

Tardive Dyskinesia in the Era of Typical and Atypical Antipsychotics. Part 2: Incidence and Management Strategies in Patients With Schizophrenia

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Objective: Tardive dyskinesia (TD), the principal adverse effect of long-term conventional antipsychotic treatment, can be debilitating and, in many cases, persistent. We sought to explore the incidence and management of TD in the era of atypical antipsychotics because it remains an important iatrogenic adverse effect.

Methods: We conducted a review of TD incidence and management literature from January 1, 1965, to January 31, 2004, using the terms tardive dyskinesia, management, therapy, neuroleptics, antipsychotics, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Additional articles were obtained by searching the bibliographies of relevant references. We considered articles that contributed to the current understanding of both the incidence of TD with atypical antipsychotics and management strategies for TD.

Results: The incidence of TD is significantly lower with atypical, compared with typical, antipsychotics, but cases of *de novo* TD have been identified. Evidence suggests that atypical antipsychotic therapy ameliorates long-standing TD. This paper outlines management strategies for TD in patients with schizophrenia.

Conclusion: The literature supports the recommendation that atypical antipsychotics should be the first antipsychotics used in patients who have experienced TD as a result of treatment with conventional antipsychotic agents. The other management strategies discussed may prove useful in certain patients.

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Clinical Implications

- TD incidence is significantly lower with atypical, compared with typical, antipsychotics.
- Atypical antipsychotics can ameliorate long-standing TD in some patients and should be the first antipsychotics used in patients who have experienced TD as a result of treatment with conventional antipsychotic agents.
- Novel management strategies including tetrabenazine, donepezil, melatonin, branched chain amino acids, and vitamin E or vitamin B₆ may prove useful in certain patients, but further study is needed.

Limitations

- TD is not always reported, so its true incidence with atypical antipsychotics may be higher.
- Other than atypical antipsychotics, none of the novel management strategies have been proven under ideal experimental conditions.

Key Words: antipsychotics, extrapyramidal symptoms, psychosis, schizophrenia, tardive dyskinesia

Atypical Antipsychotics and TD

Risperidone

Randomized, double-blind clinical trials have established the efficacy and safety of risperidone in patients with schizophrenia and in those with dementia (1–5). In most trials, risperidone produced significantly fewer movement disorders than did conventional antipsychotics, and among patients taking optimal dosages of risperidone, the proportion of patients who required antiparkinsonian medication was not significantly different from that of patients taking placebo (6,7). Moreover, long-term risperidone treatment (that is, up to 57 weeks) has been associated with a reduction or with no change in severity of preexisting movement disorders (8). One study in particular used stringent criteria for measuring TD and found a cumulative rate of approximately 2.6% after 1 year of treatment (2).

With the exception of clozapine, risperidone has the longest history among the atypical antipsychotics. In most case reports that have documented TD in patients given risperidone, the patients were predisposed to the disorder. For example, they had previous treatment with conventional antipsychotics or there was a potential pharmacokinetic explanation (for example, risperidone was administered concomitantly with fluoxetine or paroxetine) (9–12) (see Table 1, 2–24).

While the primary outcome measure for numerous large clinical studies of risperidone in various patient populations was usually efficacy, a low incidence of newly emergent TD was reported, even among such susceptible patients as those with bipolar disorder, schizophrenia, or schizoaffective disorder, as well as elderly and adolescent patients (7,25–27). In an analysis of seven 1-year clinical trials of risperidone, 2 cases of TD were reported, representing an annual incidence of less than 0.2% among the total group of 1156 patients and an incidence of 0.4% among the 503 patients exposed to risperidone for more than 1 year (6). These rates are substantially lower than the annual incidence of 3% to 5% observed among patients treated with conventional antipsychotics (28,29).

