

The ABCDs of treating tardive dyskinesia

Jonathan R. Scarff, MD

Tardive dyskinesia (TD)—involuntary movement persisting for >1 month—is often caused by exposure to dopamine receptor–blocking agents such as antipsychotics.¹ The pathophysiology of TD is attributed to dopamine receptor hypersensitivity and upregulation of dopamine receptors in response to chronic receptor blockade, although striatal dysfunction, oxidative stress, and gamma-aminobutyric acid (GABA) dysfunction may play a role.¹ Because discontinuing the antipsychotic may not improve the patient’s TD symptoms and may worsen mood or psychosis, clinicians often prescribe adjunctive agents to reduce TD symptoms while continuing the antipsychotic. Clinicians can use the mnemonic **ABCD** to help recall 4 evidence-based treatments for TD.

Amantadine is an *N*-methyl-*D*-aspartate receptor antagonist that is postulated to improve dopaminergic signaling through increased dopamine release and inhibited postsynaptic uptake, although its exact mechanism is unclear. In a double-blind, placebo-controlled, crossover study of 22 patients with TD who were treated with amantadine, the average reduction on the Abnormal Involuntary Movement Scale (AIMS) was approximately 22%.² Adverse effects include gastrointestinal upset, mood changes, and impaired concentration.

Ginkgo **B**iloba contains antioxidant properties that may help reduce TD symptoms by alleviating oxidative stress. In a meta-analysis of 3 randomized controlled trials from China (*N* = 299), ginkgo biloba extract, 240 mg/d, significantly improved symptoms of TD compared with placebo.³ Ginkgo

biloba has an antiplatelet effect and therefore should not be used in patients with an increased bleeding risk.

Clonazepam. Several small studies have examined the use of this GABA agonist for TD. In a study of 19 patients with TD, researchers found a symptom reduction of up to 35% with doses up to 4.5 mg/d.⁴ However, many studies have had small sample sizes or poor methodology. A 2018 Cochrane review recommended using other agents before considering clonazepam for TD because this medication has uncertain efficacy in treating TD, and it can cause sedation and dependence.⁵

Deutetrabenazine and valbenazine, the only FDA-approved treatments for TD, are vesicular monoamine transporter 2 (VMAT2) inhibitors, which inhibit dopamine release and decrease dopamine receptor hypersensitivity.⁶ In a 12-week, randomized, double-blind, placebo-controlled study of 117 patients with moderate-to-severe TD, those who received deutetrabenazine (up to 48 mg/d) had a significant mean reduction in AIMS score (3 points) compared with placebo.⁷ In the 1-year KINECT 3 study,

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Dr. Scarff is a Staff Psychiatrist, Behavioral Health Service Line, Kenner Army Health Clinic, Fort Lee, Virginia.

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124 patients with TD who received valbenazine, 40 or 80 mg/d, had significant mean reductions in AIMS scores of 3.0 and 4.8 points, respectively.⁸ Adverse effects of these medications include somnolence, headache, akathisia, urinary tract infection, worsening mood, and suicidality. Tetrabenazine is another VMAT2 inhibitor that may be effective in doses up to 150 mg/d, but its off-label use is limited by the need for frequent dosing and a risk for suicidality.⁶

Other adjunctive treatments, such as vitamin B6, vitamin E, zonisamide, and levetiracetam, might offer some benefit in TD.⁶ However, further evidence is needed to support including these interventions in treatment guidelines.

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