Treatment of Tardive Dyskinesia

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Abstract

Although the new generation of atypical antipsychotic agents could some day eliminate concerns about tardive dyskinesia (TD), this disorder remains a significant clinical problem for both patients and physicians. Fortunately, many, if not most, cases of TD are mild. For patients with mild to moderate TD, therapeutic efforts are primarily directed at minimizing neuroleptic exposure or, when possible, changing to atypical agents. Most cases of TD do not seem to progress, suggesting that the risk of remaining on typical neuroleptics is probably small. Patients with moderate to severe forms of TD present greater challenges. These patients frequently require medication to suppress their dyskinesias. A variety of suppressive agents have been tried with limited success. No treatment strategy has emerged that is clearly superior or even successful in most patients. Increasing doses of typical neuroleptics may be useful for short-term suppression; however, the long-term efficacy and risk of this strategy have not been studied carefully. Data on atypical neuroleptics are scant. Clozapine's short-term suppressive effects seem, at best, weak, but patients may improve with long-term treatment. Medications with relatively few side effects that may have suppressive efficacy for some patients include calcium channel blockers, adrenergic antagonists, and vitamin E. Gamma-amino-butyric acid agonists and dopamine depleters are frequently used, but have troubling side effects of their own. A variety of other medications have been employed, but are not well studied. For patients with tardive dystonia, anticholinergic agents or botulinum toxin has been particularly effective. Efforts to understand the neurobiology of TD may shed light on this persistent clinical conundrum.


History

Five years after the introduction of chlorpromazine (Delay and Deniker 1952), Schonecker (1957) described what were probably the first reported cases of TD: After 2 to 8 weeks of exposure to chlorpromazine, three elderly women developed lip-smacking dyskinetic movements. TD was first described in the American literature in 1960 (Kruse 1960). Several years later, Hunter et al. (1964) described dyskinesias in 13 female inpatients with chronic psychiatric illness, all of whom had been treated with phenothiazines. The notion that TD was uncommon persisted until studies in the late 1960s began to reveal relatively high prevalence rates. General acceptance of the association of TD with long-term neuroleptic treatment came in the early 1970s. The first therapeutic trials for TD followed shortly thereafter (Kazamatsuri et al. 1972a, 1972b; Jeste and Wyatt 1982a). In the 1970s, reports of TD in children and of severe disabling TD in adults...
(Keegan and Rajput 1973; Tarsy et al. 1977; Casey and Rabins 1978) began to appear (Tarsy 1983).

Although epidemiological studies indicate neuroleptic exposure as the most significant etiological factor in the development of TD, some authors have continued to question this relationship (Owens et al. 1982; Waddington 1986). For example, in a study comparing chronic schizophrenia inpatients treated with neuroleptics with a neuroleptic-naive group, Owens et al. (1982) did not find a significant difference between prevalence rates of spontaneous dyskinesia (53.2%) and TD (67%). When the data were reanalyzed adjusting for a difference in the age of the two groups, a slightly higher prevalence in the neuroleptic-treated patients was found (Owens 1985). More recently, Fenton et al. (1994) found that the prevalence of spontaneous orofacial dyskinesias was 15 percent among patients with schizophrenia who had never been on neuroleptics. This study highlights the difficulty of distinguishing spontaneous dyskinesias from TD in any given patient. Despite the presence of spontaneous dyskinesias in patients with schizophrenia, epidemiological studies (Kane 1984) strongly suggest that neuroleptics produce dyskinesias in patients with a wide variety of psychiatric diagnoses.

Estimates of the prevalence of TD have ranged from 0.5 to 62 percent (Kane 1984; Yassa and Jeste 1992). Several factors may complicate these estimates and explain differences among studies. These factors include variability of diagnostic criteria, assessment methods, and the duration of neuroleptic exposure; differences in patient age and gender; and the possibility of coexisting medical and neurological illnesses. Studies reported in the 1980s have estimated the average prevalence to be about 30 percent (Baldessarini et al. 1980; Casey and Hansen 1984; Kane et al. 1985; Chouinard et al. 1988).

Data on incidence provide a more accurate estimate of risk per year of exposure to neuroleptics. These data have been generated from several rigorous, large-scale, prospective studies. Results indicate that the average yearly rate of developing TD is about 5 percent per year for the first several years. The cumulative 5-year incidence rate appears to be 20 to 26 percent (Morgenstern and Glazer 1993; Kane 1995). It is unclear whether the risk levels off after 5 years or continues to increase linearly. Glazer et al. (1993) have suggested that the risk may indeed be linear for 10 years or longer, with the 10-year risk estimated to be 49 percent and the 25-year risk to be 68 percent.

Epidemiological studies have uncovered a variety of risk factors that increase the chances of developing TD (e.g., see Kane 1984; Waddington 1987; Morgenstern and Glazer 1993). Demographic risk factors include increased age, psychiatric diagnosis (mood disorders have increased risk), and gender. However, the findings regarding gender are equivocal. Initial studies suggested that females had increased rates of TD, but these findings were confounded by differences in age or treatment variables between groups. More recent, controlled studies find higher rates only in women over 65, whereas gender effects are not apparent in younger cohorts. In fact, some studies have found greater severity in young men than in young women (see Yassa and Jeste 1992 for a review).

The presence of diabetes, organic brain damage, and negative symptoms (in patients with schizophrenia) also may significantly increase risk, perhaps through their effects on corticostriatal input or on striatal function itself (see below). Studies that focus on patients with organic brain damage, patients with diabetes, or the elderly suggest these factors may increase 1-year incidence rates up to 20 percent or more.

Treatment variables associated with increased risk include higher neuroleptic dose, number of medication-free periods, and a history of acute extrapyramidal side effects (EPS). The association with increased dose has not been found in many studies, but has intuitive appeal (Morgenstern and Glazer 1993; Kane 1995). How medication-free periods and acute EPS increase TD incidence is unclear, but it could theoretically be mediated through their impact on the D1-mediated striatonigral pathway (e.g., see Egan et al. 1994).

Since the introduction of clozapine into the United States, it has become apparent that this unusual antipsychotic agent is rarely associated with TD, if at all (Kane 1995). This observation indicates for the first time that it is possible for a medication to have full antipsychotic efficacy while not causing TD. Unfortunately, the use of clozapine has been limited severely by a variety of other side effects, such as agranulocytosis. As a consequence, new medications have been designed to mimic clozapine's therapeutic profile. Several such putative, atypical agents have recently been tested in relatively brief clinical trials and appear to be promising. These agents, which include risperidone, olanzapine, seroquel (Fleischhacker et al. 1996), sertindole, and ziprasidone, seem to cause fewer acute EPS than older "typical" agents. It is unclear, however, whether their long-term use will be associated with a lower incidence of TD.

Although one hopes that the new generation of atypical neuroleptics will eliminate TD, this promise has yet to be fully realized. Many patients continue to develop and suffer from TD. In addition, for the near future, many patients will probably continue to depend on typical neuroleptics. Thus, TD remains a therapeutic conundrum. The challenges facing clinicians include how to minimize the
risk of TD and what to do with patients once they develop it.

Prevention and TD

The mainstay of TD prevention has traditionally been to limit neuroleptic exposure when possible. Unfortunately, the best treatment for many psychiatric disorders is the long-term administration of neuroleptics. For patients who require neuroleptics, most experts recommend use of the smallest effective dose (American Psychiatric Association Task Force 1992). However, the idea that a higher dose has a significant impact on the incidence or severity of TD has intuitive appeal, but limited empirical support (American Psychiatric Association Task Force 1992; Kane 1995). Most studies have actually failed to find such a relationship. Those that have are often criticized for methodological inadequacies (Kane and Smith 1982; Kane et al. 1983, 1986; Kane 1995). A recently published study that has addressed some of the typical methodological pitfalls suggested that each increase in dose equivalent to 100 mg chlorpromazine is associated with a 5 percent increase in the chance of developing TD (Chakos et al. 1996). Conversely, the risk of using very low doses is that relapse rates are higher (Johnson et al. 1983; Kane et al. 1983; Marder et al. 1987). For long-term treatment, intermediate doses (e.g., 400 to 900 mg chlorpromazine equivalents) may be as effective as the higher doses often used in acute settings (e.g., Baldessarini and Davis 1980; Van Putten and Marder 1986; American Psychiatric Association Task Force 1992).

Intermittent treatment or the use of drug holidays has been examined as a way to reduce neuroleptic exposure. Although one study suggested that this strategy may benefit some patients (Jolley et al. 1989), it is probably not useful for most. In fact, well-controlled studies suggest that intermittent neuroleptic treatment is less effective than long-term treatment in preventing psychotic relapse (Carpenter et al. 1990), does not prevent the development of TD (Jeste et al. 1979; Newton et al. 1989; Kane and Marder 1993), and may even increase the likelihood of developing TD (Jeste and Wyatt 1982b). One report found that depot neuroleptics have a higher tendency to cause TD (Gibson 1978), but this finding requires additional study. Such an association could be due to poor compliance and the subsequent intermittent treatment of patients who are given depot preparations. The long-term use of neuroleptics is indicated primarily for patients who demonstrate a clear therapeutic response. Some patients can be maintained on other agents that are much less likely to produce TD. These agents include lithium, anticonvulsants (e.g., carbamazepine and valproic acid), tricyclics, and benzodiazepines.