Abbreviations used in this article

5-HT	serotonin
ADRS	Abbreviated Dyskinesia Rating Scale
AIMS	Abnormal Involuntary Movement Scale
EPS	extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
CGI	Clinical Global Impression
SD	standard deviation
TD	tardive dyskinesia

Although the elderly have an increased risk for TD associated with conventional antipsychotic treatment, low rates of movement disorders and TD have been reported in several trials of risperidone in elderly patients with psychosis or dementia (1,2,29–34). Davidson and colleagues studied 180 elderly, chronically ill patients with psychosis who received risperidone at a mean dosage of 3.7 mg daily for up to 1 year (31). Persistent emergent TD was defined as an increase of 3 points or greater from baseline on a single item of the ESRS (35) or as an increase of 2 points on 2 or more items at 2 or more consecutive visits. Of the 139 patients without dyskinetic symptoms at baseline, 6 patients were rated as having persistent emergent TD (an annual rate of 4.5%). The severity of dyskinetic symptoms was significantly reduced in the 40 patients with dyskinesia at baseline.

Olanzapine

The efficacy of olanzapine for the treatment of symptoms and signs of schizophrenia disorders has been demonstrated in several randomized controlled trials in adults (13,14,36,37). Like risperidone, olanzapine is associated with fewer movement disorders than are conventional antipsychotics.

In the published case reports that involved patients with olanzapine-associated TD (Table 2), one patient experienced TD after only 4 months of olanzapine therapy and had no previous conventional antipsychotic use (38–41).

Tollefson and others analyzed results of 3 long-term studies of patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder who received olanzapine or haloperidol for up to 2.6 years (13). In these studies, patients without a history of TD or TD at baseline were exposed to olanzapine ($n = 707$) for a mean period of 237 days and to haloperidol ($n = 197$) for a mean period of 203 days. The mean endpoint dosage of olanzapine was 14.4 mg daily and for haloperidol was 14.7 mg daily. TD was defined as a score of 3 or greater on 1 of the first 7 categorical items on the AIMS or a score of 2 or greater on any 2 items not present at baseline. The incidence of new-onset TD at any assessment after baseline was 7.1% in the olanzapine group and 16.2% in the haloperidol group ($P < 0.001$); at the final AIMS assessment, the incidence of TD was 2.3% and 7.6%, respectively ($P = 0.001$). At the final 2 AIMS assessments, the incidence of TD was 1.0% and 4.6%, respectively ($P = 0.003$).

In a further extension of this analysis, the 1-year risk of TD among all patients was 2.6% in the olanzapine group and 8.0% in the haloperidol group ($P < 0.001$); among patients with an AIMS score of 0 at baseline, the 1-year risk was 1.1% and 7.1%, respectively ($P < 0.001$) (14). However, a significant flaw with these studies is the relatively high incidence of TD with haloperidol, which was more than 2 times higher than expected for haloperidol (3%) (28). Had a lower incidence

Table 1 TD associated with risperidone: case reports and series				
Study	Number of patients	Risperidone dosage (mg daily)	Duration of risperidone treatment	Previous conventional antipsychotic therapy
Spivak and Smart (18)	1	1.0	2 months	Yes (loxapine for 1 week)
Brown (10)	1	2.0	2 days	No (but fluoxetine–methylphenidate)
Feeney and Klyklo (11)	1	0.5 to 1.0	3 months	No (but fluoxetine–methylphenidate)
Saran (12)	1	1.0	7–9 months	No (but with fluoxetine)
Sherr and Thacker (19)	2	6.0	18 months	Yes
Snoddgrass and Labbate (20)	1	3.0	1 month	Yes
Hong and others (21)	1	1.5	5 months	No
Carroll and others (22)	1	6.0	Not reported	Not reported
Campbell (23)	4	1.5,3.0,5.0,6.0	≈ 7 to 12 months	Yes
Haberfellner (24)	1	4.0	4 months	Yes (pimozide “a few days”)
Silver and others (116)	1	4.0	2 months	Yes
Addington and others (117)	1	10.0	≈ 4 to 5 months	Yes
Woerner and others (118)	1	6.0 to 12.0	12 months	Yes
Gwinn and Caviness (119)	1	6.0	10 months	Yes
Buzan (120)	1	6.0	1 week	Yes
Silberbauer (121)	1	6.0	≈ 12 months	Yes
Daniel and others (122)	1	2.0 to 3.0	3 months	Yes
Lykouras and others (123)	2	4.5 to 6.0	3.0 and 8.5 months, respectively	Yes
Friedman (124)	1	4.0	19 months	No (but with paroxetine)
Fischer and others (125)	2	2.0	5 to 6 months	No (patients with Alzheimer's disease)
Ipekci and Birsoz (126)	1	6.0	9 months	Yes (short-term use years earlier)
Mullen (127)	1	8.0	9 months	No
Bassitt and Louza Neto (72)	1	6.0	3 years	No (but with biperiden)

≈ = approximately

rate for haloperidol been found, the differences in TD rates would likely have been much smaller. Comparison of TD rates between studies is generally difficult, because different rating scales are often used and criteria for the definition of TD often differ among studies (42).

