

Psychopharmacology for the Clinician

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. The patient described in this column is a composite with characteristics of several real patients.

Off-label antipsychotic use and tardive dyskinesia in at-risk populations: new drugs with old side effects

A 67-year old man with diagnosed generalized anxiety disorder has used different anxiolytics and antidepressants over the years, with limited response. This, in combination with increasing anxiety, led to an antipsychotic trial. Concerns about movement disorders with conventional antipsychotics and metabolic side effects with atypical agents led to a trial of ziprasidone, titrated up to 120 mg/d with good effect. In the second year of treatment, he experienced perioral movements, which were initially attributed to ongoing dental work but persisted after the work was completed. Physical disorders (e.g., Wilson disease) were ruled out and tardive dyskinesia (TD) diagnosed. Movements involved jaw/tongue protrusion and lip pursing/smacking that was continuous during waking hours and worsened by stress and fatigue.

Ziprasidone was discontinued and trihexyphenidyl (6 mg/d) initiated, without effect. Clonazepam was then tried in doses up to 2 mg/d, with minimal benefit and sedation. He switched to lorazepam (2 mg/d) and started nonprescription agents, including ginkgo biloba (240 mg/d) and vitamin E (800 IU/d), both demonstrating equivocal benefit.

It was decided to try tetrabenazine (87.5 mg/d). Improvement was mild and countered by side effects, including apathy and sedation. The dose was decreased to 37.5 mg/d over a period of months, at which point botulinum toxin injections were recommended, in part owing to the nature of the movements (i.e., localized, perioral). Within 10 days the movements were 80% im-

proved. The current plan entails reassessing the movements after tetrabenazine is tapered and discontinued, with a re-evaluation of future botulinum toxin treatments in 3 months.

This case highlights off-label use of antipsychotics; TD risk; individual risk factors, especially age; and current TD treatments and limitations.

There has been an alarming increase in off-label antipsychotic use across all age groups,¹⁻⁵ perhaps reflecting their increased tolerability and more benign reputation. In addition, the field is sanctioning broader use of these medications, with efforts to expand approved indications.^{6,7} Metabolic side effects have come to define these drugs,⁸ but other concerns remain. While preliminary data indicate decreased risk of TD with the atypical antipsychotics,⁹⁻¹¹ all currently available antipsychotics carry a risk. Clinicians may believe the often lower doses in off-label use diminish risk, but the role of dose in TD is open to debate and, in this particular case, countered by evidence of increased risk in those with nonpsychotic diagnoses and subpopulations, such as older patients. Age is the most robust TD risk factor (3–5 times greater than in younger populations). Others include duration of antipsychotic exposure, extrapyramidal symptoms (EPS), use of antiparkinsonian medications, central nervous system dysfunction, substance abuse, race, sex and genetics.¹¹⁻¹⁵ There are data linking TD to specific symptom domains (e.g., deficit, cognitive) and to schizophrenia itself.¹⁶⁻¹⁹ Studies have examined TD risk with newer agents, but data are limited.²⁰

Treatment of tardive movements has itself been hampered by our limited understanding of underlying mechanisms. Tetrabenazine, a vesicu-

lar monoamine transporter inhibitor,²¹ is the only drug approved in Canada for the treatment of hyperkinetic movement disorders. A recent review by an American Academy of Neurology Guideline Development Subcommittee identified 4 treatments with favourable results based on randomized controlled trials: clonazepam, ginkgo biloba, amantadine and tetrabenazine. Many treatments have insufficient evidence (e.g., vitamin E, botulinum toxin type A, baclofen).²² Antiparkinsonian medications and EPS have been identified as risk factors for TD, arguing against the use of trihexyphenidyl. Vitamin E was also tried, with early trials involving doses as high as 1600 IU/d, but recent controversy on health risks and high-dose vitamin E must be considered.²³ Current evidence indicates that TD is neither inevitably progressive nor irreversible²⁴ and that tardive movements are no longer seen as a single entity.²⁵

Increased off-label antipsychotic use now embraces children and elderly patients, 2 populations particularly sensitive to side effects. That some of these side effects, like TD, are both serious and potentially irreversible must be part of our clinical decision-making.

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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 650 words long. Columns can include a bibliography which will be available only on the journal website.

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