A second, emerging strategy is to use neuroleptics that may have a reduced propensity to cause TD. Clozapine, as described earlier, has a minimal risk of producing TD; however, many other side effects limit its use. Given the risk of agranulocytosis, most experts continue to recommend clozapine as a second-line agent for patients who are treatment refractory or who develop moderate to severe TD. Of those who develop moderate to severe TD, some will not respond as well to clozapine as they do to other neuroleptics.

Risperidone is the first of the new generation of putative atypical neuroleptics. Clinical and preclinical studies indicated that it is less likely to produce acute EPS (Klieser et al. 1995). Because lower acute EPS liability has been hypothesized to be associated with a lower risk of producing TD, such results are encouraging (Casey 1989). Recent case reports, however, indicate that risperidone can produce TD (Buzan 1996; Daniel et al. 1996; Woerner et al. 1996). In one case, a schizophrenia patient who had been medication-free for 6 months before risperidone was started but developed abnormal movements after 1 year on risperidone (Woerner et al. 1996). No controlled studies on the incidence of TD induced by risperidone are available, and such long-term data are critical for assessing risperidone's risk of inducing TD compared with other typical agents.

The development of additional atypical neuroleptics is proceeding rapidly. Olanzapine and sertindole have been approved recently by the Food and Drug Administration and released. Phase II and III studies convincingly demonstrated that both medications are very effective in treating psychosis and have a low incidence of EPS (Beasley et al. 1996; Schulz et al. 1996; Tollefson et al. 1996). With such limited use, it is difficult to predict whether they will assume their touted position as the medications of first choice for the treatment of psychosis. In preclinical studies, sertindole produced dose-related EPS in Cebus monkeys, but it was also effective in suppressing spontaneous dyskinesias in other monkeys (Casey 1996), suggesting that it might be effective in suppressing TD. Of course, antipsychotics that induce EPS and suppress dyskinesias also have the potential to produce TD. Nevertheless, the introduction of these two new atypical neuroleptics and indeed of the whole new generation of agents to come is perhaps the most exciting development related to TD in decades. Likely their use will become widespread.

A third, untested strategy is the prophylactic use of protective agents to reduce the incidence of TD. Data using animal models indicate that antioxidants, such as vitamin E (Klugewicz et al. 1996) and GM1 ganglioside
Natural Data from several long-term studies indicate that progression from mild to severe TD, if it does occur, happens only in a small percentage of cases. Moreover, an examination should also be performed at least semiannually on patients at risk for developing TD. However, these observations suggest that prophylactic treatment with vitamin E (1,200 to 2,000 IU/day) could reduce the risk of developing TD. Although no human studies are available to support this strategy, long-term use of vitamin E has little risk. Lithium has also been suggested to reduce the incidence of TD (Cole et al. 1984), although recent data are conflicting (Kane et al. 1986; Ghadirian et al. 1996), and the routine use of lithium for TD prevention is uncommon.

Management of Patients With TD

When symptoms of TD first appear, a thorough medical evaluation should be done, including a physical and neurological examination, laboratory testing, and a review of the differential diagnosis (Hyde et al. 1991). Fortunately, the incidence of organic disorders masquerading as TD seems to be very low (Woerner et al. 1991). The next issue is whether neuroleptics should be continued. Most published recommendations suggest that drug withdrawal or marked dose reduction, when possible, is indicated; the likelihood of psychotic relapse, however, is fairly high—a major risk of this approach. A third issue is whether additional medications are needed to suppress TD. Often, mild to moderate symptoms are either unnoticed or have little impact. Those for whom suppressive therapy is needed can choose from several mildly to moderately successful medications.

It is helpful to involve both patients and their family from the outset so that informed decisions can be made and documented. Patients educated with printed information sheets (Wyatt 1995) seem to be better informed than those educated verbally (Kleinman et al. 1989). Routine monitoring of TD is essential to track symptomatic changes and response to medications. The most popular rating procedure is the Abnormal Involuntary Movement Scale (AIMS; Guy 1976) examination. Ratings should be performed every 4 to 6 months on patients with TD and perhaps more often when medication changes are made. Moreover, an examination should also be performed at least semiannually on patients at risk for developing TD.

Natural Course of TD. Data from several long-term studies indicate that progression from mild to severe TD, if it does occur, happens only in a small percentage of cases (Gardos and Cole 1983; Casey and Gerlach 1986; Gardos et al. 1988, 1994; Gerlach and Casey 1988; Bergen et al. 1989). This finding is supported by epidemiological studies indicating that the prevalence of moderately severe TD is roughly 6 to 10 percent of patients with TD or about 4 percent of patients treated with neuroleptics (Kane et al. 1988; Yassa et al. 1990). The prevalence of very severe TD is probably lower than these figures, but estimates are difficult to obtain (Gardos et al. 1987). By far the most common course for TD is a waxing and waning of mild to moderate symptoms over many years (Barnes et al. 1983; Robinson and McCreadie 1986; Gardos et al. 1988; Bergen et al. 1992; Kane 1995). Roughly 50 percent of patients have recurrent symptoms with neither marked progression nor extended remission. Although estimates vary among studies, many suggest that roughly 10 to 30 percent will have a reduction in movements or full remission, and another 10 to 30 percent will show some degree of worsening. These data suggest that, for many patients, continued treatment with neuroleptics after the development of TD is a reasonable option.

Risk factors have been examined in an attempt to identify which patients will likely show progression or persistence of TD with continued treatment. In general, these factors are similar to the risk factors for developing TD (however, see Kane 1995). They include age (Smith and Baldessarini 1980), gender, and exposure to anticholinergic agents. Increasing age has been associated with fewer spontaneous remissions while on medication and less improvement after medications are withdrawn. Regarding the effect of gender, the literature is divided. Many suggest that female gender is associated with increased risk and persistence, although the opposite has also been found (Bergen et al. 1992; Yassa and Jeste 1992; Yassa and Nair 1992). Other risk factors include duration of exposure to neuroleptics, diagnosis (worse with organic brain syndromes and affective disorders), duration of TD (Gardos and Cole 1983; Casey and Gerlach 1986; Glazer et al. 1991; Bergen et al. 1992; Yassa and Nair 1992), and frequent on-off manipulations (Kane 1995). Overall, these data suggest that efforts to reduce or discontinue neuroleptics might be directed toward those at greater risk.

Neuroleptic Withdrawal. Although continued neuroleptic treatment may be the safest course for many patients with TD, such as those with a lower risk profile, this continuation must be weighed against the potential benefits of withdrawal. Indeed, many experts (American Psychiatric Association Task Force 1992) recommend neuroleptic withdrawal, with the critical caveat that it should be done only in patients who can tolerate it. In the first several weeks after withdrawal, TD often worsens...
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(Gardos et al. 1984; Dixon et al. 1993). For example, Gardos et al. (1984) withdrew neuroleptics from 33 patients and noted significant increases in dyskinesia severity and dysphoria in 33 percent, resulting in their early removal from the study. Glazer et al. (1989) withdrew neuroleptics for 3 weeks in 19 patients and noted a relapse of psychosis in 26 percent and TD worsening in 53 percent. The magnitude of TD exacerbation in this study is unclear.

After the withdrawal of neuroleptics, TD does seem to improve over the long term despite early exacerbation. In a comprehensive review of 20 studies, Jeste and Wyatt (1979) reported that 36 percent of patients withdrawn from neuroleptics showed improvement. Additional studies tend to support their conclusion. Jus and colleagues (1979) found improvement in 49 of 62 patients by slowly tapering neuroleptics over 4 years. Improvement has been seen up to 5 years after the cessation of treatment (Klawans et al. 1984). In a mostly nonpsychotic patient group, Fahn (1985) reported improvement in 13 of 22 patients over a 2- to 4-year period. The 22 patients in the Fahn (1985) study had concurrent treatment with reserpine or tetrabenazine. In contrast, Glazer and colleagues (1990) followed 49 patients for an average of 40 weeks after the discontinuation of neuroleptics. Complete remission was rare (2%), and dyskinesia severity decreased in only 20 percent. The rate of psychosis relapse for patients with schizophrenia approached 50 percent (Glazer et al. 1984, 1990). One difficulty with drawing conclusions from these studies is that many were unblinded or not well controlled. Nevertheless, they suggest that neuroleptic withdrawal is risky but can result in long-term remission of TD in some patients (see also Casey and Gerlach 1986).

The degree of improvement during withdrawal may be related to the same risk factors associated with the development of TD and with improvement during continued treatment. These factors include age, with patients over 65 (Smith and Baldessarini 1980) showing little improvement; organic brain damage; number of extended medication-free periods; and length of neuroleptic treatment (Jeste and Wyatt 1979). If drug withdrawal is attempted, very gradual tapering seems less likely to worsen psychosis. A variation of this strategy is an initial increase in neuroleptic dose to suppress TD, the very gradual withdrawal (e.g., 10% per month). This strategy has worked in several cases of moderate to severe TD with dystonic features (Kleinman, personal communication, May 1996) but has not been studied in controlled trials.

