

In Response To:

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Editorials

Reversibility of Tardive Dyskinesia Syndrome

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Tardive syndromes (TS) constitute a group of abnormal involuntary movements and sensory symptoms caused by exposure to dopamine receptor-blocking agents (DRBAs). The term tardive reflects the classical thought that these symptoms occur after long-term exposure to the DRBA, but it is recognized that TS may appear as early as days after receiving the first few doses of a DRBA.¹

Historically, the main source of TS was the use of first-generation neuroleptics in the treatment of psychosis. Development of the second-generation “atypical” antipsychotics led to the initial expectation of a reduction in frequency of TS, but whether prevalence of TS from the atypical antipsychotics is lower than the classic antipsychotics remains controversial. This false sense of safety may have contributed to an increased number of prescriptions for DRBAs in the past 10 years for off-label use as mood stabilizers, anti-anxiety agents, and treatments for agitation in dementia, as well as the use of prokinetic drugs such as metoclopramide.² TS have not disappeared with the introduction of atypical antipsychotics.

A distinct feature of the syndrome is the persistence of the abnormal movements despite discontinuation of the offending drugs, unlike most of the other drug-induced side effects, which reverse upon discontinuation of the drug. Available long-term studies of the natural course of TS provide a wide range of remission rates (0–73%), but most report remission rates below 25%.^{1,3–8} The main limitation of most of these studies has been that patients continued treatment with DRBAs

because of their underlying psychiatric disease, or as a symptomatic treatment for their TS. In this context, an accurate analysis of evolution of TS is difficult. The continued use of DRBAs can suppress involuntary movements and mask the diagnosis. Fernandez et al.⁸ showed a high correlation between an unexpectedly high remission rate of TS (62%) and an increase in parkinsonism in a group of patients who are using DRBAs in the long term. This suggests that TS may have been suppressed by DRBAs that produced parkinsonism. Similarly, Kane et al.⁹ showed re-emergence of dyskinesia in 34% of patients after withdrawal of neuroleptic treatment.

In the recent article by Zutshi et al.¹², the authors report a retrospective analysis of 106 patients with TS in which DRBAs were discontinued. The majority of these patients (94%) were treated for non-psychotic disorders, and the DRBAs used were mostly gastrointestinal drugs (41.7%) and atypical antipsychotics (36.1%). Patients were followed for approximately 3 years. Unexpectedly, even after discontinuation of the causing agents, the rate of spontaneous remission was only 2%, and the overall remission using specific treatments was 13%. Unfortunately, probably due to the low remission rates, the study did not identify any significant predictor of remission in the patients, their diagnoses, or in the DRBA used. This paper is one of very few reporting remission rates of TS after complete withdrawal of DRBAs, and probably the only study in which the majority of subjects took these medications for non-psychotic disorders.

As the authors acknowledge, limitations of this study are the retrospective nature, the selection bias inherent in a Movement Disorders Center with a tendency to see the most refractory patients, and a substantial proportion (13%) of the patients lost to follow-up (arguably those with milder dyskinesias). These factors may have led to an underestimation of the remission rate of TS. Nonetheless, the remission rate reported by the authors is strikingly similar to low rates noted by previous studies from decades ago, before the introduction of atypical antipsychotic drugs.^{1,4,7}

The pathophysiology of TS is not completely understood and there have been various proposed mechanisms, including upregulation and sensitization of post-synaptic D2 receptors in striatal neurons, increased glutamatergic excitotoxicity, oxidative stress, dopamine terminal loss, and maladaptive plasticity.^{10,11} Notably, it is not known how the changes in synaptic transmission produced by a receptor antagonist can lead to such persistent changes underlying TS.

On a more positive note, the authors report a general tendency for improvement of TS in most of the patients. Nonetheless, their finding stresses the need for further larger prospective studies in patients in whom DRBAs can be withdrawn and for a better understanding of the pathophysiology of TS, which defies our knowledge of the pharmacological effects of neurotransmitter receptor blockers. Importantly, the authors' study and previous studies demonstrating low remission rates of TS call for a judicious clinical practice that emphasizes prevention as the best treatment modality at this point.

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