Psychopharmacology for the Clinician
Psychopharmacologie pratique

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

Management of conventional antipsychotic-induced tardive dyskinesia

Ms. D. is a 42-year-old woman with a 16-year history of paranoid schizophrenia. After 10 years of treatment with conventional antipsychotic drugs, she developed involuntary movements with tongue chewing, lip puckering, jaw stiffness and finger piano playing while receiving haloperidol 7.5 mg /day. Haloperidol was gradually reduced and replaced by risperidone, which was gradually increased to a maintenance dosage of 6–8 mg/day. The dyskinetic movements resolved over the following 3 months, and the patient remained stable for 4 years. Then, the same dyskinetic movements reappeared. Risperidone was progressively stopped, and olanzapine 20 mg/day was substituted. Olanzapine partially improved the dyskinetic movements but was discontinued 4 months later because of the residual dyskinetic movements. Clozapine was initiated and increased gradually to 400 mg/day, and the dyskinetic movements improved dramatically. Fourteen months later, Ms. D.'s dyskinetic movements remain stable at a minimal level, as measured by the Extrapyramidal Symptom Rating Scale (Chouinard and Margolese, *Schizophr Res* 2005;76: 247-65).

Tardive dyskinesia (TD) is a chronic condition of insidious onset, characterized by involuntary movements that vary in localization and form. The severity of TD may fluctuate over time, improve in spite of continuing antipsychotic exposure and, in rare cases, spontaneously remit in the medium- to long-term. The cumulative risk of developing TD appears to increase the longer treatment continues. However, TD can also occur after short-term exposure to antipsychotic drugs. It is unknown why some patients, but not others, develop TD. Long-term antipsychotic exposure, conventional antipsychotic use and age (> 60 yr) are the most consistently implicated risk factors. The risk and severity of TD associated with conventional antipsychotic use can be reduced through an effective treatment algorithm (Margolese et al, *Can J Psychiatry* 2005;50:703-14).

Conventional antipsychotics may induce TD through prolonged D_2 receptor blockade, postsynaptic dopamine hypersensitivity, damage to gamma-aminobutyric acid (GABA) neurons and damage to cholinergic neurons. Atypical antipsychotics are thought to decrease dopamine receptor sensitivity and may be less likely to cause damage to GABA or cholinergic neurons (Margolese et al, *Can J Psychiatry* 2005;50:541-7).

As outlined in this case, switching from conventional to atypical antipsychotics remains the most efficacious treatment of conventional antipsychotic-induced TD. A major benefit of atypical antipsychotics is their lower propensity to cause TD, compared with conventional antipsychotics, even though TD may occur in patients treated solely with atypical antipsychotics. Determining which atypical antipsychotic (olanzapine, quetiapine, risperidone or ziprasidone) to use is based on the patient's clinical profile and the agent's specific side effect and pharmacological profile. A switch is also based on the characteristics of both the patient and the medication. If the switch fails to improve TD symptoms, another atypical antipsychotic should be considered. Compared with the atypical antipsychotics listed above, clozapine is thought to have a lower risk of TD and has been shown to significantly reduce dyskinetic movements in patients with TD. Clozapine's loose D_2 binding might explain this patient's positive response to this atypical antipsychotic. Clozapine is often a later choice because of its potential risk of agranulocytosis. Switching to clozapine earlier can be beneficial in patients with significant TD who agree to the blood-monitoring regime.

Discontinuing anticholinergic agents may also be a useful therapeutic option. Some literature supports the idea that central cholinergic agents can worsen TD. Thus to minimize anticholinergic exacerbation of TD, anticholinergic agents can be gradually reduced over several months until the minimum dosage required to control the patient's parkinsonism is achieved.

In patients with severe TD, conventional antipsychotics given 4 times daily may suppress or mask TD by permitting a constant level of dopamine blockade that does not allow abnormal dyskinetic movements to emerge at their worst. Used temporarily while switching to an atypical antipsychotic, this "suppressive therapy" may be an option for patients experiencing extreme respiratory alkalosis from diaphragmatic chorea.

The best treatment of TD remains prevention, by treating with atypical antipsychotics first and using conventional antipsychotics only when 1) atypical antipsychotics fail to reduce psychosis, 2) patients prefer conventional antipsychotics, or 3) patients cannot tolerate atypical antipsychotics.

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Psychopharmacology for the Clinician columns are usually based on a case report that illustrates a point of interest in clinical psychopharmacology. They are about 500 words long, and references are not necessary.
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