Although withdrawal should be considered, many patients will not be able to tolerate this approach. The risks associated with neuroleptic withdrawal include psychotic decompensation (Gilbert et al. 1995) and an increased likelihood of injury to self or others. Furthermore, untreated patients with schizophrenia may have a worse long-term prognosis than patients treated with neuroleptics (Wyatt 1991). Over the long term, some patients initially withdrawn from neuroleptics have actually ended up receiving higher total doses of neuroleptics to cope with symptom exacerbation (Johnson et al. 1983). Many factors figure in predicting the success of neuroleptic withdrawal, such as a history of dangerous behavior, current stressors, the living and working environments, and family relationships.

Switching to Atypical Neuroleptics. In lieu of typical neuroleptics, alternate therapeutic agents can be considered. Most important, one must consider switching patients to an atypical neuroleptic. These medications offer the advantage of clear antipsychotic efficacy and the significant possibility of reduced TD liability, so it is reasonable to conclude that patients with TD will have a greater likelihood of TD remission on atypical neuroleptics. Unfortunately, this conclusion has not been demonstrated clearly in clinical studies and remains conjectural. As a result, one must clearly delineate the benefits and risks to patients of the use of atypical neuroleptics. In particular the possible benefits of TD reduction from clozapine may not be worth the risk of sedation, seizures, or agranulocytosis for many patients. The fact that some patients do better on typical agents than they do on clozapine or risperidone is also a consideration.

Although a feeling of therapeutic nihilism may creep in regarding patients with TD who require continued treatment with typical neuroleptics, one action that could benefit them is to ensure adherence (limiting drug-free periods) and to vigorously treat substance abuse disorders. Anecdotal reports suggest that patients who abuse such stimulants as cocaine may develop more severe TD symptoms.

Who Needs Suppressive Therapy? In our experience, suppressive therapy should be considered if TD poses health risks, impairs function, or is otherwise bothersome to the patient, for example, if it creates problems with breathing, eating, walking, or sleeping. Many patients with moderate to severe TD are not aware of their symptoms. Furthermore, a moderate or severe rating on an item of the AIMS scale does not necessarily mean a patient is functionally impaired or disfigured. Suppression in some cases may not be worth the risk. Assessment by an occupational or physical therapist can sometimes give insight into functional impairment and may suggest nondrug strategies to cope with disabilities.

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Patients with moderate to severe TD are the most likely candidates for suppressive treatment. Severe TD is most common in younger men (under age 40) and older women (over 65) and often has a component of dystonia. A variety of functional problems can be produced by severe TD, depending on the area of the body that is affected. For example, truncal TD can interfere with walking, sitting, and even sleeping, although TD disappears for the most part once a patient is able to fall asleep. Orofacial dyskinesia can be particularly disfiguring, sometimes interfering with eating and adequate nutrition, and has been linked to reduced life expectancy (McClelland et al. 1986). Respiratory dyskinesia, often overlooked, can produce a variety of respiratory signs and symptoms, including irregular respiratory rate, tachypnea, and grunting (Chiu et al. 1991; Nishikawa et al. 1992). Patients with severe TD are at risk for aspiration.

A variety of risk factors for severe TD have been examined, such as number of medication-free periods (Yassa et al. 1990; but see Gardos et al. 1987); however, it is difficult to predict who will develop this condition. Anecdotal reports suggest that severe TD comes on quickly, developing over the course of several months, rather than being the result of a relentlessly progressive process that develops over a long period of time with continued neuroleptic exposure. Several authors have noted that increased blinking or blepharospasm may be a prodromal symptom (Gardos et al. 1987; Wojcik et al. 1991). Yet, certainly many patients with increased blinking do not go on to develop severe TD. Treatment of severe TD, as with less pronounced forms, often requires continued neuroleptic treatment with the serial addition of a variety of suppressive agents.

Pathophysiology of TD

Several comprehensive reviews (Jeste and Wyatt 1982a, 1982b; Jeste et al. 1988) have surveyed most of the published data on the treatment of TD from the 1970s and 1980s. In general, the goal of most studies was to demonstrate short-term reduction or suppression of dyskinetic symptoms.

There are no empirically validated guidelines to follow when choosing a suppressive agent. In general, therapeutic trials have attempted to manipulate one of the following neurotransmitter systems: dopamine, gamma-aminobutyric acid (GABA), acetylcholine, norepinephrine, and serotonin. These systems have received the most attention, in part due to theories about the pathophysiology of TD. Although an extensive review of this topic is beyond the scope of this article, a brief description of leading ideas may be instructive.

Dopamine Supersensitivity. The dopamine supersensitivity hypothesis of TD was first proposed in 1970 by Klawans et al. Based on the similarity between L-dopa-induced dyskinesias and TD, he suggested that chronic neuroleptic treatment produced supersensitive striatal dopamine receptors, similar to denervation-induced supersensitivity found in peripheral muscles. Since then, dopamine supersensitivity has been an important theoretical construct guiding TD research. Several inconsistencies, however, suggest that it cannot explain entirely the pathogenesis of TD. First, supersensitivity occurs within 2 to 4 weeks of initiating neuroleptic treatment, whereas TD develops after long-term use. Second, in animal studies, most subjects develop supersensitivity, in contrast to only the minority of patients who develop TD. Finally, supersensitivity disappears within weeks after neuroleptics are withdrawn, whereas TD can persist for months and years. The original version of this idea has been supplanted with the notion that D₂ supersensitivity may be a necessary first step in a path that ultimately leads to the development of TD. Interestingly, clozapine does not induce D₂ supersensitivity at standard doses.

A related idea implicates the balance between acetylcholine and dopamine and is supported, for example, by the observation that Parkinsonian symptoms are alleviated by dopamine agonists or cholinergic antagonists. Higher doses of dopamine agonists can also induce dyskinesias. If dopamine and acetylcholine work in the opposite direction, then cholinergic agonists could alleviate dyskinesias. Although this idea has been heuristically useful, cholinergic potentiation as a treatment for TD has been largely unsuccessful.

GABA Depletion. As a result of deficiencies in the dopamine supersensitivity hypothesis, considerable attention has been focused on the GABA system (Mao et al. 1977; Gale 1980; Fibiger and Lloyd 1989). Several studies point to decreased GABA turnover or increased GABA binding sites in one or more areas of the basal ganglia in rodents and primates after chronic neuroleptic treatment. This reduction in turnover is most prominent in animals that have dyskinesias (Gunne et al. 1984). Anderson and colleagues (1989), in a very small human postmortem study, found a significant decrease in subthalamic glutamic acid decarboxylase activity—the rate-limiting enzyme in the metabolic pathway for GABA—in patients with TD compared with non-TD patients. Other attempts to assess GABAergic neurotransmission in living patients have also suggested that individuals with TD have particular abnormalities (Thaker et al. 1987, 1988). GABAergic neurons play a central role in the subcortical regions that generate abnormal movements. Further study...
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Neurotoxicity. The idea that long-term neuroleptic treatment may have a toxic effect on the brain has led to many studies of evidence of neuronal injury. The neurotoxicity hypothesis is particularly engaging given the persistence of TD in some cases and the similarity between TD and degenerative diseases of the basal ganglia, such as Huntington’s. Unfortunately, most postmortem studies in animals and patients exposed to long-term neuroleptic treatment have been inconsistent or have suffered from methodological problems (Christensen et al. 1970; Pakkenberg et al. 1973; Pakkenberg and Fog 1974; Colon 1975; Gerlach 1975; Fog et al. 1976; Jellinger 1977; Nielsen and Lyon 1978). Neuroleptics could produce more subtle damage, however, through mechanisms other than simple neuronal degeneration. Dopamine is metabolized by monoamine oxidase to dihydropyrophospholacetic acid (and then homovanillic acid). A byproduct of this reaction is hydrogen peroxide, a potent oxidant. It has been hypothesized that hydrogen peroxide could generate a cascade of free radicals that react with proteins, lipids, and other cellular constituents, ultimately leading to significant neuronal dysfunction. Indeed, several groups have found evidence suggesting that free radical formation may occur both in rodents and humans treated with neuroleptics (e.g., Pai et al. 1994). Although stronger evidence is clearly required, this hypothesis has led to trials of antioxidants as a treatment for TD.

Striatal Dysregulation. Studies on the basal ganglia and movement disorders suggest that the final common pathway for dyskinesias is increased activation of the D1-mediated striatonigral (or “direct”) pathway (Albin et al. 1989; Crossman 1990; DeLong 1990). These medium spiny striatal neurons are primarily GABAergic but also use several neuropeptides as cotransmitters, including substance P and dynorphin. The direct pathway inhibits neurons in the substantia nigra, pars reticulata, and its associated nucleus, the internal segment of the globus pallidus (figure 1). These areas, in turn, project to the thalamus, which is thought to act as a filter for cortical input. The classical theory is that increased inhibition of the inhibitory GABAergic nigral/pallidal outflow produces a net increase (or loss of inhibition) of thalamocortical projections. The other major outflow tract from the striatum (Albin et al. 1989; Crossman 1990; DeLong 1990), the D2-mediated striatopallidal (or “indirect”) loop, may also play a role. The medium spiny neurons of this pathway are also GABAergic and use the neuropeptide enkephalin as a cotransmitter. Increased activity of this pathway, which results from blockade of the inhibitory D2 receptors, may facilitate the expression of D1 overactivation (Egan et al. 1994). Indeed, animal studies suggest that haloperidol increases D1 agonist-induced dyskinetic mouth movements in rodents.

