Brain Injury and Mental Retardation: Psychopharmacology and Neuropsychiatry

C. THOMAS GUALTIERI, M.D.
Medical Director
North Carolina Neuropsychiatry
Chapel Hill, North Carolina

2002

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

23

Tardive Dyskinesia and Tardive Akathisia

SUMMARY

Do the tardive syndromes deserve a chapter of their own? Are they not just relics of the bad old days when neuroleptics were used indiscriminately in nursing homes and institutions for the mentally retarded? The epidemic of tardive diskinesia a generation ago was a blight on the history of psychopharmacology, but what pertinence does it have today?

It is appropriate to reflect on historical matters, and the history of tardive dyskinesia (TD) illuminates two points that I have tried to make on several occasions: first, psychotropic drugs are safe and easy to use but can be dangerous and require careful medical follow-up. Second, the long-term effects of psychotropic drugs deserve careful study because toxicity may not be apparent until years have passed. Whether a drug is prone to long-term side effects is never evident in the short-term studies needed to win drug approval.

This chapter is more than an exercise in historical reflection. The neuroleptics are still prescribed, and even the atypical antipsychotics can occasionally cause tardive syndromes. Therefore, several clinical issues such as the vexing problem of tardive akathisia (TDAK), the little-appreciated problem of tardive pain, and the possibility of a behavioral analog of TD are discussed. This last issue is another opportunity to consider the neuropsychology of the basal ganglia.

The epidemiology of the tardive syndromes indicates that a number of treatment-related and patient-related variables predispose to the condition. Patients with neuropsychiatric disorders in general and mentally retarded patients in particular appear to be more vulnerable to the neurotoxic effects of the old antipsychotic drugs. Malignant TD, conversely, is more common in patients with affective disorders.

When one considers the pathophysiology of TD, the problem of oxidant stress is raised again. The evidence base may be shallow, but the theory is compelling. For that reason, one may be inclined to recommend antioxidant supplements to patients who are on long-term antipsychotic drug treatment. Because several other psychotropics are also capable of generating a free-radical burden, it is reasonable to propose antioxidants for patients in general who require long-term drug treatment. Will this issue ever be addressed in controlled studies? As previously stated, long-term studies of drug toxicity, or the prevention of it, are rarely, if ever, done.

NEUROLEPTIC DRUGS

The neuroleptic drugs were so-called by Delay (1955) because he believed that their antipsychotic action was necessarily correlated with a tendency to produce extrapyramidal side effects (EPS). The term is now reserved for the old antipsychotic drugs; the new atypicals are equally effective with a low propensity for EPS. They are much less likely to cause the most serious EPS, TD. For this and other reasons, they have won most of the antipsychotic market, and the problem of

TD has receded accordingly, but it is not extinct, by any means, and in some parts of the world, it continues to be a vexing problem. It merits our attention as much for its historical importance as for its clinical salience.

My familiarity with the issue stems from a series of studies done in the late 1970s that demonstrated TD and related disorders had achieved alarming dimensions in children and mentally retarded people. In those unenlightened days, it was not uncommon to prescribe neuroleptics for children with relatively minor behavioral problems such as attention deficit/hyperactivity disorder. As for mentally retarded people, if they were living in institutions, most of them were taking neuroleptics, usually at high doses and for long periods of time. In 1968, the national rate of neuroleptic prescription for retarded people was approximately 50% (1) and approximately the same in 1978 (2). It fell to approximately 30% in 1985 (3). It is now less than 20%. This reflected patterns of psychiatric care in the general population in which neuroleptics were routinely used for anxiety disorders and affective disorders during the 1960s and 1970s, and then their use declined.

The first descriptions of TD date from the mid-1950s (4,5), and complaints that the side effect was potentially dangerous came soon after (6), but little attention was paid. The problem was that continued neuroleptic treatment tends to obscure the characteristic dyskinetic movements and patients with schizophrenia are prone to abnormal grimaces and posturing as part of the condition. Institutional psychiatrists were oppressed by the job of day-to-day management of many desperate patients. They were much more impressed by the therapeutic utility of the new drugs, and justifiably so, than they were by what seemed to be at the time a minor side effect. Looking back, we can afford to shake our heads because we have learned from their mistakes.

The first report of TD in mentally retarded people on long-term neuroleptic treatment was published in 1975 (7), and there were several subsequent reports over the next few years (8,9). This was no less than 20 years after the disorder was first described by European psychiatrists, but it was contemporary with the development of serious concern about TD among American psychiatrists.

It was not until the publication of the APA Task Force Report in 1979 that medical concern was directed to the problem of TD, even for the mentally ill. Five years later, the problem gained widespread publicity, as lawsuits began to multiply, and even the public media began to address the issue. TD became a major issue for physicians who treated chronic mentally ill patients, administrators and makers of public policy, and research scientists in psychiatry and neuropharmacology. The development of an antipsychotic drug that did not cause TD became a prime focus of psychopharmacologic research.

It is possible that recognition of TD as a serious, potentially debilitating side effect of neuroleptic treatment was responsible for the dramatic decrease in neuroleptic prescription for retarded people that occurred during the 1980s (10), although other factors also played a role (e.g., the community movement, widespread skepticism of the medical model, renewed emphasis on behavioral and developmental programming, new attention to alternative pharmacologic treatments). Nevertheless, the problem of TD was a red flag around which adherents rallied to reduce the unnecessary prescription of neuroleptic drugs and to improve programmatic treatments for retarded people. It was certainly the specter of TD that led general psychiatrists to be more judicious in their use of neuroleptic drugs and child psychiatrists to abjure their use almost entirely.

