women tend to be affected more fre-

quently than men, particularly older women. Among patients with metoclopramide-induced parkinsonism, up to 70% have tremor, 70% have postural instability, and 40% have tardive dyskinesia. Once the drug is stopped, improvement typically takes 4 months.

In addition to neuroleptics and metoclopramide, there have been reports of a number of other drugs associated with DIP. These include SSRIs, dopamine depleters, bupropion, phenelzine, lithium, valproate, some cardiac drugs (amiodarone, captopril, verapamil, diltiazem, amlodipine, manidipine, methyl dopa), and estrogens.

There are a number of risk factors for developing DIP. In particular, women appear to be twice as likely as men to develop the disorder. Older age (older than age 65) is associated with a five times greater risk. Greater drug potency or dose also plays a role. Less frequently described potential risk factors include prior brain injury, dementia, HIV infection, certain psychiatric disorders (mood disorders in particular), the presence of tardive dyskinesia, and a family history of PD.

“Recognition is the key to proper management because if you recognize that the drug causes it, you stop the drug if you can and the symptoms will reverse in most patients.”

In addition, amantadine and anticholinergics are frequently used to treat symptoms. Other potential treatments include levodopa, electroconvulsive therapy, propranolol, and clozapine. ■

## Tolcapone’s Approved Label Changes Mean Less Liver Enzyme Monitoring

BY MICHELE G. SULLIVAN  
Mid-Atlantic Bureau

The Food and Drug Administration has approved new labeling that relaxes the liver enzyme monitoring recommendations for tolcapone, an adjunctive treatment for Parkinson’s disease, according to the drug’s manufacturer.

The new label recommends monitoring serum glutamic-pyruvic transaminase (SGPT/ALT) and serum glutamic-oxaloacetic transaminase (SGOT/AST) at baseline, then every 2-4 weeks for the first 6 months. After that, periodic monitoring is recommended as the prescribing physician deems clinically relevant.

The drug was approved as Tasmar in January 1998 for adjunctive use in patients whose Parkinson’s symptoms are not adequately controlled despite being on adequate doses of levodopa/carbidopa, according to the FDA. By October of that year, FDA had received reports of three cases of fatal fulminant liver failure; the agency said many more cases might have gone unreported. The reports prompted a black box warning on the drug label, citing an increased risk for liver failure of up to 100 times above the background population. The warning recommended

liver enzyme monitoring every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months, and then every 8 weeks thereafter. It also required patients to sign a consent form acknowledging that they understood the increased risk of liver failure associated with the drug.

However, based on a data analysis by Valeant Pharmaceuticals International, which makes the drug, FDA has concluded that the risk of liver failure is probably lower than initially estimated. The

analysis included more than 40,000 patient years of prescription data and laboratory test data from more than 3,400 patients who participated in tolcapone clinical trials.

“Recent data suggest that hepatic dysfunction associated with Tasmar is rare and can be addressed with less restrictive monitoring,” Dr. C.

Warren Olanow, professor and chair of neurology at Mount Sinai School of Medicine, New York, said in a statement on the company’s Web site ([www.valeant.com](http://www.valeant.com)). “The new, less restrictive changes in Tasmar’s labeling mean that doctors can now feel more confident prescribing [the drug] to a broader patient population.”

The new label information should show up soon on the drug’s packaging, said Dan Springer, a spokesman for Valeant. ■

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## Chronic Tics Did Not Worsen In Patients Taking Levodopa

LA JOLLA, CALIF. — Children and adults with chronic tic disorders who were treated with levodopa did not experience a worsening of tics, Dr. Mollie Gordon reported during a poster session at the annual meeting of the American Neuropsychiatric Association.

Treated patients did experience significant improvements in attention and hyperactivity symptoms.

“I think this challenges the way we think about the dopamine pathways in the brain,” Dr. Gordon, of the department of psychiatry at Washington University School of Medicine, St. Louis, said in an interview. “We’ve always thought of Tourette as being in a sense an excess of and when we block the dopamine, these patients do better.” But their tics do not worsen when given exogenous dopamine. In an 8-week pilot study, Dr. Gordon and her associates randomly assigned 12 children and 18 adults with Tourette syndrome or chronic tic disorder to receive 12.5 mg of carbidopa,

50 mg of levodopa, or matched placebo capsules.

The researchers found that tic severity did not increase in patients who took levodopa; instead levodopa improved attention and hyperreactivity symptoms (a 17% improvement vs. no improvement for those on placebo), and the drug was not associated with any significant side effects.

“We know that these patients have a dopamine abnormality in the brain,” Dr. Gordon said. “If it’s not a matter of being too much or too little [dopamine], the question is, how do we figure out what’s wrong? Is it a dopamine dysregulation? Do these drugs affect auto inhibitory receptors? Is there something going on in the brain that has to do with the dopamine dysregulation? If we [have] more information about the pathophysiology of these diseases, then we can figure out the best management.” The study was funded in part by the Tourette Syndrome Association.

—Doug Brunk