The Treatment of Tardive Dyskinesia and Tardive Dystonia

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The enthusiasm produced by the introduction of antipsychotic medication in the 1950s gave way to a certain frustration in the 1970s and 1980s. Despite the development of a large number of new drugs, little progress was made in treatment because these new agents were, in essence, therapeutically equivalent. This lack of progress was perhaps also related to an emphasis on tardive dyskinesia in the 1970s, i.e., the preoccupation with a negative effect of treatment. The reverse is taking place today. Clozapine and the other atypical antipsychotics are associated in people's minds with fewer or absent extrapyramidal symptoms and less tardive dyskinesia than the older typical agents. As a result, a certain amount of complacency exists. Tardive dyskinesia not only may be painful and disfiguring, but it also predicts poor outcome in patients with schizophrenia. Although many treatments have been tried, none have proven completely efficacious. The best treatment for tardive dyskinesia and dystonia is prevention, which is a function of medication choice. Pharmacologic interventions for tardive dyskinesia include clozapine and the other atypical antipsychotics. If typical antipsychotics must be used, they should be started at the lowest possible levels. Studies of risperidone suggest that it, too, should be used at very low doses to minimize the risk of tardive dyskinesia. It is also possible that schizophrenic patients taking atypical antipsychotics may experience fewer spontaneous dyskinesias, although further study is warranted.

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Tardive dyskinesia has existed since before the advent of the typical neuroleptics—before the term *tardive dyskinesia* was introduced—and its elimination by the use of atypical antipsychotic therapy seems unlikely, no matter the extent to which the novel antipsychotics reduce the rates of tardive dyskinesia in patients with schizophrenia and other disorders. In addition, the many patients who currently live with tardive dyskinesia will always need treatment and care. Nevertheless, the atypical antipsychotics represent a great leap forward in the treatment of this frustrating side effect.

In this article, the focus will be on tardive dyskinesia and tardive dystonia. These are often lumped together, which is unfortunate since they differ in significant ways, most importantly in treatment. They also differ in age at onset and the length of exposure to neuroleptic drugs. Many patients have pure dystonias that may begin with blepharospasm and be confused with Meige syndrome if no other symptoms exist. Other cases of tardive dystonia begin when retrocollis involvement develops, which may perhaps later be complicated by ballistic-like movements of the arms that could easily be mistaken for Huntington's chorea. These movements may be painful, and make it impossible to stand or to sit still in a chair and patients may develop techniques for dealing with them—passing a ball from hand to hand, for example, or manipulating a pen or other piece of material—that may often reduce or eliminate these movements. Yadalam et al.[1] reported the case of a 25-year-old man for whom walking forward was a near impossibility except when he tossed a ball from hand to hand while walking.

Tardive dystonia can arise months or years after the beginning of neuroleptic therapy and is an enduring disorder that seldom remits despite numerous approaches to treatment. Indeed, most cases of tardive dyskinesia that occur within a year of the start of medication therapy are, in this writer's experience, tardive dystonias. Burke et al.,[2] in a case series of 42 patients, found that tardive dystonia persisted for years in most of their patients. Kiriakakis et al.[3] conducted a long-term follow-up study of 107 patients with tardive dystonia. They found that patients with neuroleptic exposure of 10 years or fewer had a chance of remission 5 times greater than those with more than 10 years of neuroleptic exposure. Thus, the long-term use of neuroleptics may render the pathogenic changes in tardive dystonia irreversible.

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Table 1. Akathisia and Tardive Dyskinesia as Predictors of Response[a]

Condition	Responders (N)	Nonresponders (N)	Total (N)
Akathisia	5	17	22[b]
Without akathisia	21	8	29[b]
Tardive dyskinesia	5	12	17[c]
Without tardive dyskinesia	22	13	35[c]

[a]Data from Levinson et al.[10] Response = 40% improvement in positive symptoms.
[b]$\chi^2 = 12.36$, $p < .001$.
[c]$\chi^2 = 5.13$, $p < .05$.