TD began to be perceived as a hazard to the public health. It was widely held that neuroleptics were relatively contraindicated in mentally retarded people, children, patients with brain injury, and the elderly. Regulations at the state and federal levels reinforced those clinical beliefs. When neuroleptic prescription was considered for a patient who was not overtly schizophrenic, the treatment decision was made with great care. Written informed consent and formal TD monitoring systems came to be the standard of care. Drug withdrawal trials or gradual dose reductions were mandated at appropriate intervals to test for occult or covert TD and to determine whether continued drug treatment was necessary. It was generally accepted that any patient whose behavioral problems were so severe as to warrant neuroleptic prescription should also have a concomitant behavioral program.

Although this enlightened approach was associated with a substantial diminution in the problem of TD in special populations, even before the new antipsychotics were introduced, it was not without problems of its own. The judicious use of antipsychotic drugs was interpreted by some to mean nonuse. The pendulum was swinging too far in the other direction. This was especially true for the mentally retarded and nursing home elderly, for whom it was difficult for physicians to prescribe a neuroleptic for patients who needed it. Lawsuits, largely spurious, were filed against physicians who prescribed conventional neuroleptics, under any circumstances, if any side effect ensued at all. Many patients who might have benefited from a neuroleptic were thus deprived of a therapeutic opportunity.

Since the atypicals have been introduced, attitudes have relaxed considerably. The new drugs are much safer, monitoring requirements are less stringent, and regulatory bodies are less critical of their use. Consequently, the use of antipsychotic drugs in the mentally retarded, the elderly, children, and patients with brain injuries has rebounded. Ironically, the transfer of large numbers of retarded individuals from institutions into the community has been associated with a dramatic increase in antipsychotic prescription. This also reflects general psychiatric practice, in which the atypicals are increasingly used for severe anxiety disorders (e.g., posttraumatic stress disorder, obsessive-compulsive disorder) and treatment-refractory affective disorders.

Nevertheless, TD remains a problem, especially in mentally retarded people who may well be especially vulnerable to the side effect. Even atypical antipsychotic drugs may sometimes cause the disorder. Thus, TD remains a continuing problem, even in the face of convenient solutions. It is also a prototypical movement disorder, around which a number of interesting neuropsychiatric problems are concentrated.

It is appropriate to refer to the tardive syndromes because TD is only one of a number of related conditions associated with long-term antipsychotic treatment. In addition to TD, there is TDAK, tardive dystonia, tardive pain, tardive Tourette's syndrome, and a behavioral analog of TD that has been controversial, which will be discussed in this chapter.

SERIOUS SIDE EFFECTS OF NEUROLEPTIC DRUGS

Tardive Dyskinesia

Estimates of TD prevalence published in the psychiatric literature have varied a great deal, largely as a consequence of idiosyncrasies in measurement and definition. The average prevalence of TD based on 33 studies reported from 1970 to 1979 was 24% (11), but the true rate varies, depending on the clinical population: from 12% among outpatients in a Department of Veterans Affairs clinic to 13% in an acute psychiatric hospital to 36% in a state hospital to 67% among state hospital patients older than 65 years of age. The cumulative incidence of TD in patients with psychiatric disorders is said to be approximately 5% at 1 year, 10% at 2 years, 15% at 3 years, and 19% at 4 years (12). There is said to be a 40% cumulative rate of TD in adult patients with psychiatric disorders after 8 years of exposure to neuroleptic drugs (13). With every year of treatment, it would appear that the rate of TD increases by 5% until it reaches asymptote at approximately 67%. Does that mean that one-third of patients is immune to neuroleptic toxicity? Perhaps it does.

In fact, it is hard to be confident in the numbers generated in studies of patients who have not been withdrawn from neuroleptic drug treatment because maintenance neuroleptic treatment tends to mask the presence of the disorder. Therefore, any prevalence estimate will necessarily be influenced by the patient's medication status. A true prevalence rate can only be determined from the study of drug-free patients, and this is not done very often in studies of patients with psychiatric disorders. In one survey of patients who had no signs of TD as long as they were taking neuroleptics, new signs of TD emerged in no fewer than 34% when the neuroleptics were subsequently withdrawn (12).

The problem is illustrated by the changing prevalence of TD in mentally retarded populations. In a study by Paulson et al. (7), the prevalence was 20%, but most patients who were surveyed were still on neuroleptics. In two other surveys, conducted on the heels of medication withdrawal, the prevalence was much higher: persistent TD (34% to 45%) and transient withdrawal dyskinesia (29%) (9,14).

Epidemiologic studies of TD and related disorders are also complicated by the existence of spontaneous dyskinesias, i.e., choreic, athetoid, and tic-like movements that seem to occur quite naturally without medication in the elderly, patients with chronic schizophrenia, and mentally retarded individuals. There is a 4% rate of mild involuntary movements in healthy elderly volunteers (11), but a much higher rate, approaching 40%, in the elderly with dementia (15).

One cannot argue that the estimate of TD occurrence in people with mental retardation is inflated because they are given to a wide range of abnormal movements, even in the absence of neuroleptic treatment. The assessment of dyskinetic movements in people with severe to profound retardation may be problematic because they are prone to a number of abnormal movements and the patients may not cooperate with the examination procedure. Conversely, Kalachnik et al. (9) arrived at a true prevalence rate for TD by subtracting the basal rate of dyskinesia in drug-free controls.

In a unique prospective study of haloperidol treatment for children with autism, most of whom were mentally retarded, the incidence of TD after 6 to 30 months of follow-up was 25% (16). The dyskinesias that arose were transient, however, as one might expect in young patients treated with low doses of a neuroleptic for a relatively short period. Conversely,

the fact that an early form of TD arose in one-fourth of treated patients within the span of 30 months suggests, to me at least, that neuroleptics are relatively contraindicated in this group.