Although the hypothesis that TD is a result of such alterations in basal ganglia physiology remains unproved, it suggests that a variety of neurotransmitters and receptors could play a role; for example, D1 and D2 receptors, cholecystokinin (CCK), neotensin, GABA, N-methyl-D-aspartate receptors, and opiate receptors (mu, kappa, and possibly delta). Drugs targeting these transmitter systems.
may affect TD symptoms. Unfortunately, animal studies using such agents have generally been inconclusive, and human studies are limited.

Suppressive Therapies for TD

The competing theories on TD have led to clinical trials of a wide variety of medications. None has been successful in the majority of patients. As a result, one may have to try several medications in series before finding one with some utility. In general, selection is guided by a benefits-risk analysis, success in prior studies, potential side effects of the suppressing agent, and interactions with other medications.

Typical Antipsychotics. Neuroleptics themselves may be effective to some degree in suppressing TD. A 1979 review of 50 studies, totaling 501 patients, found that 67 percent showed clinical improvement with neuroleptic suppression, the highest improvement rate of any suppressive strategy (Jeste and Wyatt 1979). However, a more recent review (Jeste et al. 1988) suggested a lower rate of response. Suppressing effects are most pronounced in short-term studies (Doongaji et al. 1982; Jeste and Wyatt 1982a; Perenyi et al. 1985; American Psychiatric Association Task Force 1992); although some well-controlled studies have found that suppression is often minimal (e.g., Lieberman et al. 1988a, 1988b). The therapeutic efficacy of long-term (more than 8 weeks) suppression is unclear, in part due to problems with study design. Most studies have first withdrawn patients from neuroleptics and then compared changes between neuroleptic and placebo treatment (Roxburgh 1970; Singer and Cheng 1971; Kazamatsuri et al. 1972b, 1973; Glazer and Hafez 1990). This design may be a better measure of the neuroleptics' ability to suppress withdrawal dyskinesias than persistent TD. Other studies were either unblinded or did not use appropriate control groups (Roxburgh 1970; Curran 1973; Jus et al. 1979; Smith and Kiloh 1979). Of three particularly well-controlled studies, two found significant long-term suppression (Frangos and Christoudoulides 1975; Gerlach and Casey 1983), while the third did not (Korsgaard et al. 1984). A fourth study using depot neuroleptics showed brief improvement (i.e., 1–2 days) along with increased blood levels immediately after drug injection in 4 of 6 patients (Barnes and Wiles 1983). Although these findings are suggestive, the safety and efficacy of increased neuroleptic dose for long-term suppression remain questionable.

A primary concern with using higher neuroleptic doses for suppression is the potential that TD could become worse. Nevertheless, in severe cases with life-threatening complications, increasing the dose may be the only maneuver that will help. Higher potency neuroleptics, such as haloperidol, may be more effective in suppressing movements than those of lower potency, such as molindone. In patients with withdrawal TD, Glazer and colleagues (1985a) were able to suppress symptoms in 66 percent of those using haloperidol versus only 39 percent of those using molindone. If withdrawal dyskinesias are similar pharmacologically to persistent dyskinesias, they may also be suppressed more effectively by high-potency neuroleptics. Giving medications in divided doses throughout the day has also been helpful in masking symptoms of TD. In a variation of this strategy, we have seen improvement in several patients after stopping neuroleptic treatment for several weeks, then restarting it at a lower dose. This strategy has not been studied under controlled conditions, however, and the two patients who improved had a marked Parkinsonian tremor in addition to TD.

Atypical Neuroleptics. In addition to their use as drugs with lower TD liability, atypical neuroleptics, particularly clozapine, have also been tried as suppressive agents. Although early experience with clozapine was generally disappointing (Gerlach et al. 1974; Gerlach and Simmelsgaard 1978; Caine et al. 1979), more recent studies have been mixed (Lieberman et al. 1991). A description of published reports provided in table 1 includes 16 clozapine studies—7 case reports, 4 open trials, 1 single blind, and 4 double-blind, controlled, or crossover studies. All seven case reports, not surprisingly, found improvement: two described rapid TD suppression (Carroll et al. 1977; Meltzer and Luchins 1984), and four observed dramatic responses only after months or years (Lamberti and Bellnier 1993; Friedman 1994; Trugman et al. 1994; Levkovich et al. 1995). Four open, uncontrolled trials (Cole et al. 1980; Gerbino et al. 1980; Small et al. 1987; Lieberman et al. 1991) also found beneficial effects with clozapine. The most significant results were observed after at least 4 weeks of treatment and for patients with severe TD and tardive dystonia (Carroll et al. 1977; Meltzer and Luchins 1984; Lieberman et al. 1991). In most cases, TD symptoms returned to baseline after the discontinuation of clozapine (Cole et al. 1980; Gerbino et al. 1980; Small et al. 1987; Lieberman et al. 1991), which suggests that TD was suppressed.

Of four double-blind, controlled or double-blind, crossover studies, two found significant improvement with clozapine (Simpson et al. 1978; Tamminga et al. 1994). In both positive studies, clozapine was administered for 22 to 52 weeks. In contrast, the negative studies lasted only 3 to 5 weeks. The study by Tamminga et al. (1994) was particularly lengthy and included a control
Table 1. Studies of the effect of atypical neuroleptics on tardive dyskinesia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Design</th>
<th>Duration</th>
<th>Maximum dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerlach et al. (1974)</td>
<td>Clozapine</td>
<td>Double-blind, crossover</td>
<td>3 weeks</td>
<td>225 mg/day</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Caine et al. (1979)</td>
<td>Clozapine</td>
<td>Double-blind, placebo-</td>
<td>3-5 weeks</td>
<td>425 mg/day</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Gerlach and Simmelsgaard (1978)</td>
<td>Clozapine</td>
<td>Crossover</td>
<td>4 weeks</td>
<td>62.5 mg/day</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Carroll et al. (1977)</td>
<td>Clozapine</td>
<td>Case report</td>
<td>18 days</td>
<td>1,000 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Simpson et al. (1978)</td>
<td>Clozapine</td>
<td>Single-blind, placebo-</td>
<td>22 weeks</td>
<td>523-775 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Cole et al. (1980)</td>
<td>Clozapine</td>
<td>Open, uncontrolled</td>
<td>Up to 12 weeks or more</td>
<td>100-500 mg/day</td>
<td>Significant improvement, mainly after &gt; 12 weeks</td>
</tr>
<tr>
<td>Gerbino et al. (1980)</td>
<td>Clozapine</td>
<td>Open</td>
<td>4 weeks and 12 months</td>
<td>4 weeks: 650 mg/day; 12 months: down to 50% of initial dose</td>
<td>Significant improvement at both times</td>
</tr>
<tr>
<td>Meltzer and Luchins (1984)</td>
<td>Clozapine</td>
<td>Case report</td>
<td>2 weeks</td>
<td>900 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Small et al. (1987)</td>
<td>Clozapine</td>
<td>Open, uncontrolled</td>
<td>7 weeks</td>
<td>340 mg/day</td>
<td>Significant improvement in only 7 of 19 patients</td>
</tr>
<tr>
<td>Van Putten et al. (1990)</td>
<td>Clozapine</td>
<td>Case report</td>
<td>14 weeks</td>
<td>250 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Lieberman et al. (1991)</td>
<td>Clozapine</td>
<td>Open, uncontrolled</td>
<td>36 months</td>
<td>486 mg/day (average daily dose at endpoint)</td>
<td>At least 50% improvement in 43% of patients</td>
</tr>
<tr>
<td>Lambert and Bellnier (1993)</td>
<td>Clozapine</td>
<td>Case report</td>
<td>11 months</td>
<td>300 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Friedman (1994)</td>
<td>Clozapine</td>
<td>Case report</td>
<td>&gt; 3 years</td>
<td>350-500 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Tamminga et al. (1994)</td>
<td>Clozapine</td>
<td>Double-blind controlled, randomized, non-crossover</td>
<td>12 months</td>
<td>293.8±171.9 mg/day (average daily dose at endpoint)</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Trugman et al. (1994)</td>
<td>Clozapine</td>
<td>Case report</td>
<td>4 years</td>
<td>625 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Levkovitch et al. (1995)</td>
<td>Clozapine</td>
<td>Case report</td>
<td>48 months</td>
<td>450-550 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Meco et al. (1989)</td>
<td>Risperidone</td>
<td>Crossover, placebo-</td>
<td>4 weeks</td>
<td>6 mg/day</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Kopala and Honer (1994)</td>
<td>Risperidone</td>
<td>Case report</td>
<td>4 weeks</td>
<td>4 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Chouinard (1995)</td>
<td>Risperidone</td>
<td>Double-blind, parallel</td>
<td>8 weeks</td>
<td>6-16 mg/day</td>
<td>Significant improvement</td>
</tr>
</tbody>
</table>

A group of 32 patients treated with haloperidol during a 12-month blind treatment period. Comparison of the different studies is complicated by the use of different doses of clozapine, lack of appropriate controls, and inconsistent patient follow-up. Two noteworthy trends are that a long duration of treatment is needed and that dystonic features
may be more responsive than dyskinetic ones (Lieberman et al. 1991). The mixed results in controlled studies suggest that further investigations of clozapine’s suppressive properties are warranted.

