Tardive Dyskinesia Circa 2006

The history of tardive dyskinesia holds many instructive lessons regarding long-term adverse drug effects. First described in the late 1950s shortly after the introduction of antipsychotics, it took many years before its prevalence, incidence, and long-term course were well investigated. At first there was resistance and skepticism from many quarters as to the risk of this condition and its apparent association with long-term exposure to antipsychotic medications.

The introduction of antipsychotics had been such a dramatic advance in the management of psychotic disorders, particularly schizophrenia, that it was perhaps difficult to fully acknowledge and accept a major drawback. Some might argue that it was not until the threat of litigation became more and more a reality that clinical practice included adequate consideration of and monitoring for tardive dyskinesia. To complicate matters, it also became apparent that some abnormal involuntary movements are associated with untreated schizophrenia, although the risk is substantially increased by long-term exposure to dopamine receptor antagonists (1).

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It has been over 2 years since a report on tardive dyskinesia appeared in the *Journal,* and in fact, the last article was a review by my colleagues and me (2) of the available evidence on the relative risk of tardive dyskinesia associated with the newer second-generation ("atypical") antipsychotics in contrast to the older (conventional) medications. In that report we concluded that despite a broad range of methodologic issues in the available studies, the risk of tardive dyskinesia is substantially lower (although not absent) with the newer medications. Therefore, it is not surprising that tardive dyskinesia has been somewhat less of a focus among clinicians and investigators.

The results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (3) have led to a renewed interest in tardive dyskinesia. One of the major advantages of the newer antipsychotics was assumed to be the lower risk of neurologic side effects, i.e., extrapyramidal symptoms and tardive dyskinesia. The CATIE study was intended to compare the efficacy and tolerability of atypical and typical antipsychotics in the treatment of schizophrenia. The trial was intended to be "pragmatic," that is, a hybrid of efficacy and effectiveness trial designs. A total of 1,460 patients who were judged to meet DSM-IV criteria and who were not in their first episode or "treatment resistant" were eligible for the trial. One important factor in the design was that patients with tardive dyskinesia at baseline (231 subjects) were not eligible to be randomly assigned to the conventional, or "typical," medication (perphenazine) included in the trial.

There were no significant differences between perphenazine and the atypical medications in terms of the incidence of extrapyramidal side effects, akathisia, or movement disorders as reflected by rating scale data. There was a higher incidence of apparent abnormal involuntary movements across the treatment groups (13%–17%) than of extrapyramidal symptoms (4%–8%) or akathisia (5%–9%). (Patients with tardive dyskinesia at baseline were not included in these rates of abnormal involuntary movements.) It is im-

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portant to recognize, however, that following a cohort of patients who began taking antipsychotic medication a mean of over 14 years earlier is not necessarily an adequate test of potential differences between medications in the risk for precipitating or exacerbating abnormal involuntary movements. Furthermore, the CATIE subject population, many of whom had been treated with neuroleptic drugs for a number of years, may not be particularly sensitive to the development of tardive dyskinesia. Data from a long-term prospective study by my colleagues and me suggest that the risk of new cases of tardive dyskinesia can diminish considerably after 15 years of treatment (Kane et al., unpublished data, May 2006). In addition, the median duration of continuing with the initial medication in the CATIE trial was approximately 6 months. Hence, it is difficult to make any definitive estimates of tardive dyskinesia risk associated with particular medications.

Because the CATIE trial did not find consistent advantages in effectiveness for the newer medications, the results have led to renewed debate about the potential clinical role of conventional medications. The high incidence of weight gain and metabolic syndrome associated with some of the second-generation antipsychotics also prompts reconsideration of the risks of first-generation drugs. The current preponderance of prescriptions of second-generation antipsychotics means that a new generation of clinicians has been trained without the extensive exposure to tardive dyskinesia that older clinicians and patients experienced.

The literature has fairly consistently estimated the risk of tardive dyskinesia with conventional antipsychotics as 3%–5% per year of exposure (at least for the first 5 years) (4). In addition, the risk in elderly subjects has been reported to be as high as 25% within the first year of exposure to conventional antipsychotics (5). Although there are numerous methodologic problems in many of the studies comparing the risk of tardive dyskinesia with second-generation and first-generation antipsychotics (2), the weight of the evidence supports a lower risk with newer medications. There are insufficient data from drug-naive, first-episode schizophrenia patients randomly assigned to first- or second-generation medications to provide meaningful comparisons of tardive dyskinesia risk; however, those studies comparing extrapyramidal side effects (even with low-dose conventional antipsychotics) support a lower (but by no means absent) risk of extrapyramidal side effects with the newer agents. Although a meta-analysis (6) suggested that low-dose, low-potency conventional antipsychotics have no greater risk of extrapyramidal symptoms than second-generation medications, the efficacy comparison in the same analysis indicated that the second-generation drugs were significantly more efficacious in controlling symptoms.

The study reported by Tenback and colleagues in this issue of the *Journal* determined the incidence of new cases of tardive dyskinesia in a 1-year prospective study of over 9,000 patients with schizophrenia. The naturalistic effectiveness study, sponsored in Europe by Eli Lilly and Company, recruited one-half of its subjects from patients taking olanzapine and one-half from patients taking other neuroleptics. Nine percent of the patients had tardive dyskinesia at baseline, and an additional 3% developed tardive dyskinesia during the year. The study tested the clinical observation that the presence of other extrapyramidal symptoms predicts the later development of tardive dyskinesia. Predictors of tardive dyskinesia would be useful in identifying among younger patients a group that is at high risk for tardive dyskinesia. The results are mixed. While the presence of other extrapyramidal symptoms doubled the likelihood that a patient would develop tardive dyskinesia within the year, the results were not specific enough to identify a high-risk group definitively. The authors appropriately conclude that the prevention of tardive dyskinesia requires strategies to reduce risk in the entire population of patients exposed to antipsychotic drugs, not only those who have extrapyramidal symptoms.

Based on available information, there are several points that should be emphasized. Although the balance of the data suggest a substantial reduction in the risk of tardive dyskinesia with the second-generation medications, there remain unanswered ques-

tions about the differences in relative risk, the role of dose, and comparisons with a variety of different conventional agents. At the same time, the risk of tardive dyskinesia continues to exist and it is important that clinicians maintain appropriate awareness and vigilance for emerging cases regardless of what medication(s) the patient is receiving. In addition, the use of long-term antipsychotic treatment should be well justified with appropriate consideration of alternative treatments. Lowering the dose, discontinuing the implicated agent, or switching to another agent with potentially lower risk should be considered when early signs of abnormal involuntary movements occur. Another important point is that undoubtedly there are individual patient characteristics that contribute to vulnerability, and it is hoped that further progress in pharmacogenetics might ultimately help in reducing existing risk even further (7).

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