Table 2. Relation of Neuroleptic Dose to Dyskinesia Score[a]

Modified Simpson Dyskinesia Scale	Low Dose (N = 25) Mean	Low Dose (N = 25) SD	Standard Dose (N = 26) Mean	Standard Dose (N = 26) SD	p Value
Baseline score	0.64	1.07	0.31	0.88	NS[b]
Endpoint score	0.52	1.00	1.04	2.42	.026[c]

[a]Data from Kane et al.[11] Low dose = 1.25–5.0 mg/2 wk fluphenazine decanoate; standard dose = 12.5–50 mg/2 wk fluphenazine decanoate.
[b]By t test.
[c]By analysis of covariance; endpoint score by treatment with baseline score, as covariate p value is 1-tailed.

Risperidone has been implicated in the occurrence of tardive dystonia. Simpson and Jaffe[4] reported a case of dystonia that developed in a patient taking risperidone and remitted when the patient was switched to olanzapine. In addition, Fdhil et al.[5] and Krebs and Olie[6] have reported cases of dystonia seemingly induced by risperidone.

TREATMENT OF TARDIVE DYSTONIA

Tardive dystonia and tardive dyskinesia are treated differently. A variety of treatments have been proposed for tardive dystonia, a fact suggesting that none is very effective. For example, benzodiazepines or other muscle relaxants may be used with mild benefits. Other common treatments are tetrabenazine/reserpine, trihexyphenidyl, and surgery.

Tetrabenazine/Reserpine

The pharmacologic intervention that appears most effective for tardive dystonia is tetrabenazine, which Fahn and others[2,7] have reported. Tetrabenazine is an experimental drug and not readily available, but it is pharmacologically similar to reserpine. Alternatively, reserpine in doses of 1 to 5 mg/day may be beneficial for some patients.[1] How long to continue reserpine therapy is unclear, but after a few months of significant diminution in movements, the medication can be slowly withdrawn and, if there is a recurrence of symptoms, reintroduced.

Trihexyphenidyl

Trihexyphenidyl has also been used successfully to treat patients with tardive dystonia, but the medication should be given in high dosages, perhaps to the limits of tolerance. Doses of 40 mg/day and higher have been used; the medication should be gradually withdrawn after the dystonic movements have subsided.[1]

Surgery

Before the advent of clozapine, surgery was also recommended for severe cases and could be beneficial. Yadalam et al.[1] reported the case of a 31-year-old man whose incapacitating dystonias remained in complete remission 1 year after a bilateral thalamotomy.

Atypical Antipsychotics

For some time now, clozapine has been recommended for the treatment of dystonias.[8] Modest doses—200 mg/day or less, for example—may suffice. The effectiveness of other atypical antipsychotics in treating dystonias has yet to be established, but Chong et al.[9] reported the case of a 47-year-old Chinese schizophrenic patient whose tardive dystonic and dyskinetic movements remitted completely after 7 months when risperidone, 1 mg/day, was added to trihexyphenidyl, 6 mg/day, and diazepam, 12 mg/day. The role of other atypical antipsychotics in treating dystonias has not been established fully.