If clozapine is shown to have therapeutic effects in TD, several mechanisms could play a role. An early acute response to clozapine suggests a suppressive effect similar to classical neuroleptics. Long-term improvement could be due to a passive mechanism in which dyskinetic movements improve over time in the absence of the offending agent. A third possibility is that clozapine has an active, not simply suppressive, therapeutic effect on dyskinetic movements.

Little is known about the effect of risperidone on TD. An early, controlled study (see table 1) found no evidence of suppression (Meco et al. 1989). More recently, a case report found suppression of severe TD with risperidone (Kopala and Honer 1994), and more convincingly, the Canadian Multicenter Risperidone Study showed an antidyskinetic effect in a double-blind, placebo-controlled trial (Chouinard 1995). Thus, risperidone could be useful as a suppressive medication, although since it may also induce TD (Buzan 1996; Daniel et al. 1996; Woerner et al. 1996), the risk of long-term exacerbation is unknown.

The development of new atypical antipsychotics may provide alternatives for the treatment of TD. Olanzapine, sertrindole, seroquel, and ziprasidone have been shown to be efficacious for the treatment of psychosis and to produce fewer EPS than traditional neuroleptics (Seeger et al. 1995; Beasley et al. 1996; Borison et al. 1996; Schulz et al. 1996; Tollefson et al. 1996). Like clozapine, these drugs are more effective in blocking the 5-hydroxytryptamine2 (5-HT2) than the D2 receptor site. In contrast to clozapine, however, all are relatively potent D2 antagonists. The finding that clozapine is associated with a lower incidence of TD (Casey 1989) and may suppress TD suggests that there are important advantages to using clozapineline medications with selectivity for the 5-HT2 receptor. However, it is unclear whether these putative atypical neuroleptics will be effective in suppressing TD.

**Dopamine Depleters.** Medications that work primarily by reducing or depleting presynaptic stores of dopamine have sometimes been helpful in reducing TD severity. Dopamine depleters act by several different mechanisms. Reserpine and tetrabenazine (not available in the United States) disrupt the storage of dopamine in presynaptic vesicles. Alpha-methyl-dopa reduces dopamine synthesis by competitive inhibition of dopa decarboxylase and the formation of a false neurotransmitter. Alpha-methyl-tyrosine (AMPT) also reduces dopamine (and norepinephrine) synthesis via its actions on tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis.

Studies of dopamine-depleting medications suggest that they may alleviate symptoms in up to 50 percent of patients with TD. For example, using reserpine, Huang et al. (1981) found at least 50 percent improvement in 5 of 10 patients, whereas Fahn (1985) showed improvement in 8 of 17 patients who were not taking neuroleptics. Nasrallah et al. (1986) found improvement in 5 of 10 patients in a 4-week, double-blind study using AMPT; only patients who remained on neuroleptics in addition to AMPT improved. Although not all studies have found this degree of success (Lang and Marsden 1982), previous reviews of both uncontrolled case reports and controlled studies support the 50 percent estimate (Jeste and Wyatt 1979; Jeste et al. 1988). For example, a review of five studies performed from 1961 to 1977 found that tetrabenazine improved TD in 29 of 42 patients. In the same review, 17 of 38 patients from another five reports improved on reserpine, and 18 of 32 improved on AMPT (Jeste and Wyatt 1979). Although larger, well-controlled studies are needed to validate these findings, the limited available data support the use of dopamine-depleting medications for TD suppression. Unfortunately, side effects, including hypotension (reserpine, alpha-methyl-dopa), impotence, and depression, as well as Parkinsonism and akathisia, often limit their use. Depression, a relatively frequent side effect, has been treated successfully with concurrent antidepressant administration.

**Dopamine Agonists.** In animal studies, dopamine agonists downregulate dopamine receptors and theoretically could be useful in TD. A major drawback is that they can initially exacerbate both TD and psychotic symptoms. Direct (apomorphine and bromocriptine) and indirect (amantadine and levodopa) dopamine agonists have been tried in humans. Some positive case reports or single-blind studies have been published, but most double-blind studies show little improvement (Jeste et al. 1988; Lieberman et al. 1989). One exception is a recent report of 35 inpatients with severe orofacial TD who showed marked improvement on L-dopa after 3 months. Symptoms returned when L-dopa was discontinued and again responded when treatment was restarted (Ludatscher 1989). This study, which suffers from several methodological shortcomings, needs to be replicated in a double-blind, crossover study but is encouraging nonetheless.

Dopamine autoreceptor agonists—for example, n-N-propyl-3-(3-hydroxyphenyl)piperidine (3-PPP)—decrease the release of dopamine and present another possible mechanism to treat TD. 3-PPP has been shown to improve TD in monkeys (Kovacic et al. 1988), but it has not been tried in humans. In low doses, apomorphine is an autoreceptor agonist, whereas in high doses it is a postsynaptic receptor agonist. Theoretically, low doses should decrease
dopamine release and improve symptoms of TD, whereas high doses should do the opposite. Paradoxically, one study showed that high doses, up to 6.0 mg, reduced TD movements (Smith et al. 1977). The usefulness of apomorphine may be limited by such side effects as nausea and vomiting at therapeutic doses.

Noradrenergic Antagonists. Although noradrenergic innervation of basal ganglia structures is sparse and limited primarily to the thalamus, noradrenergic agents have been used to treat TD. The beta-adrenergic antagonist, propranolol, has been reported in open studies to partially suppress TD in 11 of 15 patients (Jeste and Wyatt 1982b). In a double-blind study of four patients, two improved with long-term treatment (Schrodt et al. 1982). Unfortunately, no larger or more recent studies are available, and it is unclear whether or not propranolol's suppressive effect is due to increased neuroleptic blood levels. In contrast, pindolol, another beta blocker, was unsuccessful in suppressing TD in a small placebo-controlled study (Greendyke et al. 1988). Clonidine, an alpha2 agonist, decreases the release of norepinephrine by autoreceptor stimulation and has been reported to have antidysochronic properties in a majority of patients (Freedman et al. 1982; Nishikawa et al. 1984; Browne et al. 1986). Clonidine may also have antipsychotic properties (Freedman et al. 1982) and has relatively few side effects (hypotension, sedation). Other noradrenergic antagonists with apparent suppressive effects are disulfiram (Jeste et al. 1986) and fusaric acid, both dopamine beta-hydroxylase inhibitors. Oxypertine depletes norepinephrine and dopamine and may also improve dyskinesias (Soni et al. 1984). Unfortunately, this line of treatment has not been pursued in large well-controlled studies. At the present time, noradrenergic antagonists, particularly clonidine, seem to be relatively safe and somewhat effective as suppressive agents.

Anticholinergics. As mentioned above, dopamine and acetylcholine seem to have opposite effects on behaviors mediated by the striatum. One could predict that anticholinergics would make TD worse. Although this effect has been found in some reports (Klawans 1973), others have found either no change (Wirshing et al. 1989) or even improvement in TD with anticholinergics. For example, in an acute challenge study using intravenous administration, Lieberman and colleagues (1988a, 1988b) showed that benztropine tended to decrease movements, whereas phystostigmine worsened them (see also Moore and Bowers 1980). This finding suggests that dopamine and acetylcholine are not simply functional antagonists in the basal ganglia. In general, however, most data indicate that long-term treatment with anticholinergics either does not help or may actually worsen TD (Jeste and Wyatt 1982a, 1982b; Friis et al. 1983), and their discontinuation may be helpful in up to 60 percent of patients (Jeste et al. 1988; Yassa 1988). An important exception is tardive dystonia, which may markedly improve with moderate to high doses (20 mg/day and higher) of anticholinergics such as trihexyphenidyl (Artane) (Burke et al. 1982; Fahn 1983).

Anticholinergics have been also hypothesized to predispose patients to develop TD (Klawans 1976), although this has been disputed (Yassa 1988). The issue may be that patients exhibiting acute EPS, who are more likely to be treated with anticholinergics, are more susceptible to TD than patients who do not exhibit acute EPS (Keepers and Casey 1991). Despite such theoretical considerations, for many patients anticholinergics remain useful for acute EPS.

Cholinergics. Just as anticholinergics theoretically should worsen TD, cholinergic agonists should improve it. Numerous studies conducted primarily in the 1970s with several acetylcholine precursors generally yielded disappointing results (Jeste and Wyatt 1979, 1982a). These agents include deanol, choline, and lecithin, a naturally occurring precursor of choline. One difficulty with interpreting these negative findings is the issue of how such drugs like deanol actually boost central cholinergic neurotransmission. Phystostigmine, a centrally acting cholinesterase inhibitor, has been used to investigate the pharmacology of TD, with mixed results (Lieberman et al. 1988a, 1988b; Yagi et al. 1989). An encouraging preliminary study using the cholinergic releasing agent meclofenoxate found improvement in 5 of 11 patients (Izumi et al. 1986). Tacrine (or THA) is a recently released cholinesterase inhibitor primarily used for the treatment of Alzheimer's disease. Although this agent is clearly effective in boosting central acetylcholine neurotransmission, we are not aware of studies of its use involving TD. While future experience may alter this surprising omission, cholinergic agents do not currently play a significant role in the treatment of TD.

