Tardive dyskinesia (TD) is a potentially disabling adverse effect in patients treated with dopamine receptor-blocking agents. Its prevalence among patients treated with neuroleptics is estimated to be as high as 15% to 20%, and it may coexist with tardive dystonia in up to 0.4% to 4% of patients. It includes a spectrum of symptoms such as involuntary, often rapid, repetitive abnormal movements (choreic movements) that typically affect the mouth and tongue but that sometimes are localized to the limbs or trunks. It can also manifest as sustained muscle contraction leading to abnormal axial posture (ie, dystonia), which often dominates the clinical picture in young patients. These symptoms can interfere with activities of daily living, can be disfiguring, and can also be irreversible. Medical management, consisting of benzodiazepines, anticholinergics, muscle relaxants, dopamine-depleting agents, and botulinum toxin injections, is often insufficient and accompanied by adverse effects.

Tardive dyskinesia may have some mechanisms in common with other abnormal movement disorders, such as dysfunction of the GPi. It is alleged that chronic dopamine receptor blockade with dopamine antagonists leads to hypersensitivity of nigrostriatal postsynaptic dopamine receptors. With typical antipsychotics, which primarily block D2 receptors, this hypersensitivity may develop, especially in D1 receptors as they are repeatedly stimulated by endogenous dopamine. The D1-mediated striatal output is primarily directed at the GPi and substantia nigra pars reticulata; thus, hypersensitivity of D1 receptors may lead to overactivity of the GPi. Another hypothesis indicates that it is caused by a lesion to the GABAergic interneurons, which regulate the balance of direct and indirect pathways via feed forward inhibition. This lesion, which is probably caused by excitotoxicity and oxidative stress, is attributed to free radicals produced with increased dopamine turnover.

It is still not clear whether the beneficial effect of DBS is mediated through stimulation or inhibition of the target nucleus, or possibly through a combination of both. One study reported that DBS increased the output of the GPi. Other studies have suggested that...
there are abnormal patterns of activation of the prefrontal, premotor, and anterior cingulate cortex, and that clinical improvement induced by GPi stimulation is mediated by a reduction of activation in the primary motor and prefrontal cortex and in the cerebellum.11

**CASE**

Ms. G is a 51-year-old, married, white woman who has suffered from schizoaffective disorder for the past 33 years and has had more than 12 inpatient hospitalizations. She was prescribed several antipsychotic medications, mainly haloperidol, which she used intermittently during the past 32 years. The patient developed TD after 8 years of haloperidol use. The initial symptoms of TD were arm dystonia, and then involuntary smacking of lips that progressed to difficulty speaking. She had no family history of dystonia or other causes of secondary dystonia or dyskinesia. Her symptoms were not improved after discontinuation of the haloperidol or after administration of atypical antipsychotics (benzatropine and diphenhydramine). The patient’s symptoms began to worsen and she had difficulty breathing, eating, and walking. Botulinum toxin injections were given but they did not improve her condition. Other comorbidities included type 2 diabetes mellitus, hypertension, and a cerebrovascular accident that occurred 2 years prior with residual general weakness and gait disturbance.

Due to the treatment resistance and the disabling character of the TD, the patient was offered DBS of the GPi at Hackensack Medical Center. Her TD symptoms were assessed before and after the procedure by using the Abnormal Involuntary Movement Score (AIMS). DBS electrodes were implanted without complications to target the GPi bilaterally. The electrode was maintained bilaterally at 2.5 V to 3 V, with 130 Hz frequency and 190-microsecond pulse width.

**At the 6-month follow-up, her AIMS had decreased from 38% (before the procedure) to 17%.**

The patient’s symptoms significantly improved after the procedure. She was able to walk, eat, and speak, and her breathing improved, as well. At the 6-month follow-up, her AIMS had decreased from 38% (before the procedure) to 17%. Her akathisia was decreased by 21% according to the Barnes Akathisia Scale.

**DISCUSSION**

Most reported cases of DBS treatment of the GPi have been for tardive dystonia, due to the success of DBS treatment. The criteria for the diagnosis of tardive dystonia include the presence of chronic dystonia, a history of antipsychotic drug use preceding or concurrent with the onset, exclusion of other causes, and absence of family history.12 Although tardive dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures,13 and TD is characterized by choreoathetoid dyskinesias in the orofacial, limb, and truncal regions, there is still considerable overlap of the two, and the distinction between them is not always clear, especially when there are phasic dystonic movements. The close examination and classification of phenomenology in tardive syndromes is important, because it may influence how patients will respond to GPi-DBS, including timing of onset, and degree and duration of improvement.12

Our patient had an AIMS score reduction of 55%, which is close to the mean of 56% seen in other case reports.13 Among those patients, the onset and duration of improvement varied widely. The majority of cases required up to 6 months to show improvement,14 but others showed almost immediate improvement, sometimes within 30 seconds.15 Follow-up of cases ranged from 5 months to 80 months, and during that time, rebound dyskinesia occurred in only two cases, both of whom developed tolerance to treatment and required an escalation of stimulation.15,16

Surgical complications commonly reported are perioperative infection, premature battery failure, lead migration, defective lead wire, and hardware fracture.17 The complication rate of 66 cases described in 21 reports was 9%,3 which is similar to the complication rates reported in other studies of GPi-DBS.18

The stimulation parameters have been variable among cases. The majority of cases have been stimulated in monopolar mode. The stimulation amplitude ranged
from 1.0 V to 6.5 V, pulse width from 60 microseconds to 450 microseconds, and frequency from 40 Hz to 185 Hz. Voltage amplitude was adjusted for optimal response. There was no correlation between stimulation standards and optimal response.

CONCLUSION

Despite its mechanism of action not being conclusively established, our experience adds to the growing literature that GPi-DBS might be a much-needed option for patients with TD. The literature reviewed confirms the long-term efficacy and safety of the procedure in refractory TD patients. However, more studies with longer follow-ups and more patients are necessary to conclusively establish the role of GPi-DBS in the management of TD.

REFERENCES