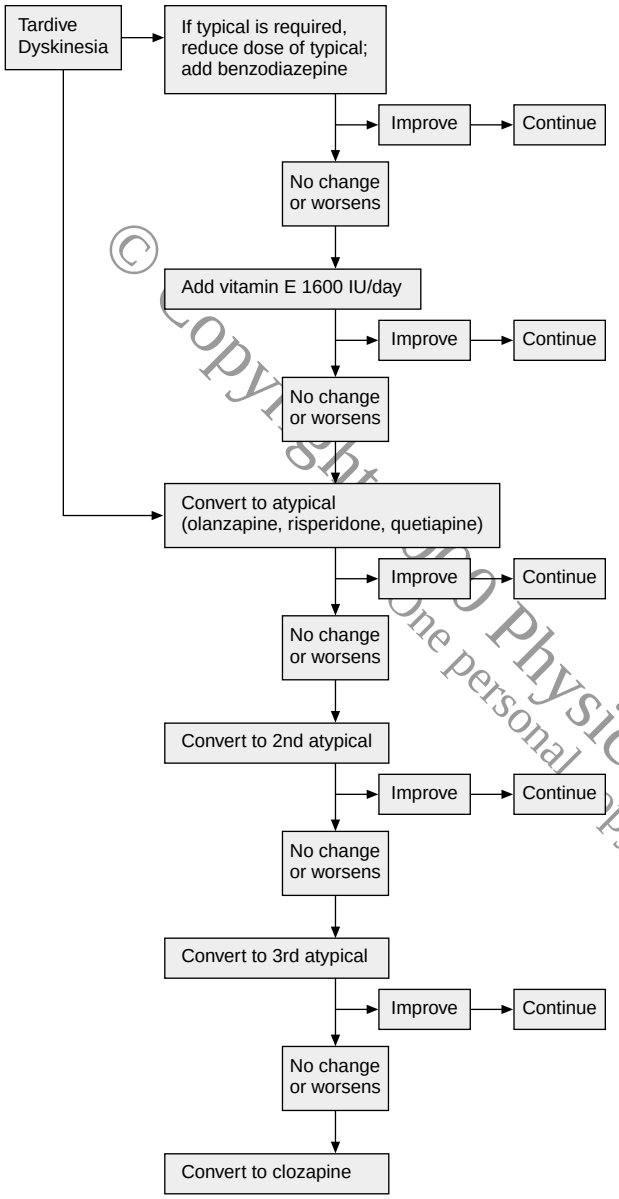
TREATMENT OF TARDIVE DYSKINESIA

Tardive dyskinesia, by far the most common tardive condition, remains a problem for many psychiatric patients, with effects beyond its troubling esthetic ramifications. A fluphenazine study by Levinson et al.[10] demonstrated that side effects—akathisia and tardive dyskinesia in that study—can affect outcome (Table 1). Doses of 10, 20, or 30 mg/day of oral fluphenazine were administered to a group of patients who met Research Diagnostic Criteria for schizophrenic, schizoaffective, or other nonaffective psychoses. Both akathisia and tardive dyskinesia predicted poor outcome. Kane et al.[11] have also demonstrated that tardive dyskinesia is related to medication dose. In a group of patients treated with low versus standard doses of fluphenazine decanoate for 1 year, scores on the Simpson Dyskinesia Scale decreased in the low-dose group and increased in the standard-dose group (Table 2).

Typical Antipsychotics

The first step in treating tardive dyskinesia is to assess whether a typical or atypical antipsychotic is indicated. While atypical antipsychotics are becoming first-line treatment for psychosis, typical antipsychotics continue to be used in patients who have responded well and for those who fail to respond to atypical agents. If a typical neuroleptic must be used in the treatment of schizophrenia, it is important to use the lowest possible dose. Even with long-acting drugs, clinicians tend to use a higher dose than is necessary.[11] The typical neuroleptic might be augmented

Figure 1. An Algorithm for the Treatment of Tardive Dyskinesia[a]



[a]Each treatment period should continue for at least 2 months.

with a benzodiazepine as a muscle relaxant and also for its GABAergic effects, which might influence outcome.

Vitamin E. The efficacy of some other potentially useful agents in the treatment of tardive dyskinesia has yet to be reliably established. For example, vitamin E has had positive effects on tardive dyskinesia in some controlled studies,[12,13] but a large, multicenter Veterans Administration study could not replicate those positive results.[14] Nonetheless, sufficient data and anecdotal reports suggest that drug treatment of tardive dyskinesia should be augmented with vitamin E, up to 1600 IU/day, if tardive dyskinesia in a patient taking a typical neuroleptic augmented with a benzodiazepine fails to respond or worsens.