Quetiapine

Double-blind, controlled clinical trials suggest that quetiapine is effective and well tolerated in the treatment of the acute phase of schizophrenia in adults (15,16,43,44). Data regarding the drug's long-term impact on TD are limited. Two

studies using the AIMS or ESRS report 1-year rates of 2.7% and 0.74%, respectively (15,16). In a double-blind, placebo-controlled, 6-week trial, the prevalence of movement disorders associated with quetiapine was not significantly different from that associated with placebo (44). However, incidence cannot be properly assessed with a 6-week study. TD associated with quetiapine use is documented (45–47); however, in one case, the drug might have unmasked TD in a schizophrenia patient who had a history of conventional antipsychotic use (45). In the other case, a patient with bipolar disorder who received quetiapine along with lithium and

Table 2 TD associated with olanzapine, quetiapine, and ziprasidone

Study	Number of patients	Medication	dosage (mg daily)	Duration of treatment (months)	Previous antipsychotic therapy
Herran and Vazquez-Barquero (38)	2	Olanzapine	10, 20	2,10	Yes
Ananth and Kenan (39)	1	Olanzapine	20	57	Yes
Snoddgrass and Labbate (20)	1	Olanzapine	5	1	Yes (first had TD with risperidone, see Table 4)
Benazzi (40)	1	Olanzapine	5	2	Yes
Bella and Piccoli (41)	1	Olanzapine	10	18	No
Ghelber and Belmaker (45)	1	Quetiapine	150 to 300	6	Yes
Ghaemi and Ko (46)	1	Quetiapine	125	3	Yes (only risperidone and olanzapine)
Rosenquist (50)	1	Ziprasidone	100	4	Yes (risperidone and olanzapine)
Keck (51)	1	Ziprasidone	100	2.25	Yes (haloperidol 6 days; quetiapine 12 months)

gabapentin developed TD and had only previous short-term exposure to olanzapine (1 month) and risperidone (1 week) (46) (Table 2).

Ziprasidone

As with quetiapine, data regarding the long-term impact of ziprasidone on TD are limited, but short-term, double-blind clinical trials demonstrating the drug's efficacy and safety in the treatment of schizophrenia have found no difference in the incidence of movement disorders, including TD, among patients given ziprasidone and those given placebo (48,49). Thus, as with quetiapine, no conclusion can be drawn. A few cases of ziprasidone-associated TD have recently been reported (50,51) (Table 2).

Clozapine

Clozapine reduces the severity and frequency of schizophrenia symptoms and exhibits a favourable movement disorder and TD profile; however, agranulocytosis risk and required blood monitoring prevents clozapine from being used as first-line therapy for schizophrenia (52). TD associated with clozapine has been reported (Table 3) (53–58); however, in all cases, conventional antipsychotics were previously administered to these patients. As Kane and others noted, a definite association between TD and a given antipsychotic would be established by evidence of new-onset TD in either patients without a history of the disorder who had been receiving conventional antipsychotics or in those who had received only

atypical antipsychotics (55). Such evidence has not yet been demonstrated with clozapine. Further, beneficial effects on TD management have been reported (see TD Management).

TD Management

The risk and severity of TD associated with conventional antipsychotic use can be reduced through a methodical approach that begins with a switch to an atypical antipsychotic other than clozapine. Other management considerations include, as necessary and in order, 1) discontinuation of anticholinergic therapy, 2) a switch to clozapine, 3) initiation of suppressive therapy with a conventional antipsychotic agent or with tetrabenazine, and 4) addition of one of the more experimental treatments, including donepezil, melatonin, branched chain amino acids, vitamin E or vitamin B₆, and drug reduction (see Figure 1). However, the more experimental treatments cannot be recommended at this time without more data (except possibly donepezil).