In the face of such extraordinary figures, one is compelled to warn patients on long-term neuroleptic treatment that the development of TD is a likely event. Conversely, it is also appropriate to assure patients that TD can be prevented by judicious use of neuroleptic drugs and by careful and knowledgeable medical supervision. It has been suggested that even patients with chronic psychotic disorders can be maintained on neuroleptic doses that are 10% to 20% of those in common use (17). After all, the highest rates of TD are found in public institutions for the mentally ill and mentally handicapped, where drugs have been used in lieu of programming and medical supervision is sometimes less than optimal. If neuroleptics are used in low-to-moderate doses, even for a sustained period, the level of risk is probably acceptable. If the novel antipsychotics are used, in preference to the conventional neuroleptics, whenever they are effective, the risk of TD is even lower, and the annual incidence is much lower than 5%.

The issue of TD prevalence, however, obscures a more important issue: the need to distinguish between the prevalence of severe and debilitating cases of TD and those that are relatively mild and persistent cases and those that will only last a few months or a year or two. Prevalence rates from 25% to 33% should ordinarily be cause for alarm. If only a few of those cases, however, are severe and persistent and most are mild or self-limiting, then the problem is manageable. If severe cases can be prevented by careful monitoring, then physicians will have the right to reassure patients and their families.

Conversely, if severe and persistent cases comprise a significant fraction of the population of patients with TD, then draconian measures will be required to reduce neuroleptic prescription. Most psychiatrists would say that severe cases are only a minority of patients with TD, and I have never argued with that contention. When the issue is put to the test, however, severe TD variants have been observed in more than one-fifth of all diagnosed TD cases (18).

Tardive Dyskinesia Variants

The typical case of TD is characterized by irregular choreoathetoid movements occurring predominantly in the buccal-lingual-masticatory musculature and distal extremities. It is the most common manifestation of the syndrome (93% of TD cases). Tardive dystonia is characterized by sustained contractions of skeletal musculature; it has been found to account for 26% of all TD cases referred to a movement disorder clinic. TDAK is estimated to comprise 18% of TD cases. Tardive Tourette's syndrome is characterized by motor and phonic tics (5% of cases) (18). Tardive pain syndrome is a curious phenomenon and is described below.

Extrapyramidal Reactions

TD is a late extrapyramidal syndrome associated with neuroleptic treatment, as distinguished from the early EPS. These, of course, are pseudoparkinsonism, acute dystonia, akathisia, akinesia (19), and aphonia (20). In fact, the term neuroleptic was coined because it was thought that the therapeutic action of antipsychotic drugs was necessarily correlated with their tendency to produce EPS. (Clozapine, risperidone, olanzapine, quetiapine, and ziprasidone should be called antipsychotics because they are less prone to produce EPS; they defy the correlation.)

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a devastating, sometimes fatal neuroleptic side effect arising early in treatment, especially with high-potency drugs. The symptoms are muscular ("lead-pipe") rigidity, mental state changes (e.g., delirium), and autonomic changes (e.g., hyperthermia, hypertension, tachycardia), accompanied by elevation of the whole blood cell count and serum creatine phosphokinase. If the disorder is not recognized promptly and proper treatment measures are not instituted immediately, the patient may die of renal failure. Treatment is neuroleptic withdrawal, fluid replacement, and dantrolene or dopamine agonists (e.g., bromocriptine). It is said that NMS occurs in 1% to 2% of neuroleptic-treated patients and that 10% to 20% of cases are fatal (21). That estimate is probably too high, but there is no denying that increased familiarity with this extraordinary syndrome leads to increased recognition.

Although NMS is most likely to occur early in treatment, it may arise at any point, even when the patient is on a stable maintenance dose (22). Risk factors include a state of psychomotor agitation before neuroleptic treatment, high doses of neuroleptics that are increased rapidly, and intramuscular administration (23). Other risk factors are the use of high-potency neuroleptics and patient-related variables, such as a dehydrated or physically exhausted state or a history of neuroleptic toxicity. It is incredible that a side effect so severe and presumably so common went unrecognized for so many years (24).

NMS is a major problem for nursing personnel because the keys to successful treatment are early recognition and a high index of suspicion. Any patient on neuroleptic treatment with rigidity and mental state changes should be reported to the attending physician immediately as a medical emergency, and neuroleptics should be withheld until an examination can be done and the appropriate laboratory tests can be done. Dealing with NMS requires special training for nurses who care for patients on neuroleptic treatment and careful monitoring by physicians who are familiar with the syndrome. NMS, more than any movement disorder, should limit the widepread use of neuroleptics. Neuroleptics are not routine treatments to be administered by primary care physicians with no special training in psychopharmacology.

The atypical antipsychotic drugs are much less likely to cause NMS.

Tardive Akathisia

Akathisia is a Greek word that means "not to sit still." (In fact, the Greek word is *kathisia*, which refers to the act of sitting, and akathisia is a neologism.) The word describes the subjective state of motor restlessness and dysphoria that occurs in many clinical conditions. It was first adopted by Haskovec (25) to refer to patients whose problems were hysterical in origin. Later, Bing (26) described akathisia in patients with postencephalitic parkinsonism. Since then, akathisia has been considered a disease of the basal ganglia (27).

Soon after the introduction of neuroleptic drugs, clinicians noted patients who had symptoms of restlessness and dysphoria (4,28,29). The term neuroleptic-induced akathisia (NIA) joined pseudoparkinsonism and dystonia in the trio of acute extrapyramidal reactions caused by neuroleptic drugs. The prevalence of NIA has been estimated at approximately 20%, although the figure may be as high as 45% (30).

Early reports of NIA also included descriptions of patients whose symptoms arose only after several years of neuroleptic treatment and co-occurred with symptoms of TD (6,28,31,32). In 1977, Simpson suggested that late-onset NIA was persistent, even after neuroleptic withdrawal, and that it was virtually untreatable. In 1983, Munetz and Cornes introduced the term TDAK: "an akathisia-like syndrome (characterized by) late onset, treatment resistance, and potential irreversibility despite discontinuance of neuroleptics." The overt symptoms of TDAK are indistinguishable from those of NIA, and the direct examination of the patient yields the same findings. The symptoms of patients with TDAK, of course, tend to increase when the neuroleptic dose is lowered, whereas the symptoms of patients with NIA tend to improve.