Atypical Antipsychotics

Failure to respond adequately to any of the agents previously discussed should lead to conversion to olanzapine, risperidone, or quetiapine (Figure 1). The definition of atypicality stems from clozapine's beneficial effects on positive and negative symptoms as well as on tardive dyskinesia and from its failure to produce parkinsonism or even akathisia. The data showing a relationship between parkinsonism and the future development of tardive dyskinesia[15] added to this definition of atypicality, since other atypical drugs produced little or no parkinsonism and in general appeared to have beneficial effects on the symptoms of schizophrenia without producing EPS. Data from the other atypical antipsychotics are only beginning to be presented, and adequate prospective studies remain to be carried out. All of the newer atypical antipsychotics should be tried before clozapine, which, because of the risk of agranulocytosis, requires frequent blood monitoring.

Risperidone. Brecher et al.[16] found only 1 treatment-emergent case of tardive dyskinesia in a 1-year, open-label study of 330 institutionalized patients with dementia who received a mean modal dose of risperidone equaling 0.96 mg/day. The 1-year survival rate of patients free of persistent tardive dyskinesia was 97.4%. In contrast, Jeste et al.[17] reported a 1-year incidence of tardive dyskinesia of 26% in an elderly population treated with conventional neuroleptics. The Brecher et al. data indicate a much lower figure for patients treated with risperidone. Patients who did have symptoms of tardive dyskinesia at baseline had significant reductions in Extrapyramidal Symptom Rating Scale dyskinetic movements, hyperkinesia, buccolinguomasticatory factor, choreoathetoid movements, and clinical global impression of dyskinesia scores. This study suggests that there is a very low incidence of tardive dyskinesia in patients receiving low dosages of risperidone. However, many clinicians are prescribing risperidone at 8 mg/day or higher, and it would not be surprising if tardive dyskinesia developed in their patients. There is little evidence to support such high doses.

A study conducted by Jeste et al.,[18] part of a long-term study of outpatients over the age of 45 (mean age = 66 years) receiving neuroleptics or risperidone, seems to confirm the finding that rates of tardive dyskinesia are low in patients taking low doses of risperidone. In this prospective longitudinal study, patients were matched for age, diagnosis, and length of neuroleptic exposure with a group of haloperidol-treated patients. The diagnosis of tardive dyskinesia was based on specific research criteria, and the raters were blind to the patients' medication despite the open-label design. The median dose of each medication was 1.0 mg/day. The Abnormal Involuntary Movement

Scale (AIMS), modified Simpson-Angus scale for extrapyramidal symptoms, Brief Psychiatric Rating Scale, and Mini-Mental State Examination were administered at baseline, 1 month, and 3, 6, and 9 months. The patients treated with haloperidol were significantly ($p < .05$, Peto-Prentice) more likely to develop tardive dyskinesia than the patients who were treated with risperidone. Moreover, it appeared that the small amount of tardive dyskinesia produced by risperidone (around 5%) peaked at 3 months and remained constant, while the level of tardive dyskinesia produced by haloperidol rose to approximately 30% at the end of the 9 months.

Olanzapine. Beasley et al.[19,20] and Tollefson et al.[21] participated in American and international trials of olanzapine. One trial,[20] the acute phase of the North American double-blind olanzapine trial, compared 3 ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) with a fixed dose of olanzapine (1.0 mg/day) and a dose range of haloperidol (15 ± 5 mg/day) in 431 schizophrenic patients. Patients who responded to the acute treatment phase were continued for up to an additional 32 months. Another trial,[19] the acute 6-week phase of the international double-blind olanzapine trial, compared 3 dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) with a dose range of haloperidol (15 ± 5 mg/day) and placebo in 335 schizophrenic patients. The third trial,[21] which also examined the first 6 weeks of the international trial, compared olanzapine, 5 mg/day, with haloperidol, 5 mg/day, in 1996 patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. Patients who responded to acute treatment continued double-blind treatment for up to an additional 19 months.

Tollefson et al.[22] analyzed long-term data from these 3 trials in order to compare the incidence of tardive dyskinesia in patients taking olanzapine (N = 707) with that in patients taking haloperidol (N = 197). Olanzapine-treated patients took doses of up to 20 mg/day and had 237 median days of exposure. Haloperidol-treated patients took up to 20 mg/day, with 203 median days of exposure. Olanzapine-treated patients had statistically significantly lower incidence rates of newly emergent tardive dyskinesia at any visit after baseline ($p < .001$), at the final visit ($p < .001$), and at 2 last clinical assessments ($p < .003$).