Switching From Conventional to Atypical Antipsychotics

Patients in whom TD develops after undergoing conventional antipsychotic therapy should be given an atypical antipsychotic and switched from the typical to the atypical gradually or abruptly, depending on both the patient and the medication characteristics (59–62). An atypical antipsychotic agent is usually selected on the basis of a patient's clinical profile and in consideration of the agent's efficacy data and specific adverse-effect profile.

Table 3 TD associated with clozapine: case reports and series

Study	Number of patients	Clozapine dosage (mg daily)	Duration of clozapine treatment	Previous conventional antipsychotic therapy
de Leon and others (53)	1	150	2 weeks	Yes
Doepf and Buddeberg (58)	1	450	23 days	Yes (exacerbation of preexisting TD)
Davé (54)	2	600 and 700, respectively	20 and 11 months, respectively	Yes, in both patients (mild TD at baseline in patient 2)
Kane and others (55)	2/28	Not reported	9 years (both patients)	Yes (both with questionable TD at baseline; TD rated mild)
Miller (56)	1	875	10.5 years	Yes
Kumet and Freeman (57)	1	250	5 months	Yes

The positive effects of risperidone and olanzapine on TD symptoms have been reported in clinical trials (1,2,13,14, 33,63) and in case studies (Table 4). Chouinard reported an antidyskinetic effect of risperidone in the multicentre Canadian trial (63).

In a 12-month study, quetiapine ($n = 22$) was found to be significantly superior to haloperidol ($n = 23$) in reducing TD at 6, 9, and 12 months, as measured by the CGI dyskinesia subscale and at 6 and 9 but not at 12 months, as measured by the ESRS dyskinesia subscale, despite high rates of failure to complete the trial in both groups ($n = 10$ quetiapine; $n = 8$ haloperidol) (64). In a report by Farah, quetiapine reduced the severity of TD symptoms in 2 patients (Table 4) (65). However, more data are needed on quetiapine to reach a definite conclusion.

Because blood monitoring is necessary during clozapine therapy, other atypical agents, including quetiapine or low dosages of either risperidone, olanzapine, or ziprasidone, are usually chosen first. Compared with conventional antipsychotics, these agents have a relatively low affinity for the D_2 dopamine receptor and a high affinity for the 5-HT receptor, thus producing the high 5-HT₂ D_2 ratio that is thought to underlie the superior side effect profile of atypicals (66).

Discontinuation of Anticholinergic Agents

Central anticholinergic medications can exacerbate or unmask TD, but this effect may be reversible if the anticholinergic is discontinued (31). Some studies have demonstrated a positive association between the severity of TD and administration of anticholinergic drugs (67); this link may reflect an association between TD and the acute movement disorders for which the anticholinergic was prescribed (31). Other studies have not found such an association (28,68,69).