TDAK was further described in a series of clinical reports (33–37), and it was operationally defined in a systematic study by Barnes and Braude (30). The prevalence of TDAK was reported to be 18% in patients referred for evaluation at a TD clinic (18) and 6% to 14% in mentally retarded patients treated with neuroleptics (38,39).

TDAK is a relatively common and severe problem, causing distress to the patient and demanding a great deal of attention by physicians and direct care personnel. Because akathisia is a state of restless, dysphoric hyperactivity, it may also be the occasion of secondary behavioral problems, a "setting event" for the occurrence of difficult behaviors such as aggression (40) or self-injury (41). The emergence of what are referred to as target behaviors (e.g., disorganization, agitation, aggression, hyperactivity, self-injurious behavior) in the circumstances of neuroleptic withdrawal might represent the recurrence of a preneuroleptic psychiatric condition or alternatively the manifestation of TDAK. The diagnostic and therapeutic dilemma is daunting.

People with akathisia are miserable. They feel as if they were crawling out of their skin, and they have to pace constantly just to win a small degree of relief. They are irritable, unhappy, and emotionally unstable. They are so unhappy and find it so hard to understand what is happening to them that they may erupt in explosions of aggressive, destructive, or self-injurious behavior. They may be described as hyperactive, disorganized, or psychotic. In other words, they may develop, as a consequence of long-term neuroleptic treatment, persistent symptoms that are identical to the problem behaviors for which neuroleptics were originally prescribed.

Dysphoria, Anxiety, and Pain

Several other unpleasant subjective states may also occur in association with neuroleptic treatment, occurring as side effects of acute treatment, as tardive syndromes, occurring in association with better known EPS such as akathisia, or standing alone. One example is neuroleptic-induced dysphoria (without motor restlessness), especially with haloperidol, which can also cause anxiety and even overt panic attacks (42). Acutely treated patients may also complain of painful sensations (43). These are usually described as poorly localized, intermittent, aching sensations involving all four limbs symmetrically and sparing the head and ventral torso. Complaints of pain tend to be more frequent in patients who also have pseudoparkinsonism or

akathisia (44). Oral and genital pain have been described as a tardive syndrome, said to be an example of pure cognitive akathisia (45). Analogously, patients with postencephalitic or idiopathic parkinsonism experience distressing and ill-defined sensations, commonly referred to as primary sensory symptoms (46). The lesson is that "all the side effects of neuroleptics have already been described between 1920 and 1935 as a sequela of (von Economo) encephalitis" (47).

The sensation of pain as an EPS of neuroleptic treatment illuminates the role of opioid drugs (codeine, propoxyphene, nitrous oxide), which seem to be effective for NIA but not for TDAK. This may have to do with the presence of opiate receptors on presynaptic dopaminergic neurons and on neurons that carry the postsynaptic dopamine receptors (48). The striatum contains high concentrations of both dopamine and opioid receptors, and the number of opioid binding sites is reduced after denervation of dopaminergic neurons (49).

Restless Legs Syndrome

Patients with restless legs syndrome also improve when they are treated with low doses of opiates (48). The syndrome was first described by Ekbom who described restless movements of the legs arising spontaneously in some people especially in the elderly and especially at night (50). The condition is autosomal dominant, but it may also be manifest as a variant of NIA or TDAK.

The symptoms of restless legs syndrome include painful paresthesias of the legs, especially in the calves, occurring at rest. The patient finds relief only by moving his or her lower extremities. Because the problem is most intense at night, the patient experiences severe insomnia and all the secondary problems that arise from it. The paresthesias are often described as burning or a deep ache.

It is interesting that virtually all the treatments recommended for NIA and TDAK have also been useful (on occasion) for cases of restless legs syndrome, most notably, carbamazepine, vitamin E, folate, beta-blockers, benzodiazepines, clonidine, and tryptophan (51). The opiates, then, are hardly unique. None of these treatments, however, is uniformly effective. Recently, gabapentin has come to be one of the most successful treatments for restless legs syndrome. It may also be useful for NIA and TDAK.

Treatment

Akathisia, acute or tardive, is often treated with beta-blockers (52–54) or clonidine (54,55). The frequent success of such drugs in the treatment of akathisia suggests an effect of chronic neuroleptic blockade on noradrenergic neurotransmission. Neuroleptics are known to increase cerebrospinal fluid and brain levels of norepinephrine; the mechanism may be presynaptic dopamine blockade, a neuroleptic effect that has been determined to increase norepinephrine release, at least in laboratory animals (56).

Lorazepam or clonazepam may also be used, with only occasional success; benzodiazepines may even be used in conjunction with beta-blockers. There have been reports of successful treatment with amantadine (57), which I have been unable to confirm, and with buspirone (58), which we have. Gabapentin and tiagabine are other alternatives.

As in severe cases of TD, the only effective treatment may well be reinstitution of neuroleptics. In the past, atypical neuroleptics such as molindone or thioridazine were recommended, but not any more. They never worked very well, and the pharmacologic treatment of TDAK was for a very long time as unsuccessful as Paulson et al. (7) suggested in 1975. Since clozapine, however, the clinical picture has changed dramatically, and since the other atypical antipsychotics were introduced, it has improved even more. Today, one recommends the introduction of an atypical antipsychotic in the usual doses and then a very gradual withdrawal.

Tardive Akathisia in the Mentally Handicapped

Because neuroleptic drugs have been prescribed quite often for mentally retarded adults (1,2), there has been a strong movement in recent years to reduce unnecessary or excessive neuroleptic drug use. In many clinical facilities, however, the reduction of neuroleptic prescription has led to the unmasking of neuroleptic side effects such as TD and TDAK (39). In 1993, I reported the results of a longitudinal study of TDAK and its behavioral concomitants (59). The study was undertaken at a large residential facility for the mentally handicapped. Of a population of 356, no fewer than 180 residents had been treated long term with neuroleptic drugs. TDAK was diagnosed in 25 patients (14% of the population at risk).