GABA Agonists. A variety of experimental and commercially available GABA agonists have been used to treat TD, some with significant success. Jeste and Wyatt's review (1982a) described 19 studies totaling 204 patients, with 54 percent having greater than 50 percent improvement, making GABA agonists the most effective nonneuroleptic class of drugs reviewed. In a 1988 review of nine additional studies, the efficacy of GABA agonists fell to about 30 percent (Jeste et al. 1988). In contrast, a selective review of the effects of benzodiazepines by Thaker et
al. (1990) found that, in 15 reports involving a total of 158 patients, 83 percent of patients improved to some degree. Although side effects, such as sedation, ataxia, and addiction, may limit the use of many GABA agonists, they have an important role, at least as second-line agents, for the suppression of TD.

Experimental GABA agonists have produced mixed results in clinical studies. For example, 4,5,6,7-tetrahydrodiosoxazolo-(5,4-c)pyridine-3-ol, a GABA<sub>α</sub> agonist (Thaker et al. 1987), and gamma-vinyl-GABA, a GABA-transaminase inhibitor (Stahl et al. 1985), improved TD, but only to a minor degree. Muscimol, another GABA<sub>α</sub> agonist, produced a 45 percent reduction in seven patients (Tamminga et al. 1979). Several reports suggested that progabide, a mixed GABA<sub>α</sub> and GABA<sub>β</sub> agonist, may have significant therapeutic effects, but more studies are needed. Although the efficacy of these experimental agents supports a role for GABA in the pathophysiology of TD, they have limited clinical use.

The most-studied commercially available GABA agonists are valproate, diazepam, clonazepam, and baclofen. A 1979 review described three studies using valproate that had mixed results (Jeste and Wyatt 1979). Since then, three additional reports were not encouraging. In one, 3 of 6 patients improved (Friis et al. 1983), whereas in a second, none of 10 improved (Nasrallah et al. 1986). In the third, a well-controlled, double-blind study, 33 patients treated for 6 weeks with valproate were not significantly different from 29 patients treated with placebo (Fisk and York 1987). Diazepam, in contrast, has been more effective. Four studies before 1979 reported improvement in 26 of 29 patients on diazepam (Jeste and Wyatt 1979). More recently, in a single-blind study, diazepam was again effective in 11 of 20 patients (Singh et al. 1983). One drawback of diazepam is that it can be habit forming or cause sedation, depression, or, less commonly, impulsiveness and belligerence. Clonazepam is an effective alternative. Two open studies found markedly different results, with 42 of 42 patients benefiting in one (O’Flannagan 1975) but only 2 of 18 improving in the other (Sedman 1976). In a more recent, well-controlled, double-blind study by Thaker et al. (1990), suppression was observed in 26.5 percent of patients with choreoathetosis and 41.5 percent of patients with dystonia. Tolerance can develop to clonazepam’s therapeutic effects, but it may be overcome by a brief withdrawal period (Thaker et al. 1990). In a selective review of eight studies with baclofen, Glazer et al. (1985b) noted only two that showed significant results. In one study, 75 percent of 20 patients improved on 15 to 60 mg per day (Korsgaard 1976), whereas in the second study, TD ratings were reduced by 40 percent in 18 patients (Gerlach et al. 1978). Baclofen seems to act primarily on GABA<sub>β</sub> receptors, which may not be as important in TD.

In summary, among GABA agonists, benzodiazepines have been the most effective in clinical studies for suppressing TD. On average, 58 percent of patients in open studies and 43 percent in double-blind studies have improved (Gardos and Cole 1995). Thus, clonazepam and diazepam are important therapeutic options in treating TD. Valproate and baclofen are probably less effective and cannot be strongly endorsed. Newer agents, such as gabapentin, have not been employed in controlled studies.

Antioxidants. One of the more interesting new treatments for TD is vitamin E, an antioxidant and free radical scavenger. The use of this compound was originally motivated by the notion that neuroleptics produce toxic free radicals that can cause neuronal dysfunction or cell death. In table 2, eleven double-blind, placebo-controlled studies have examined the effects of vitamin E (Lohr and Caligiuri 1996). Of these, three reported no evidence of a therapeutic effect (Schmidt et al. 1991; Shriqui et al. 1992; Lam et al. 1994). These negative studies were either brief (2 weeks), included older patients, or studied patients with a relatively long duration of TD. In contrast, the other eight studies found some evidence of reduced TD severity with doses ranging from 1,200 to 1,600 IU for 4 to 12 weeks. Vitamin E’s effects have been most pronounced in patients with relatively recent onset (e.g., within 5 years) (Egan et al. 1992; Adler et al. 1993; Lohr and Caligiuri 1996). Overall, improvement in positive studies has ranged from 18.5 to 43 percent. In addition, several open trials or case reports have also found evidence for vitamin E’s therapeutic effects in TD or tardive dystonia (Spivak et al. 1992; Peet et al. 1993; Coupland and Nutt 1995). An ongoing large, multicenter study funded by the Department of Veterans Affairs may help clarify issues about therapeutic efficacy and subpopulations that respond favorably.

Despite the positive data regarding vitamin E, several caveats are indicated. First, a therapeutic effect of vitamin E does not necessarily validate the free-radical hypothesis of TD. Vitamin E may have other neurobiological effects, such as reducing D<sub>2</sub> supersensitivity (Gattaz et al. 1993) or altering monoamine metabolism (Jackson-Lewis et al. 1991). Furthermore, several other drugs with antioxidant properties (e.g., selegiline and coenzyme Q) have not been effective in TD. Finally, in most cases, the effects of vitamin E are fairly minor. Thus, although vitamin E could be a reasonable addition to the therapeutic armamentarium, its beneficial effects seem to be limited. Case reports have suggested an association between vitamin E and thrombophlebitis in the elderly (Roberts 1981), but
Table 2. Studies of the effect of vitamin E on tardive dyskinesia (TD)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Maximum dose</th>
<th>Design</th>
<th>Duration of TD</th>
<th>Number of patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lohr et al. (1988)</td>
<td>1,200 IU</td>
<td>Double-blind, crossover</td>
<td>2.6 ± 1.9 year</td>
<td>15</td>
<td>43% improvement</td>
</tr>
<tr>
<td>Elkashef et al. (1990)</td>
<td>1,200 IU (4 weeks)</td>
<td>Double-blind, crossover</td>
<td>3.8 ± 2.8 years</td>
<td>8</td>
<td>27% improvement</td>
</tr>
<tr>
<td>Schmidt et al. (1991)</td>
<td>1,200 mg (2 weeks)</td>
<td>Double-blind, crossover</td>
<td>10 patients &gt; 1 yr; 9 patients &lt; 1 yr</td>
<td>19</td>
<td>No overall effect</td>
</tr>
<tr>
<td>Egan et al. (1992)</td>
<td>1,600 IU (6 weeks)</td>
<td>Double-blind, crossover</td>
<td>5.9 ± 4.8 years</td>
<td>18</td>
<td>No overall effect; 9 patients with TD ≤ 5 years showed 18.5% improvement</td>
</tr>
<tr>
<td>Junker et al. (1992)</td>
<td>1,200 mg</td>
<td>Double-blind, crossover</td>
<td>Not significant</td>
<td>16</td>
<td>Significant improvement in patients over age 40</td>
</tr>
<tr>
<td>Shriqui et al. (1992)</td>
<td>1,200 IU (6 weeks)</td>
<td>Double-blind, crossover</td>
<td>&quot;Long duration&quot;</td>
<td>27</td>
<td>No effect</td>
</tr>
<tr>
<td>Adler et al. (1993)</td>
<td>1,600 IU (8–12 weeks)</td>
<td>Double-blind, parallel</td>
<td>9 patients &gt; 5 years; 4 patients &lt; 5 years</td>
<td>28</td>
<td>32% improvement on vitamin E; patients with TD &lt; 5 years did better (52% vs. 27%)</td>
</tr>
<tr>
<td>Aktar et al. (1993)</td>
<td>1,200 mg (4 weeks)</td>
<td>Double-blind, parallel</td>
<td>6.5 years</td>
<td>32</td>
<td>Greater improvement in patients on vitamin E (20%)</td>
</tr>
<tr>
<td>Dabiri et al. (1994)</td>
<td>1,200 IU (12 weeks)</td>
<td>Double-blind, parallel</td>
<td>14 weeks</td>
<td>11</td>
<td>36% improvement</td>
</tr>
<tr>
<td>Lam et al. (1994)</td>
<td>1,200 IU (4 weeks)</td>
<td>Double-blind, crossover</td>
<td>Not available</td>
<td>12</td>
<td>No difference; older patients (mean age 61.8 years); long duration of illness (&gt; 20 years)</td>
</tr>
</tbody>
</table>

Lohr and Caligiuri (1996) | 1,600 IU (2 months) | Double-blind, parallel | 11 months           | 35                 | 24% improvement                               |

This or other serious side effects have not been found in well-controlled studies. Generally, vitamin E is safe, producing few side effects. Rarely, patients report abdominal pain, headaches, muscle cramps, nausea, or fatigue. Vitamin E may elevate triglycerides and cholesterol and decrease thyroid indices, although it has not been reported to cause hypothyroidism. These abnormalities and symptoms all disappear after its discontinuation. Vitamin E may also interact with coumadin to prolong bleeding time. Additional research is needed to establish the therapeutic efficacy of vitamin E.