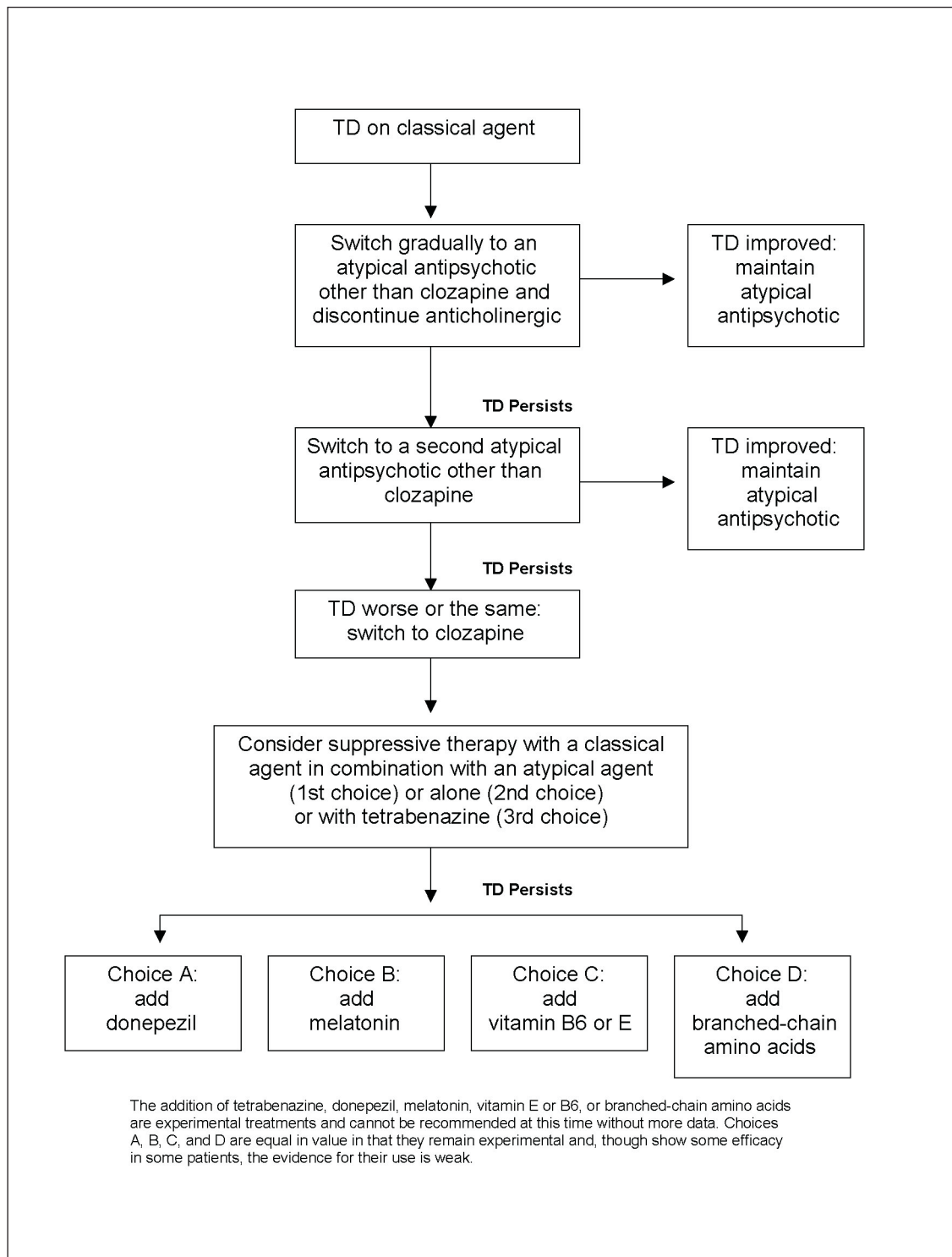
Overall, it appears that central anticholinergics have a reversible unmasking effect. When tardive dystonia and (or) late-onset, persistent Parkinsonism coexists with TD, anticholinergics can be gradually reduced over periods of months until there is improvement of tardive dystonia and (or) Parkinsonism. The focus should remain the discontinuation of the offending drug.

Switching to Clozapine

Long-term clozapine therapy improves motor symptoms in patients with TD, which suggests that patients may benefit from a switch to clozapine. This effect was demonstrated by investigators who reported on 32 schizophrenia patients with moderate or severe TD who received a mean (SD) dosage of 293.8 mg (SD 171.9) daily of clozapine ($n = 19$) or 28.5 mg (SD 23.8) daily of haloperidol ($n = 13$) (70). Over the course of the study, patients who received haloperidol did not experience an improvement in TD scores, but the patients who received clozapine showed significant improvement, starting at 4 months of treatment ($P = 0.0014$), as measured by the Maryland Psychiatric Research Center Involuntary Motor Scale (70).

Numerous other studies have demonstrated the potential beneficial effects of clozapine on TD (71–91). The strongest evidence lies in prospective reports, including randomized, double-blind, placebo-controlled, studies (74,86,87). In a combined retrospective-prospective study, schizophrenia patients on long-term clozapine monotherapy ($n = 100$) were retrospectively matched with patients who received perphenazine, flupenthixol, or zuclopenthixol and were prospectively evaluated for movement disorders (86). Patients who received clozapine had significantly less severe TD than did the matched patients receiving other antipsychotics ($P < 0.05$), as measured by the St Hans Rating Scale for EPS,

Figure 1 Algorithm for the management of TD



which contains 8 items for dyskinesia. This improvement was principally related to the lower number of new cases and amelioration of existing TD within the clozapine group (86).