Three years after the patients with TDAK were first identified, I found that 10 patients (40%) succeeded in remaining neuroleptic free. Their clinical status was unstable at first, but it gradually improved. Symptoms of akathisia and target behaviors had abated, and there was no need for continued neuroleptic treatment. Fifteen patients (60%) had to remain on neuroleptics, despite the TDAK, because of

severe behavioral problems that could not be controlled by alternative interventions.

One year later, the original 10 patients remained stable and neuroleptic free. The other 15 continued on neuroleptics, albeit on comparatively lower doses. With selective concomitant treatment (e.g., beta-blockers, benzodiazepines) or substitution of novel antipsychotics, they also stabilized, with no further progression of TDAK (59).

It was encouraging that a substantial number of retarded people with TDAK could be successfully withdrawn from neuroleptic drugs and that their symptoms gradually abated. It was discouraging that three-fifths of the group could never be withdrawn from the offending agents, but at least TDAK was not progressive as long as their management was judicious.

The problem of TDAK generates difficult clinical situations that seem to be unique to patients who are mentally retarded and patients with brain injury. Many are patients who never respond very well to neuroleptics to begin with but who grow much worse after they are withdrawn. Their behavior deteriorated sharply after the neuroleptic dose is lowered beyond a certain point, but they remain difficult and hard to manage even after the dose is returned to what had earlier been a therapeutic level. Their TD symptoms are accompanied by high levels of hyperactivity and restlessness; they are extremely dysphoric when neuroleptics are withdrawn and seem to be manageable with any pharmacologic agent. The problem is usually TDAK, and the only reasonable solution is to switch to an atypical antipsychotic drug and then gradually lower the dose.

A Behavioral Analog of Tardive Dyskinesia

For a long time, my colleagues and I were preoccupied with the possibility of a behavioral analog of TD (60). It was an important question that seemed to beg solution. If neuroleptics were prescribed for people who were cognitively impaired and behaviorally unstable to begin with, how could one know whether cognitive impairment or behavioral instability, emerging after neuroleptic withdrawal, was in fact the result of drug treatment.

In 1979, Davis and Rosenberg raised the question of a limbic equivalent of TD, that is, behavioral toxicity as a consequence of neuroleptic-induced changes in mesolimbic dopamine receptors. In the same year, investigators reported more intellectual deterioration in neuroleptic-treated patients with TD than in non-TD controls (61). Two questions were then posed: Could neuroleptic treatment lead to behavioral deterioration, and could neuroleptics cause dementia? In other words, whether higher cortical functions might be damaged, much in the same way that motor control systems were damaged. You can imagine the excitement and dismay this question raised. It was a difficult point to prove one way or the other.

Cases of supersensitivity psychosis were described by Chouinard and Jones (62) (who coined the term), Sale and Kristall (63), and Caine et al. (64). These were neuroleptic-treated patients who developed a dramatic, rapid-onset psychosis as soon as neuroleptics were withdrawn. The psychosis was held to be a consequence of neuroleptic treatment, not simply the reemergence of a preexisting disorder. The psychiatric community has not found this contention particularly believable (12), although it would be imprudent to dismiss it.

There is near unanimity, however, on the issue of dementia because virtually every study that has researched the issue has found an association between TD and signs of dementia or so-called negative symptoms of schizophrenia. When patients with TD are compared with similar patients who do not have TD, clear evidence of cognitive dysfunction is almost invariably demonstrated in the TD group (65–74). What is at issue is how to account for the finding. The usual explanation is that patients with preexisting neuropsychological deficits are more vulnerable to the neurotoxic effects of neuroleptic drugs. The alternative explanation is that neuroleptics cause cognitive decline in some patients, that neuroleptic treatment may cause subcortical dementia (73) or frontal lobe syndrome (66). This idea is supported by a recent positron emission tomography study that demonstrated long-term neuroleptic effects on brain glucose metabolism in patients with schizophrenia in the direction of decreased metabolism in the frontal lobes (hypofrontality) and enhanced metabolism in the corpus striatum (75). Neither alternative is attractive to physicians who treat patients who are retarded, elderly patients who are demented, or patients with head injury. Either encephalopathy is a risk factor for the development of TD or it is a risk inherent to long-term neuroleptic treatment.

Because TDAK has been clearly established as one of the tardive syndromes attributed to neuroleptic treatment, the arguments over a behavioral or cognitive analog to TD can be considered settled (10). Stahl (76), for example, suggested that TDAK is both a movement disorder and a mental disorder because it has both objective and subjective components. In other words, TDAK is a movement disorder with a psychological dimension. As discussed previously, it

may manifest itself as a purely subjective state without the movement disorder.

Akathisia, like TD, and all the hyperkinetic movement disorders are manifestation symptoms of basal ganglia disease. Postmortem studies (77,78) and magnetic resonance imaging studies (79,80) have demonstrated basal ganglia lesions in patients with TD, especially in the caudate nucleus. Lesions of the basal ganglia may evoke movements that are indistinguishable from TD.

Parkinson's disease (PD), Huntington's chorea (HC), and Wilson's disease (WD) are progressive diseases of the basal ganglia that are very similar to TD. Akathisia, for example, is a symptom of PD and choreoathetosis is a symptom of HC and WD. Although persistent TDAK and TD appear to be static not progressive encephalopathies, their similarity to the major diseases of the basal ganglia goes deeper than the surface manifestations of akathisia and dyskinesia.