Calcium Channel Blockers. Observations that calcium channel blockers may help alleviate TD symptoms have been published. Suppressive efficacy is most convincing for nifedipine. Two open, one single-blind, and one double-blind study all found significant improvement with nifedipine. Data on verapamil are more limited; three case reports (Barrow and Childs 1986; Buck and Harvey 1988; Abad and Ovsiew 1993) and one single-blind, placebo-controlled study of nine patients (Reiter et al. 1989) found that verapamil suppressed moderate to severe TD. Case reports suggested that diltiazem may also have at least a temporary suppressive effect (Ross et al. 1987; Falk et al. 1988). Similarly, an acute, single-dose, double-blind challenge study concluded that diltiazem suppressed TD (Leys et al. 1988). In contrast, in a 3-week double-blind crossover study, diltiazem was no different from placebo (Loonen et al. 1992).
Table 3. Studies of the effect of calcium channel blockers on tardive dyskinesia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Design</th>
<th>Duration</th>
<th>Maximum dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kushnir and Ratner (1989)</td>
<td>Nifedipine</td>
<td>Open</td>
<td>1–8 months</td>
<td>20–80 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Duncan et al. (1990)</td>
<td>Nifedipine</td>
<td>Single-blind</td>
<td>7–14 days</td>
<td>60 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Stedman et al. (1991)</td>
<td>Nifedipine</td>
<td>Open</td>
<td>6 weeks</td>
<td>60 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Suddath et al. (1991)</td>
<td>Nifedipine</td>
<td>Double-blind, crossover</td>
<td>8 weeks</td>
<td>90 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Barrow and Childs (1986)</td>
<td>Verapamil</td>
<td>Case report</td>
<td>Unspecified</td>
<td>320 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Buck and Harvey (1988)</td>
<td>Verapamil</td>
<td>Case report</td>
<td>6 months</td>
<td>320 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Reiter et al. (1989)</td>
<td>Verapamil</td>
<td>Single-blind</td>
<td>2–5 days</td>
<td>160–320 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Abad and Ovsiew (1993)</td>
<td>Verapamil</td>
<td>Case report</td>
<td>1 week and &gt; 1 month</td>
<td>1 week: 240 mg/day; &gt;1 month: 360 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Ross et al. (1987)</td>
<td>Diltiazem</td>
<td>Case report</td>
<td>Few hours to 3 weeks</td>
<td>120–240 mg/day</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Falk et al. (1988)</td>
<td>Diltiazem</td>
<td>Case report</td>
<td>25 weeks</td>
<td>240 mg/day</td>
<td>Temporary improvement</td>
</tr>
<tr>
<td>Leys et al. (1988)</td>
<td>Diltiazem</td>
<td>Single-dose, double-blind, placebo-controlled</td>
<td>180 minutes</td>
<td>60 mg</td>
<td>Temporary improvement up to 90 minutes</td>
</tr>
<tr>
<td>Adler et al. (1988)</td>
<td>Diltiazem</td>
<td>Single-blind</td>
<td>2–12 days</td>
<td>240 mg/day</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Loonen et al. (1992)</td>
<td>Diltiazem</td>
<td>Randomized, double-blind, crossover</td>
<td>3 weeks</td>
<td>240 mg/day</td>
<td>No significant effect</td>
</tr>
</tbody>
</table>

Although the paucity of controlled, double-blind studies of calcium channel blockers limits conclusions about their efficacy, several trends emerge from prior reports. First, of the three, nifedipine may be the most effective (Kushnir and Ratner 1989; Duncan et al. 1990; Stedman et al. 1991). Second, regardless of the calcium channel blocker used, there seems to be a dose-related response (Adler et al. 1988; Kushnir and Ratner 1989; Reiter et al. 1989; Stedman et al. 1991). Third, older rather than younger patients may respond better to nifedipine (Buck and Harvey 1988; Kushnir and Ratner 1989).

Several mechanisms could be involved in the action of calcium channel blockers. It may be due to trivial pharmacokinetic effects, as nifedipine has been shown to increase plasma neuroleptic activity (Stedman et al. 1991). Alternatively, these drugs may exert therapeutic effects by their actions on dopamine neurotransmission. In animals, calcium channel antagonists have been reported to block postsynaptic D2 receptors and inhibit presynaptic dopaminergic activity (Mena et al. 1995). Single photon emission computed tomography studies show that calcium channel blockers reduce [123]iodobenzamide (a D2 ligand) binding to D2 receptors in the striatum, suggesting a weak antidopaminergic effect (Brucke et al. 1995). Finally, calcium channel blockers exert several indirect effects (Sabria et al. 1995), such as reducing noradrenergic activity, that could be related to the apparent decrease in TD severity. Well-controlled clinical studies and more data on the neurochemical effects are needed, but the data to date suggest that these agents may be worth considering for patients requiring TD suppression.

Serotonin. Preclinical studies have shown that serotonin modulates striatal dopamine release and could theoretically influence dyskinetic movements (Seibyl et al. 1989). There is increasing evidence that serotonergic agents may affect TD in humans, although their efficacy as suppressive agents is not clear. For example, buspirone, a serotonin 5-HT1A partial agonist, has been observed to suppress TD (Neppe 1989) and levodopa-induced dyskinesias (Kleedorfer et al. 1991). Subsequent reports, however, raise doubts about the utility of buspirone as a robust suppressive agent. Of two open trials, one found that TD improved in eight patients (Moss et al. 1993), while in the
second, if anything, buspirone worsened TD in seven patients (Brody et al. 1990). In a third open trial of 19 patients treated for 6 weeks, a nonsignificant 25 percent reduction in TD severity was observed; haloperidol levels, however, were significantly increased by 26 percent (Goff et al. 1991). Paradoxically, buspirone has also been reported to induce akathisia (Newton et al. 1986), dystonia (Boylan 1990), and oral dyskinesia (Strauss 1988). Buspirone’s disparate effects could be attributed to neurotransmitter systems other than serotonin; it is weakly antidopaminergic with mixed D2 agonist/antagonist properties, and it reverses neuroleptic-induced D2 supersensitivity in rats (McMillan 1985). It is also a sigma receptor antagonist. Based on these few reports, routine use of buspirone for TD suppression cannot be recommended. In patients who have failed other modalities, however, it could be considered.

Serotonin re-uptake inhibitors (SRIs) are a second class of serotoninergic medications that sometimes seem to affect hyperkinetic disorders. Preclinical studies show that SRIs reduce dopamine synthesis in a variety of brain areas, including the striatum (Baldessarini and Marsh 1990). In monkeys, SRIs inhibit amphetamine-induced repetitive movements and worsen neuroleptic-induced Parkinsonism (Korsgaard et al. 1984). Furthermore, in humans, SRIs have been noted to exacerbate Parkinsonian symptoms (Bouchard et al. 1989). Theoretically, one might expect SRIs to improve symptoms of TD. Surprisingly, these medications seem to induce “oral hyperkinesias” in monkeys (Korsgaard et al. 1984), although it is difficult to know the relationship between these movements and TD. Case reports have suggested that SRIs might rarely produce TD in humans as well (Budman and Bruun 1991; Stein 1991; Arya and Szabadi 1993). Finally, unpublished observations by Egan and Daniel in 1991 of a double-blind, placebo-controlled trial of fluvoxamine in patients with TD have not been impressive. These limited observations, although supporting a role for serotonin in movement disorders, do not indicate a prominent role for SRIs as suppressive medications.

If SRIs fail to improve TD, one might try the opposite strategy by using a serotonin antagonist. Two such studies have noted some improvement with cyproheptadine (Goldman 1976; Kurata et al. 1977); a third found no effect (Gardos and Cole 1978). In general, interventions using the serotonin system have not been rewarding (but see earlier discussion of clozapine).

Botulinum Toxin. Advances in treating other movement disorders are often put to use to treat TD. This strategy has been particularly successful with the recent introduction of botulinum toxin to treat tardive dystonia. Botulinum toxin (type A) blocks acetylcholine release at the neuromuscular junction, producing a chemical denervation. The resulting focal muscle paralysis persists for up to 3 or 4 months (Hughes 1994). Botulinum toxin injections have been used to treat blepharospasm, laryngeal dystonia, hemifacial spasm, and torticollis. Patients responsive to botulinum injections may also do well with a newly described surgical procedure involving selective peripheral denervation of the involved musculature (Braun and Richter 1994).