A double-blind, controlled 6-week study (1 week washout and 5 weeks of active treatment) compared clozapine,

chlorpromazine, and placebo in 31 hospitalized schizophrenia patients with acute psychosis (87). Patients who received clozapine did not develop new-onset movement disorders, including TD, and 2 patients with long-standing (> 12 months) TD showed considerable improvement (87). In a second double-blind study, 23 treatment-refractory

Table 4 TD treated with risperidone, olanzapine, or quetiapine: case reports and series

Study	Number of patients	Medication	dosage (mg daily)	Time to response	
				Initial	Maximum
Chen and others (128)	5 to 9 responded	Risperidone	6.7 (mean)	Unknown	At dosage 6.0 mg daily
Kopala and Honer (129)	1	Risperidone	4	"gradual"	3 months
Chong and others (130)	1	Risperidone	1	"gradual"	12 months
Kooptiwot and Settachan (131)	1	Risperidone	2	Unknown	9 months
Soutullo and others (132)	2	Olanzapine	15.0 and 20.0, respectively	1 month (both patients)	9 and 7 months, respectively
Lykouras and others (133)	1	Olanzapine	17.5	1.75 months	6 months
Littrell and others (134)	4	Olanzapine	20.0	Unknown	6 months (all 4)
Almeida (135)	1	Olanzapine	10.0	1.25 months	1.25 months
O'Brien and Barber (136)	1	Olanzapine	5.0	0.75 month	6 months
Durst (137)	1	Olanzapine	10.0	0.75 month	12 months
Khan and Farver (138)	1	Olanzapine	2.5	3 days	22 days
Ipekci and Birsoz (126)	1	Olanzapine	10.0	0.5 month	Unknown
Agarwal and Kumar (139)	2	Olanzapine	5.0 and 10.0, respectively	0.5; 1 month	1.5; 2.0 months
Farah (65)	2	Quetiapine	100.0 and 75.0, respectively	4 days, 2 weeks	2 weeks for both; maintained 6 to 8 months

schizophrenia patients randomly received dosages of 100 mg, 300 mg, or 600 mg clozapine in a crossover fashion for 4 months at each dosage (85). When the ADRS was used to assess patients with TD at baseline, those who received 600 mg clozapine experienced significant improvement over baseline ($P < 0.03$) (85). This dose dependency may translate to other atypical antipsychotics as well.

Factor and Friedman's review of clozapine TD treatment studies concluded that, although the drug does clearly ameliorate TD, there is a variability of clinical responses (92). This variability may be related to methodological differences between the studies, since not all the studies used the same drug dosages or duration of treatment, nor did they all include proper control groups. In addition, the variability could be linked to the heterogeneity of TD itself. The researchers suggest that patients with tardive dystonia may be more likely to respond to clozapine than patients with TD (92). Of all the antipsychotics, clozapine has the most evidence to support the various proposed mechanisms of TD amelioration (for example, suppression and [or] direct effect on pathophysiology).

Treatment With Donepezil, Melatonin, Vitamins E or B₆, Branched-Chain Amino Acids, and Clonazepam

The agents reviewed here have been recently evaluated but have not yet been established as treatments for TD. Large-scale clinical trials are necessary before these agents can be recommended.

Donepezil. Miller and Chouinard proposed that TD is caused by the damage or destruction of striatal cholinergic neurons (93). On the basis of this hypothesis, donepezil, a cholinesterase inhibitor, would inhibit any remaining acetylcholine hydrolysis. In a study by Caroff and colleagues, 10 patients with schizophrenia or schizoaffective disorder and TD, as defined by DSM-IV criteria, received open-label donepezil (5 to 10 mg daily) for 6 weeks (94). By the end of the treatment period, total AIMS scores in the group decreased significantly ($P = 0.0009$), with 9 of 10 patients demonstrating a positive response. The mean AIMS scores were 12 (SD 5) at baseline and 6 (SD 6) by week 6 (94). The study suggests that a 6-week trial of 5 or 10 mg daily is sufficient to determine whether donepezil is of benefit for TD. Further studies will be needed to confirm these results.