Beasley et al.[23] assessed 1714 patients with schizophrenia from these 3 trials in order to compare the incidence of tardive dyskinesia during long-term treatment of patients with olanzapine (N = 1192) or haloperidol (N = 522). Tardive dyskinesia was defined as reaching Research Diagnostic Criteria for Tardive Dyskinesia (RD-TD) during 2 consecutive assessments made using AIMS and RD-TD. Estimations of the risk of tardive dyskinesia, the relative risk, the incidence rate, and the incidence rate ratio were made. The relative risk of tardive dyskinesia for the overall follow-up period for haloperidol versus olanzapine was 2.66. The 1-year risk of tardive dyskinesia, based on data following the first 6 weeks of observation, was 0.52% in patients treated with olanzapine (N = 514) and 7.45% in patients treated with haloperidol (N = 114), a significantly lower risk of tardive dyskinesia in the olanzapine-treated patients than with the haloperidol-treated patients.

Table 3. Olanzapine vs. Haloperidol: Incidence of Tardive Dyskinesia (TD)[a]

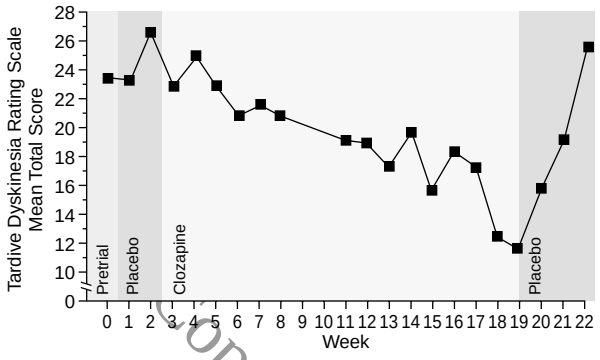
Therapy	Patients (N)	TD Cases (N)	Haloperidol-Olanzapine Incidence Rate Ratio (95% CI)	p Value
AIMS = 0			5.67 (2.45 to 13.10)	
Olanzapine	813	9		
Haloperidol	367	14		< .001
AIMS > 0			2.55 (1.15 to 5.68)	
Olanzapine	379	15		
Haloperidol	155	10		.018

[a]Data from Beasley et al.[23] Abbreviation: AIMS = Abnormal Involuntary Movement Scale.

Beasley et al.[23] also looked at this group in terms of AIMS scores. Of the 813 patients on olanzapine therapy who had an AIMS score of 0 at baseline, 9 (1.1%) patients developed tardive dyskinesia. In 367 patients taking haloperidol, 14 (3.8%) developed tardive dyskinesia. In the group of patients that had AIMS scores greater than 0 at baseline, the results were essentially similar, and olanzapine produced significantly less tardive dyskinesia than did haloperidol (Table 3). In a study[24] of patients from 3 controlled clinical trials, 129 patients with presumptive tardive dyskinesia were rated weekly for the first 6 weeks and then every 2 to 8 weeks for up to 30 weeks, depending on the study. Presumptive tardive dyskinesia was defined as a severity rating of moderate or worse in at least 1 of 7 body regions evaluated with AIMS at 2 consecutive drug-free baseline visits. Mean AIMS total scores were ascertained at each visit. The baseline (week 0) mean AIMS total score was 10.55. By week 1, the mean AIMS total score had decreased significantly ($p < .05$). Mean AIMS scores had reduced 55% at week 6 and 71% at week 30. These dramatic reductions may well be associated with all atypical antipsychotics, but need to be confirmed in prospective studies.

