

# Strategies for managing drug-induced tardive dyskinesia

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Fifteen years ago, Mr. L, age 40, was given a diagnosis of schizophrenia, which has been treated with haloperidol, 10 mg/d. Approximately 1 year ago, he began experiencing consistent lip smacking, a sign of tardive dyskinesia. Vitamin E was added to the treatment regimen, after which the tardive dyskinesia symptoms resolved.

A few months later, however, those symptoms returned and became worse. In addition to lip smacking, Mr. L now also describes involuntary bilateral twitching and muscle spasms in both legs.

Haloperidol and vitamin E are discontinued and Mr. L is switched to olanzapine, 20 mg/d. Although olanzapine is effective for Mr. L's symptoms of schizophrenia, tardive dyskinesia persists, and he gains 60 pounds and develops diabetes. Olanzapine is discontinued and he begins a trial of risperidone, 4 mg/d.

While on risperidone, blood sugar control, measured by hemoglobin A<sub>1c</sub>, and insulin resistance improve, but Mr. L continues to have symptoms of tardive dyskinesia. Vitamin E is added again, but is ineffective. The treatment team switches Mr. L to clozapine but symptoms of tardive dyskinesia do not improve.

Mr. L is frustrated. His symptoms inhibit activities of daily living, and switching medications does not seem to work. There are no

treatment recommendations for patients such as Mr. L; as a last resort, his physician adds tetrabenazine, a vesicular monoamine transporter type-2 inhibitor that is FDA-approved for chorea associated with Huntington's disease.

After a few weeks of treatment, Mr. L's symptoms subside.

Extrapyramidal side effects are common with first-generation antipsychotics (FGA) such as haloperidol. Types of antipsychotic-induced movement disorders include dystonias, akathisias, pseudoparkinsonism, and tardive dyskinesia. Of these, tardive dyskinesia is the most concerning because it often is difficult to treat and may be irreversible.

## Practice Points

- First-generation antipsychotics (FGAs), which result in greater D2 blockade, are more likely to cause movement disorders than second-generation antipsychotics.
- Tardive dyskinesia occurs in approximately 5% of patients taking an FGA.
- Common signs and symptoms of tardive dyskinesia include lip smacking, tongue protrusions, and puffing the cheeks.
- No medications are FDA-approved for treated tardive dyskinesia, but several are used off-label.
- Tetrabenazine might be useful for patients with difficult-to-treat symptoms; close monitoring for depressive symptoms and suicidality is needed.

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## Disclosures

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Table

## Off-label medications for tardive dyskinesia

Drug	Possible dosage	Common side effects
Tetrabenazine	12.5 mg twice daily titrated to a maximum of 150 mg/d in 2 or 3 divided doses	Somnolence, insomnia, depression, and akathisia
Reserpine	≥0.25 mg 4 times daily, to 8 mg/d	Depression, diarrhea, dizziness, somnolence
Vitamin E	400 units/d to 1,600 units/d	Dosages >3,000 units can cause symptoms of hypervitaminosis, which include nausea, weakness, and intestinal cramps
Melatonin	2 to 10 mg daily for 4 to 6 weeks	Drowsiness
Vitamin B <sub>6</sub>	100 to 400 mg/d for 4 to 8 weeks	Sensory neuropathic syndromes
Donepezil	5 to 10 mg/d for 6 weeks	Nausea, diarrhea, insomnia, fatigue, vomiting

Medications are in order by most recent evidence  
 Source: References 4-6

Tardive dyskinesia involves abnormal, involuntary movements, usually involving the face and, sometimes, the limbs. Common symptoms include lip smacking, tongue protrusions, and puffing the cheeks<sup>1</sup>; severe tardive dyskinesia may affect the larynx and diaphragm, which can be life-threatening. The incidence of tardive dyskinesia is approximately 5% after the first year of FGA treatment and 1% with second-generation antipsychotics (SGAs).<sup>2</sup> The risk increases with higher doses and longer duration of treatment, with a prevalence of 20% to 25% with long-term FGA use.<sup>3</sup>

### Treatment strategies

There are no FDA-approved drugs for tardive dyskinesia (Table).<sup>4-6</sup> The best strategy is to prevent tardive dyskinesia with judicious use of an antipsychotic. If a patient taking a FGA develops tardive dyskinesia, the first-line treatment is to switch to a SGA. Risperidone, olanzapine, quetiapine, and clozapine have a low risk of tardive dyskinesia. Newer agents, such as lurasidone, asenapine, iloperidone, and aripiprazole, might have a lower risk of tardive dyskinesia, possibly because of differences in dopamine blockage between these agents and FGAs. Clozapine is least likely to cause tardive dyskinesia, but it often is used as a last resort because of the risk of agranulocytosis and the need for frequent tests to measure white blood cells.<sup>1,4</sup>