Melatonin. Melatonin, a potent antioxidant, was recently evaluated in a double-blind, placebo-controlled, crossover study of 22 patients with schizophrenia and TD (95). Although patients in the melatonin group demonstrated a greater reduction in AIMS scores (mean 2.45, SD 1.9 vs mean 0.77, SD 1.11 among patients in the placebo group; $P < 0.001$) after 6 weeks of treatment, the results might have been skewed by the 2 patients who demonstrated an extreme response (one with a decrease of 8 points, the other of 6 points). Four other patients demonstrated a reduction of 4 points on the total AIMS score; one showed a reduction of 3 points, and the remaining patients showed a reduction of 2 points or fewer. Seven of 22 patients responded to treatment with 10 mg daily of controlled-release melatonin over 6 weeks (95). No final conclusion can be drawn from this study unless results can be replicated.

Vitamin E. The use of the antioxidant vitamin E for the treatment of TD was first tried more than a decade ago, in 1987 (96). The conclusions reached by a Cochrane review most accurately reflect the potential role of vitamin E in the treatment of TD (97). One of the larger studies included in the Cochrane review was the Veterans Affairs Cooperative Placebo-Controlled Study, which found that, in 158 subjects with TD on antipsychotics, vitamin E was tolerated as well as placebo but had no efficacy in treatment (98). Although vitamin E is safe and well tolerated, it has not been found efficacious in most clinical trials and thus cannot be recommended (97,98).

Vitamin B₆. Because of its antioxidant properties, vitamin B₆ has been suggested as a treatment for TD. The results of one double-blind, placebo-controlled, crossover study of 15 patients with schizophrenia and schizoaffective disorder also suggest that the agent may have a beneficial effect (99). After a 4-week treatment period, patients who received 400 mg vitamin B₆ daily had a greater reduction on the TD subscale of the ESRS than did those who received placebo (mean 68.6%, SD 14.4% vs mean 32.8%, SD 57.0%, respectively). Further studies are necessary to assess the effects of vitamin B₆ on TD.

Branched-Chain Amino Acids. On the basis of the possibility that high-protein meals can temporarily reduce TD, a placebo-controlled study of branched-chain amino acids (222 mg per kg 3 times daily) was conducted in 36 patients with a long history of antipsychotic use and long-standing TD symptoms (100). Significant and marked differences were observed for the treatment group, compared with the group who received placebo, in the number of responders who had 30% ($P < 0.005$) and 60% ($P < 0.02$) reduction in TD movements after only 3 weeks of treatment. The study suggests that a 3-week trial of 222 mg per kg 3 times daily, or 15 g 3 times daily for a 70-kg person (available as a

nutritional supplement from Scientific Hospital Supplies International under the trade name Tarvil™) is sufficient to determine whether branched-chain amino acids are of benefit for TD. Further study would be needed before this treatment can be recommended.

Clonazepam. Clonazepam has been used for treatment of TD, as illustrated in case reports (101–103). Its effects on TD were studied in a double-blind, controlled study, and clonazepam was found to be better ($P < 0.10$) than lithium in a crossover design (104). However, there are no large-scale controlled clinical trials to support its efficacy.

Suppressive Therapy

In patients with severe TD, conventional antipsychotic medication 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 (105,106). There may be a relation between suppression and the mechanism of action of atypicals in ameliorating TD. Because there is a threshold for this masking effect, suppressive therapy is best reserved for patients in whom TD is life-altering or life-threatening and in patients for whom TD is unlikely to remit following withdrawal of antipsychotic (for example, in those with long-standing symptoms). Used temporarily while switching to an atypical agent, suppressive therapy may be an option for patients experiencing extreme respiratory alkalosis from diaphragmatic chorea or severe and painful dystonic opisthotonic posturing. Also, patients with oral dyskinesia or severe motor impairment may require suppressive therapy. Given the possibility of improving TD with atypical antipsychotics and given that long-term use of conventional antipsychotics can exacerbate TD, suppressive therapy with conventional antipsychotics should be considered only as a last resort.