The issue is especially relevant to the putative cognitive and behavioral analogs of TD. PD, for example, is associated with depression and dementia (81–83). HC and WD are associated with affective instability, psychosis, and dementia (84–88). If behavioral instability and intellectual impairment are inevitably a part of PD, HC, and WD, should they not also occur in TD?

Patients with PD, HC, and WD also have neuropathologic changes in cortical structures, and therefore it is not possible to attribute all the cognitive and behavioral elements of those conditions to lesions in the basal ganglia. Conversely, intellectual impairment has been noted in patients with PD with lesions in the subcortical nuclei but not in the cortex (89) and in patients with PD after *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure, who had neither cortical lesions nor motor impairment (90). In WD, the severity of neuropsychological impairment is correlated with abnormalities in the basal ganglia but not in the cortex or cerebellum (91). We also know that circumscribed lesions in the basal ganglia are sometimes associated with significant psychiatric conditions (92, 93) or neuropsychological deficits (94–97).

The basal ganglia may be the "dark basement" of the brain, but they are not without intelligence of their own. The basal ganglia do participate in, and may even regulate, some intellectual activities, particularly those involving complex or sequential motor activities (81). The corpus striatum subserves a number of frontal lobe functions in the juvenile primate (98). The frontal lobes are richly connected with areas in the neostriatum (99). Neostriatal lesions mimic the effects of frontal lesions (100,101) and lesions in either the frontal lobes or neostriatum disturb and slow down neural activities throughout the frontostriatal circuit (99). Even more compelling, the mosaic of deficits caused by lesions of the frontal lobes is reflected by similar deficits caused by lesions in striatal areas to which the frontal cortex projects (102–104).

One may surmise, therefore, that affective instability and intellectual impairment may be the consequence of neuropathology at the level of the basal ganglia. Because TD is the result of neurotoxicity in the basal ganglia, some patients with TD may be expected to have behavioral and cognitive deficits as well. TDAK is one manifestation of that effect. There are probably others.

Is This Really Tardive Akathisia?

The emergence of troublesome behaviors, accompanied by dysphoria and restlessness, when a retarded person is withdrawn from neuroleptic medication, is sufficient to suggest the diagnosis of TDAK, especially when the patient has concomitant signs of drug-induced neurotoxicity (i.e., TD). Conversely, as previously mentioned, the diagnostic problem is daunting because the diagnosis is no more than presumptive, and the alternative construction is that the patient is simply manifesting the reemergence of the problem behaviors that led physicians to prescribe neuroleptics in the first place. Retarded children who are hyperactive, aggressive, and easily agitated are likely to be given a strong psychotropic drug. When that drug is withdrawn, is it any surprise that they are again hyperactive and dysphoric?

There is a theoretical answer to that question, as described in the foregoing section. There is unfortunately no direct clinical measure to decide the issue in the individual case. In practice, one may be told that a patient with presumed TDAK was, in fact, "just like that" before neuroleptics were ever prescribed. In contrast, one does see young patients who are retarded and autistic who are restless, impulsive, irritable, and emotionally unstable. They are like that, never having been treated with neuroleptic drugs.

The difference is that for the past 10 or 15 years "children like that" have not been treated with neuroleptics in high doses. They have been treated with serotonergics, or amantadine, or α_2 agonists, or mood stabilizers—drugs that are more specific for the organic affective disorders, which is what we usually deal with. Never having been exposed to neuroleptics, their outcomes have been much more sanguine; when the drugs are withdrawn, they do not revert to their original pattern of hyperactive, disorganized behavior.

Long-term treatment of retarded people with neuroleptics may cause TDAK. Alternatively, long-term treatment may have another kind of neurotoxic effect—interfering with learning and preventing development in an already compromised brain. The reemergence of difficult behaviors after the withdrawal of neuroleptics may represent the failure of the development of cognitive systems that lend control to a primitive, undifferentiated state of irritability and hyperreactivity.

The atypical antipsychotics are less neurotoxic, and the few cognitive studies that have been done to date do not indicate impairment of function. Developmental studies have not been undertaken. We assume that, like the new antidepressants, the atypical antipsychotics are at least neutral with respect to cognitive performance and brain development. That is, of course, no more than an assumption. As the drugs are used more often in handicapped children, we will have an opportunity to test its validity.

RISK FACTORS FOR TARDIVE DYSKINESIA

Patient-Related Risk Factors

Three patient-related risk factors seem to be associated with increased risk for TD: age, gender, and affective disorder. A fourth, preexisting brain damage may be also be associated, although the data are by no means definitive. As a general rule, a risk factor that is linked to a higher likelihood of developing TD will also be linked to severity and to persistence.

The risk factor most consistently identified with the development of TD and severe persistent TD is age. Elderly patients are more prone to the disorder, an effect that is probably independent of cumulative neuroleptic dose or the duration of neuroleptic exposure (12,105). It is possible that this association is related to the age-related decline in dopamine neurons in the striatum, an idea that is strengthened by the spontaneous occurrence of buccal-lingual dyskinesias in elderly patients who have never taken neuroleptic drugs (70).

It appears that females are at greater risk than males to develop TD and severe forms of the disorder are likelier to occur in females (11). This may speak to estrogen-related dopamine sensitivity (106). Nicotine can also sensitize the dopamine receptor, and therefore tobacco addiction must be counted among the risk factors for TD (107). Cannabis may also predispose to TD and possibly alcohol (108,109).

Clinical lore holds to the ironic contention that TD is more likely to occur in patients who do not respond particularly well to neuroleptic treatment, but whether this is related to high-dose treatment, frequent dose changes, conjunctive treatment, or some other factor is not known. It may be that the neuroleptic nonresponders are people with affective disorders.

It appears that patients with affective disorders are peculiarly vulnerable to malignant TD (110). This is very important for the treatment of mentally retarded people, among whom affective disorders tend to be underdiagnosed, and it may explain why the tardive syndromes have been so troublesome in this population.