Other treatments include melatonin, donepezil, vitamin B<sub>6</sub>, and vitamin E.<sup>4</sup> These agents can reduce symptoms, but no large clinical trials have proved that they are efficacious. Last-resort treatments include suppressive treatment using FGAs several times a day, because the constant dopamine blockade may stop symptoms for a short time; this approach is not recommended because it can exacerbate symptoms of tardive dyskinesia.<sup>4</sup>

Other suppressive treatments used in severe or refractory cases include reserpine and tetrabenazine, which are used off-label and work by blocking monoamine transporters. This blockage results in a reduction in neurotransmitters such as dopamine, which have been implicated in the development of tardive dyskinesia. Compared with tetrabenazine, reserpine has a higher affinity for cells in the periphery and therefore causes side effects such as hypotension and diarrhea.<sup>7</sup>

**Tetrabenazine** is indicated for chorea associated with Huntington's disease and is used off-label for treating tardive dyskinesia. Tetrabenazine is thought to work by inhibiting human vesicular monoamine transporters. Blocking these transporters prevents monoamines such as dopamine from entering synaptic vesicles.<sup>8</sup> Because of its side-

### Clinical Point

The best strategy is to prevent tardive dyskinesia with judicious use of an antipsychotic

## Clinical Point

Several medications can be used off-label to relieve symptoms of tardive dyskinesia, including vitamin E and tetrabenazine

## Related Resources

- National Organization for Rare Disorders. Tardive dyskinesia. [www.rarediseases.org/rare-disease-information/rare-diseases/byID/493/viewFullReport](http://www.rarediseases.org/rare-disease-information/rare-diseases/byID/493/viewFullReport).
- Caroff SN, Miller DD, Campbell CE. Is there a rational management strategy for tardive dyskinesia? *Current Psychiatry*. 2011;10(10):22-32.

### Drug Brand Names

Aripiprazole • Abilify	Lurasidone • Latuda
Asenapine • Saphris	Olanzapine • Zyprexa
Clozapine • Clozaril	Quetiapine • Seroquel
Donepezil • Aricept	Reserpine • Serpasil
Haloperidol • Haldol	Risperidone • Risperdal
loperidone • Fanapt	Tetrabenazine • Xenazine

effect profile, lack of large clinical trials, and high cost, tetrabenazine is used as a last-line treatment in severe cases of tardive dyskinesia. Adverse effects include somnolence (31%), insomnia (22%), depression (19%), and akathisia (19%). Tetrabenazine carries a black-box warning for depression and suicidality and is contraindicated in patients with untreated or inadequately treated depression or who are suicidal.<sup>8</sup> Assessing the patient's mental state is important when using this medication.

A review by Chen et al<sup>7</sup> found that 9 of 11 studies had positive results for tetrabenazine treatment for tardive dyskinesia. Most of the studies were small and retrospective. The biggest prospective blinded study was a videotaped study by Ondo et al of 20 patients with tardive dyskinesia.<sup>9</sup> At least 30 days before beginning the study patients discontinued the medication that caused their tardive dyskinesia and any treatments for tardive dyskinesia. Each patient was videotaped before starting tetrabenazine and an average of 20.3 weeks after starting the drug. Investigators' scores showed an average of 54.2% improvement in movement scores and participants' subjective scores reported an average of 60.4% improvement. One patient withdrew because of somnolence. The remaining 19 patients did not experience more than mild side effects and continued treatment with tetrabenazine after study completion.<sup>9</sup>

## Treatment recommendations

Tardive dyskinesia is a difficult condition to treat; it is best, therefore, to prevent its onset by using the minimally effective antipsychotic dose, by preferential use of an SGA rather than a FGA, and by regular screening for tardive dyskinesia using a standardized rating scale such as the Abnormal Involuntary Movement Scale. Symptoms associated with tardive dyskinesia are more likely to resolve if caught early. If a patient develops tardive dyskinesia while taking a FGA, switching to a SGA may alleviate the symptoms.

Several medications can be used off-label to relieve symptoms, including vitamin E and tetrabenazine, which both have the most—although not considerable—literature-based support. Although some studies show benefit with tetrabenazine for tardive dyskinesia, larger clinical trials are needed to more strongly support its use. Tetrabenazine might be a good option for patients with refractory tardive dyskinesia but, given the associated risk of suicidality and depressive symptoms, careful monitoring of suicide risk is essential and may preclude its use for tardive dyskinesia in patients who are experiencing depressive symptoms.

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