Miscellaneous Therapeutic Agents. A variety of other drugs and neurotransmitter systems have been implicated in the physiology of dyskinetic movements and could theoretically play a role in the suppression of TD. However, many potential therapeutic agents are described only in case reports, small series, animal studies, or unblinded trials, making conclusions problematic. One particularly interesting approach has been to use ceruletide, a CCK analog. CCK is a neuropeptide coexpressed in dopaminergic neurons and seems to function as a neuromodulator in the striatum. It purportedly exhibits neurolepticlike effects on dopamine receptors, metabolism, and behavior. Ceruletide itself seems to inhibit some of the behavioral effects of amphetamine, reduces striatal dopamine metabolism (Matsumoto et al. 1984), and blocks dyskinetic mouth movements in an animal model of TD (Stoessel et al. 1989). Ceruletide has been found to be beneficial in one study of seven patients (Nishikawa et al. 1988) that included several patients with severe TD. In a much larger (n = 77) well-controlled, parallel study, long-lasting moderate to marked improvement was seen in 42.5 percent of patients receiving the active drug compared with 9.1 percent improvement in the placebo group (Kojima et al. 1992). Although seemingly promising, one difficulty with interpreting these data is that ceruletide is a peptide that, administered peripherally, may not get into the brain in appreciable amounts (Passaro et al. 1982). On the other hand, peripherally administered ceruletide has been shown to have central effects on dopamine neuronal activity (Skirboll et al. 1981) and on metabolism in rats (Matsumoto et al. 1984).

Lithium is frequently mentioned in conjunction with TD, although limited data on its effects are available. Lithium seems to prevent dopamine supersensitivity in rats when used with neuroleptics (Klawans et al. 1977). In humans, epidemiological data suggest that when lithium is added to neuroleptic treatment, the incidence of TD is reduced (Kane 1995). In contrast, lithium has not been successful as a suppressive agent (Gardos and Cole 1995).

Anecdotes of successful treatments with a panoply of other, often unusual, interventions abound. A very low
dose of prednisolone, for example, surprisingly produced a complete remission in two patients with severe TD (Benecke et al. 1988). Estrogen replacement produced marginal improvement in postmenopausal women (Glazer et al. 1985c). The use of dentures and the correction of other dental problems have been observed to markedly reduce oral TD. Canes, braces, or biofeedback may offer limited benefit in severe cases. Electroconvulsive therapy (ECT) has had variable effects, with a few patients reportedly showing dramatic improvement (Hay et al. 1990).

Other Experimental Approaches: Striatonigral Inhibition. Theoretically, attempts to reduce the D$_1$-mediated striatonigral pathway should reduce hyperkinetic movements by increasing GABAergic projections from the substantia nigra to the thalamus. This increase, in turn, would decrease thalamocortical activity and ultimately motor activity (see figure 1). What is not clear, however, is how to reduce striatonigral activity. One strategy from animal behavioral work is to use D$_1$ antagonists. Several investigators have looked at the role of D$_1$ antagonists in movement disorders and dyskinesia (e.g., see Boyce et al. 1990). Although no D$_1$ antagonist is currently available for clinical use in the United States and controlled studies are few, at least one trial of a mixed D$_1$ and D$_2$ antagonist elicited no better results than a more pure D$_2$ antagonist in suppressing TD (Lublin et al. 1991). Furthermore, despite preclinical data from rats and primate studies (e.g., Boyce et al. 1990; Nutt 1990) suggesting a role for D$_1$ receptors in L-dopa-induced dyskinesias, at least one study in humans did not support this notion (Braun et al. 1987).

A second approach is to reduce neurotransmission of the colocalized neuropeptides, in this case dynorphin and substance P. In humans, several case reports suggest that intravenous naloxone, a relatively nonspecific opioid receptor antagonist, reduces L-dopa-induced dyskinesias (Sandyk and Snider 1986) and TD (Blum et al. 1984; see also Lindenmayer et al. 1987). In contrast, naltrexone failed to improve L-dopa-induced dyskinesias in Parkinsonian patients (Rascol et al. 1994). Such case reports are suggestive, but more data are needed before the clinical utility or feasibility of striatonigral inhibition is clear.

Summary

Despite the promise of a new generation of neuroleptics with reduced EPS, TD remains a vexing clinical issue. Prevention is still an important approach; clinicians must consider whether other treatments are more effective than neuroleptics. This is particularly true for high-risk groups, such as the elderly and patients with brain damage or diabetes. Switching to an atypical agent is becoming a common first step, although the efficacy of this approach is unclear (figure 1). If typical agents are needed, the dose should be tapered to the lowest possible effective level. Adding vitamin E to typical agents may also be worthwhile. For many patients, however, neuroleptics are unavoidable for the treatment of chronic psychosis.

Fortunately, the incidence of severe TD is relatively low. When TD does cause distress or disfigurement or affects health or function adversely, suppressive agents may be needed. Preliminary data suggest that atypical neuroleptics may be useful in such cases, although more data are needed. At present, many consider them to be a first-line treatment for suppression. Clozapine is often considered a second-line agent due to the complications associated with its use. As a third step, suppression can be tried using drugs that are fairly safe and have at least some moderate record of success, including vitamin E, calcium channel blockers, and adrenergic antagonists such as clonidine. Medications that have more side effects or risks but are probably more effective in the short term include benzodiazepines and dopamine-depleting agents. These fourth-line agents are sometimes used first by movement disorder specialists when a rapid response is needed. A fifth approach is to increase the dose of typical neuroleptics in an attempt to achieve temporary suppression, followed by a gradual reduction. This strategy does not always produce suppression and runs the theoretical risk of producing long-term worsening. More experimental agents can be tried when other attempts fail: agents such as cholinergic agonists (e.g., tacrine), dopamine agonists (e.g., amantadine), buspirone, GABA agonists (e.g., gabapentin), an SRI, cyproheptadine, opioid antagonists, estrogen, steroids, or even ECT. When dystonia is a prominent feature, specific therapeutic agents include anticholinergics and, if sufficiently localized, botulinum toxin injections.

The use of suppressive agents is typically a highly individualized process: one approach is outlined in table 4. However, this approach should be considered only a proposal based on our experience. It has not been evaluated prospectively, and other experts may have differing strategies. Furthermore, it may not be the best approach in all circumstances. Many patients will have special needs indicating that third- or fourth-line agents should be tried first. Often, a trial of several drugs is needed before an effective one is found. In our experience, success can sometimes be achieved by patiently trying several agents, one after another. This approach requires not only familiarity with the many strategies already described, but also a strong working alliance with the patient.

TD will remain a major public health issue in psychiatry at least for the near future. With better understanding
Table 4. Possible treatment approach to tardive dyskinesia (TD)

A. For mild to moderate TD that does not require suppression
   1. Reevaluate need for antipsychotics; use other classes of medications when possible.
   2. If an antipsychotic is required, switch to a putative atypical antipsychotic (olanzapine, risperidone, seroquel, sertindole).
   3. If typical antipsychotics must be used, taper to lowest possible levels and follow for improvement in TD.
   4. Add vitamin E to neuroleptic if TD persists. If no improvement in 3 months, discontinue vitamin E.
   5. If symptoms progress, consider clozapine.

B. For suppression of moderate to severe TD
   1. Switch to a putative atypical agent; begin with olanzapine. Increase dose until TD is suppressed or maximum dose is reached. Gradually taper to lowest effective dose that suppresses psychosis and TD. Consider other putative atypical agents (risperidone, seroquel, sertindole) if no response is seen to the first.
   2. Switch to clozapine.

   If steps 1 and 2 fail, try adding the following medications, one at a time, to whatever antipsychotic (typical or atypical) is being used. For careful evaluation of response, antipsychotic dose should remain stable. If no response is seen after an adequate trial, one suppressive agent should be discontinued before trying the next.
   3. Add vitamin E to antipsychotic.
   4. Add calcium channel blocker (e.g., nifedipine) to antipsychotic.
   5. Add noradrenergic antagonist (e.g., clonidine) to antipsychotic.
   6. Add benzodiazepine (e.g., clonazepam) to antipsychotic.¹²
   7. Add dopamine depleter (e.g., reserpine) to antipsychotic.¹
   8. Increase dose of typical antipsychotic until TD is suppressed, then very gradually taper dose.³
   9. Try other possible suppressive agents³: cholinergic agonists (e.g., tacrine), dopamine agonists (e.g., amantadine), buspirone, GABA agonist (e.g., gabapentin), an SRI, cyproheptadine, opioid antagonists, estrogen, steroids, ECT.

C. For suppression of tardive dystonia
   1. Add anticholinergics (increase gradually to "high" doses).
   2. Add vitamin E.
   3. Add clonazepam.
   4. Go to steps 1, 2, 4, 7, and 8 in part B.
   5. Consider botulinum injections.

Note.—GABA = gamma-amino- butyric acid; SRI = serotonin re-uptake inhibitor; ECT = electroconvulsive therapy.

¹May be tried first, particularly if rapid relief is needed.
²Be cautious when adding to clozapine due to case reports of respiratory depression.
³These therapies should be considered experimental. Although the other therapies have some support for their efficacy in well-controlled studies, in general these have less support. Clear benefit and risk data may not be available.

of the mechanisms of action of atypical neuroleptics and the physiology of the basal ganglia, continued improvements can be anticipated. As the new millennium dawns, perhaps these advances will leave TD as a footnote in the history of medicine.

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