Tetrabenazine, a monoamine depletor and dopamine receptor blocker, has been investigated for suppressive therapy in TD. A study of 20 patients videotaped before and after tetrabenazine treatment (mean dosage 57.9 mg daily) demonstrated that, when movements were rated by the AIMS scale by raters blinded to pre- or posttreatment status, treatment significantly reduced scores (107). Tetrabenazine was well tolerated, and all patients continued on tetrabenazine therapy after the study was concluded. The study suggests that between 25 mg and 150 mg daily, starting at 12.5 mg twice daily and titrating to a maximum of 50 mg twice daily, depending on patient response, over a period of 20 weeks, is sufficient to determine whether tetrabenazine is of benefit for TD. Beneficial effects, as with classical antipsychotics, are not usually long-lasting, and abnormal movements will return upon discontinuation of tetrabenazine. Further, both depression and anxiety are common side effects of tetrabenazine (108,109).

Discontinuation of Conventional Antipsychotic Treatment

Although discontinuing conventional antipsychotic treatment can resolve TD symptoms in some patients over the long term (110–112), more than 50% of schizophrenia patients experience a psychotic relapse within 12 months (112). Moreover, the withdrawal of antipsychotic therapy can trigger an immediate worsening of TD symptoms (82), which may not be tolerated by all patients (112). In addition, a medication-free period (that is, a drug holiday) can increase the risk of both psychotic relapse and TD (113) and may be associated with higher risk of persistent TD (114). Therefore, drug discontinuation needs to be carefully considered. Discontinuation of conventional antipsychotic therapy with substitution by an atypical antipsychotic is recommended.

Conclusions

Atypical antipsychotics provide effective treatment of psychosis and are associated with lower rates of EPS and TD than conventional agents, and they ameliorate preexisting TD. The mechanism for this is unknown. The literature reviewed shows multiple cases and studies of this beneficial effect, as well as low rates of TD found with atypical antipsychotic use. Treatment with risperidone, olanzapine, quetiapine, or clozapine has proved beneficial, and other general strategies for the management of TD can be employed exceptionally. Suppressing therapy with classical antipsychotics (preferably to tetrabenazine) may be necessary on a temporary basis in severe and persistent TD. Other new treatment strategies (such as melatonin, branched-chain amino acids, and vitamin B₆), with the possible exception of donepezil, cannot be recommended at this time. The best approach for TD, however, remains prevention, by limiting exposure to conventional antipsychotics and treating psychosis with atypical agents as monotherapy.

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Résumé : La dyskinésie tardive à l'âge des antipsychotiques typiques et atypiques, 2^e partie : incidence et stratégies de prise en charge des patients souffrant de schizophrénie

Objectif : La dyskinésie tardive (DT), principal effet indésirable d'un traitement antipsychotique classique de longue durée, peut être débilante et dans bien des cas, persistante. Nous avons cherché à explorer l'incidence et la prise en charge de la DT à l'âge des antipsychotiques atypiques, parce qu'elle demeure un important effet iatrogène indésirable.

Méthodes : Nous avons mené une revue de la documentation sur l'incidence et la prise en charge de la DT, du 1^{er} janvier 1965 au 31 janvier 2004, à l'aide des mots dyskinésie tardive, prise en charge, thérapie, neuroleptiques, antipsychotiques, clozapine, olanzapine, rispéridone, quétiapine, ziprasidone et aripiprazole. Les articles additionnels ont été obtenus en recherchant les bibliographies d'articles pertinents. Nous avons retenu les articles qui contribuaient à la compréhension actuelle tant de l'incidence de la DT avec les antipsychotiques atypiques que des stratégies de prise en charge de la DT.

Résultats : L'incidence de la DT est significativement plus faible avec les antipsychotiques atypiques qu'avec les antipsychotiques typiques, mais des cas de DT *de novo* ont été repérés. Les données probantes suggèrent que le traitement aux antipsychotiques atypiques améliore la DT de longue durée. Cet article présente les stratégies de prise en charge de la DT chez les patients souffrant de schizophrénie.

Conclusion : La documentation soutient la recommandation selon laquelle les antipsychotiques atypiques devraient être utilisés en premier chez les patients qui ont souffert de DT par suite d'un traitement aux agents antipsychotiques classiques. D'autres stratégies de prise en charge présentées peuvent se révéler utiles chez certains patients.