Whether preexisting brain damage may actually predispose to TD or severe and persistent TD is not known, although it is an important question for practitioners who deal with patients with mental retardation, dementia, or neurobehavioral sequelae of traumatic brain injury (111). Neuroleptics have always been frequently prescribed for these groups (10).

Treatment-Related Risk Factors

Several factors related to treatment with neuroleptic drugs have been associated with increased risk of TD, but only one, early development of EPS, has gained wide acceptance on the basis of controlled experiments.

Results from the New York Longitudinal Study suggest that patients who develop TD are more likely to have EPS early in their treatment (112). The association does not appear to be related to treatment with selected neuroleptics with a low proclivity for EPS; rather, patients who are prone to early EPS are at greater risk for TD by virtue of some unique pharmacodynamic tendency (113).

If concomitant anticholinergic treatment is associated with TD at all, the effect is probably mediated by the occurrence of early EPS. That is, patients who develop early EPS are more likely to receive anticholinergics; the former confers risk, not the latter.

One would think that neuroleptic dose has something to do with the development of TD, but the clinical literature is equivocal. Cumulative neuroleptic dose was found to be associated with severe TD in one study of mentally retarded patients (114), but not in studies of patients with schizophrenia and other psychiatric disorders. It is likely that there is no linear association between cumulative dose and TD but that a minimum cumulative dose is necessary to evoke the phenotype in patients who are vulnerable to TD by virtue of other risk factors. The importance of idiosyncrasy cannot be minimized because some patients have been known to develop TD after short-term treatment with very low neuroleptic doses, whereas

others seem to be free of the disorder even after years of high-dose treatment.

Until clozapine, there was never a particular neuroleptic that was more or less likely to cause TD. Other serious side effects, such as agranulocytosis and hepatotoxicity, are more likely with the low-potency neuroleptics thioridazine and chlorpromazine, and those drugs exhibit more cytotoxicity in tissue cultures (115). Among the conventional neuroleptics, however, there is no rank order.

An appreciation of TD risk factors is essential to clinical treatment because it allows the physician to recognize cases that require very careful monitoring, more frequent neuroleptic withdrawals or at least dose reductions, and a more aggressive approach to identifying pharmacologic alternatives. The informed consent process should address the patient's individual vulnerability to TD. To reiterate, established risk factors for neuroleptic-induced TD are advanced age, female gender, smoking, affective disorder, early EPS, and possibly brain damage and cumulative neuroleptic dose.

Protective Factors

What may be done to reduce the likelihood of a tardive syndrome? Reduce the number of patients who are exposed to neuroleptic drugs, maintain patients on long-term treatment on a minimum effective dose, and use the novel antipsychotics instead of the conventional neuroleptics. The neuroleptics have joined the ranks of "archaic" drugs, which include the sedating anticonvulsants and tricyclic antidepressants. Nevertheless, there are still occasions when the prescription of an archaic drug is necessary, and sometimes, high-dose neuroleptics are necessary for patients with severe affective disorders, even older female patients who drink, toke, and smoke.

In the history of psychopharmacology, several possible protectants have been proposed, for example, lithium and amantadine. None has worked. So it was hardly surprising that psychiatrists greeted with skepticism the news that various megavitamin combinations actually exerted a protective effect. One formula, arrived at empirically, contained niacin, pyridoxine, ascorbate, and vitamin E (116).

The free-radical theory of cytotoxicity that was current among neurologists who study PD led to a series of trials of vitamin E that were for the most part disappointing. At the same time, however, it was suggested that the neuroleptics might be cytotoxic because by increasing catecholamine turnover and metabolism, there should necessarily be increased production of highly reactive free radicals (117). The theory was supported by the findings that patients with TD had higher levels of thiobarbituric acid–reactive substances, an indicator of lipid peroxidation (i.e., free-radical damage to body fats) (117,118) and that vitamin E (with or without selenium) prevented the development of TD in dopamine-hypersensitive rats (119,120). Clinical studies of patients with TD have actually demonstrated reduction in AIMS scores when they are treated with vitamin E in doses as high as 1,600 IU per day (121–124).

There is no reason why neuroleptic-treated patients should not take concomitant vitamin E, perhaps with some of the other free-radical scavengers such as selenium. It seems to be the psychopharmacologic equivalent of one baby aspirin every other day.

BIOLOGICAL MECHANISMS

The prevailing view of the pathophysiology of TD is that chronic blockade of striatal D_2-dopamine receptors leads to a state of denervation supersensitivity and that the abnormal movements are a manifestation of dopamine hypersensitivity (125). Support for this idea comes from animal studies in rats, cats, and primates in which chronic neuroleptic administration is known to increase the number and density of striatal dopamine binding sites (126), to elicit behaviors such as gnawing or rotation that are mediated by dopamine (127), and to cause choreoathetoid movements that are typical of TD (128). The abnormal movements of TD are topographically identical to dyskinesias that characterize other hyperdopaminergic states: HC, Tourette's syndrome, and L-dopa–induced dyskinesias (129).

The dopamine supersensitivity hypothesis is not sufficient to explain the phenomenon, however. For example, the dyskinesias that arise in animal models of TD are early onset and readily reversible. With prolonged neuroleptic administration, the dopamine receptor hypersensitivity actually disappears (130). In human postmortem studies, patients with TD are not invariably found to have D_1 or D_2 hypersensitivity (131), nor do they show cerebrospinal fluid or neuroendocrine indices of dopamine sensitivity (130). The supersensitivity hypothesis may underlie the occurrence of transient or withdrawal dyskinesias, but the pathophysiology of persistent unremitting TD is unknown (132).