Quetiapine. Quetiapine is the newest atypical antipsychotic to be approved by the U.S. Food and Drug Administration, and at present there are few data concerning it. In particular, we lack data concerning the incidence of tardive dyskinesia in patients treated with quetiapine. Ghelber and Belmaker[25] reported the case of a 44-year-old woman with schizophrenia and chronic active psychosis who was resistant to conventional antipsychotic therapy. On a regimen of quetiapine for 6 months, she recovered from her psychotic features and negative symptoms. When quetiapine, 300 mg/day, resulted in a strong sedative effect, the dose was reduced to 150 mg/day. Tardive dyskinesia developed, and the treatment was stopped. Ghelber and Belmaker em-

Figure 2. Tardive Dyskinesia During Clozapine Treatment and After Abrupt Withdrawal[a]



[a]From Simpson et al.,[26] with permission.

phasized that the tardive dyskinesia might have been due to the late effects of previous classical neuroleptic treatment. To date, there have been no reported cases of dystonia, parkinsonian symptoms, or akathisia associated with the use of quetiapine, which appears to have a benign side effect profile.

Clozapine. If 3 atypical antipsychotics have been tried and the patient has failed to improve or has worsened, clozapine should be introduced. Should it become necessary to discontinue clozapine therapy, the agent should be tapered gradually to prevent rebound dyskinesia. Simpson et al.[26] conducted an 18-week study of clozapine in the treatment of tardive dyskinesia. This study revealed that clozapine had a pronounced beneficial effect on tardive dyskinesia, but abrupt clozapine withdrawal resulted in nausea, vomiting, delirium, and a substantial rebound in tardive dyskinesia (Figure 2). In addition, 2 patients developed neutropenia, 1 developed convulsions, 3 developed marked withdrawal effects, and 1 developed hypotensive collapse with atrial fibrillation. Ahmed et al.[27] reported a case series of 4 patients who developed severe limb-axial and neck dystonias 5 to 14 days after clozapine withdrawal. All 4 patients experienced significant improvements in their mental state and movement disorders—2 after returning to clozapine, 1 after starting low-dose risperidone therapy, and 1 after starting olanzapine therapy. My colleagues and I have seen dyskinesias that were more severe after the abrupt withdrawal of clozapine than they were at baseline. If such a rapid withdrawal is required, the addition of benztropine may help to prevent some of the cholinergic rebound symptoms. De Leon et al.[28] reported withdrawal dyskinesia in 2 patients, a woman and a man, receiving high doses of clozapine (900 mg/day reduced to 450 mg/day in the former case, and gradually increasing doses up to 350 mg/day in the latter). The woman was treated with trihexyphenidyl, 12 mg/day (reduced to 10 mg/day after 1 week), augmented with lorazepam, 1 or 2 mg/day, after clozapine withdrawal. Twelve days after clozapine therapy had been discontinued, the patient began taking loxapine plus trihexyphenidyl, 10 mg/day, without cholinergic rebound. The male patient complained of gastrointestinal distress after having missed clozapine for 2 days. He was given 2 mg/day q.i.d. of trihexyphenidyl for 3 days—his gastrointestinal symptoms remitted after 1 dose—after which the dose was reduced and discontinued after 1 week.

CONCLUSION

Tardive dystonia can be mistaken for tardive dyskinesia. No single medication therapy is clearly effective for tardive dystonia, but a number of therapies have proven helpful in some instances. These include tetrabenazine, trihexyphenidyl, and clozapine.

The best treatment for tardive dyskinesia is prevention. If clinicians use atypical antipsychotics as first-line medications, tardive dyskinesia is likely to be reduced in both old and young patients. Patients who have tardive dyskinesia and are taking typical neuroleptics are candidates to be transferred to an atypical antipsychotic. Dosages should be low, whether typical or atypical antipsychotics are used, because any of these drugs can probably cause tardive dyskinesia—which might be indistinguishable from spontaneous dyskinesias—in some patients. If the early studies are confirmed, though, patients receiving atypical antipsychotic therapy may also experience fewer spontaneous dyskinesias than those receiving typical neuroleptic therapy. There are likely to be fewer cases of tardive dyskinesia with any of the atypical antipsychotics, which should be used both to prevent and to treat tardive dyskinesia.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), diazepam (Valium and others), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), olanzapine (Zyprexa), quetiapine (Seroquel), reserpine (Serpasil and others), risperidone (Risperdal), trihexyphenidyl (Artane and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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