If receptor supersensitivity cannot account for cases of severe and persistent TD, then it is necessary to consider alternative hypotheses. The facts that the disorder can be irreversible, refractory to

treatment, and occasionally associated with continued deterioration even after drug withdrawal (133) lead inevitably to the idea that neuroleptics may exercise, in some patients at least, a cytotoxic effect. This may conceivably be a cytotoxic metabolite, perhaps a selective product of neuroleptic metabolism in patients vulnerable to severe TD. Alternatively, TD may be the consequence of oxidative stress. The neuroleptics are, comparatively speaking, metabolically active compounds and strong free-radical generators. Neuroleptic drugs increase the turnover and metabolism of dopamine, with the formation of dopamine quinines and hydrogen peroxide. Long-term exposure to neuroleptics in animals increases manganese and iron, which are free-radical catalysts, in the central nervous system (134). Neuroleptic treatment has been found to retard recovery from brain injury in rats (135).

Neuroleptic blockade of presynaptic dopamine D_2 receptors increases the synaptic release of aspartate and glutamate in the striatum. Persistent activation of glutaminergic ionotropic receptors causes neuronal degeneration, an effect that is mediated by increased oxygen free-radical generation and oxidative damage to the cell membrane, cellular proteins, and DNA. Markers for enhanced excitatory neurotransmission have been discovered in the central nervous system of patients with schizophrenia with TD (136). This represents a cogent rationale for the use of antioxidants, especially vitamin E, for the prevention and possible treatment of TD. As a preventive agent, vitamin E is promising, at least on theoretical grounds; as a treatment measure, especially in advanced cases, it may not be effective (134).

Dopamine neurons are remarkably stress sensitive and that is why parkinsonian symptoms are so common, even with normal aging. Occasional reports of postmortem findings in patients with TD have demonstrated neuronal degeneration in the substantia nigra (77) and caudate nucleus atrophy (78,137). Nielson and Lyon (138) observed cell death in the corpus striatum of rats given neuroleptics long term.

DIAGNOSIS

The diagnosis of TD requires more than the simple administration of a rating scale like the AIMS or the DISCUS. Those are only screening instruments and are useful because they can be reliably administered by a nonphysician and because they raise the level of staff consciousness concerning TD. They are complements to the neurologic examination and the process of differential diagnosis, not a substitute for it.

The first step in diagnosis requires a thorough description of the patient's abnormal movements, including a topographic analysis of the distribution of dyskinesia and an accurate description of its nature. The topographic categories are orofacial, buccal-lingual-masticatory, truncal (or axial), centrifugal (i.e., involving the extremities), and holokinetic (i.e., all over). The different types of dyskinesia are choreoathetoid, dystonic, myoclonic, ballistic, and tic-like movements (so-called tardive Tourette's syndrome).

Topography and dyskinesia interact in relatively predictable patterns. Choreiform movements are often centrifugal, whereas dystonic movements are more commonly axial in distribution. The area of distribution is significant because severe TD may sometimes have a total body distribution and thus render the patient incapacitated by virtue of holokinetic movements. Movements that are circumscribed in area are not as likely to be incapacitating unless they are dystonic or involve the oropharyngeal or respiratory musculature. These elements are essential for determining the severity of TD and may also aid in the prediction of outcome. Severe and persistent TD is most often associated with mixed types of movements with a generalized distribution or with dystonic movements with a more local distribution.

The next step involves the process of differential diagnosis. The topography and classification of dyskinesia do not establish diagnosis. Indeed, many other movement disorders may resemble TD. Stereotypies and manneristic behaviors are common in patients with severe mental retardation and autism. These movements may be suppressed by neuroleptics and reemerge when the drug is reduced in dose or discontinued entirely. Such movements are usually more complex than those seen in TD and are usually stereotyped in quality. Nevertheless, TD coinciding with stereotypies may pose a diagnostic problem.

The differential diagnosis of TD includes Tourette's syndrome, choreoathetosis attendant on cerebral palsy, HC, WD, and other disorders of the basal ganglia; Hallervorden-Spatz syndrome (dystonia); familial dystonia and chorea; ballistic movements related to vascular disease; and other drug-induced dyskinesias, e.g., those related to phenytoin (139), carbamazepine (140), valproate, tricyclic antidepressants, or stimulants. Dyskinesias may arise spontaneously in elderly patients or patients with dementia. Idiopathic calcification of the basal ganglia is associated with dyskinesia and other neuropsychiatric symptoms (141,142).

Other causes of movement disorder include Sydenham's chorea, systemic lupus erythematosus, and some encephalitides. Disturbance in thyroid and parathyroid

function may be associated with dyskinesia (113). The differential diagnosis of dystonia has been addressed most recently by Burke et al. (143).

The evaluation of a patient with possible TD may involve a series of steps to exclude alternative causes of dyskinesia, especially treatable conditions such as WD. A family history is very important. Laboratory diagnosis may rule out infectious, endocrine, metabolic, and degenerative disorders. Appropriate studies include a toxic drug screen, serum electrolytes, sedimentation level, ASO titers, thyroid and parathyroid studies, serum ceruloplasmin, lupus erythematosis (LE) prep, and antinuclear antibodies. Appropriate neurodiagnostic studies include computed tomography or magnetic resonance imaging, at least in selected cases. Calcification of the basal ganglia, iron deposition in the globus pallidus, or degeneration of the caudate and other subcortical structures may provide etiopathogenic evidence that can influence clinical decisions.

The differential diagnosis is important, but a thorough neurodiagnostic evaluation is not necessary for most cases of TD. The most important diagnostic element is a history of toxic exposure (to neuroleptics or other dopamine blockers such as metaclopramide) and a high index of suspicion on the part of the treating physician. A patient with dyskinesia and a history of neuroleptic exposure has TD until proven otherwise.

TREATMENT

It is not easy to discuss the treatment of TD because no treatment is reliably effective. The basic treatment is to withdraw neuroleptics, keep the patient drug free, and wait for the disorder to remit. If antipsychotics cannot be withdrawn, substitute a novel antipsychotic. There is reason to believe that clozapine may be an effective treatment for the tardive syndromes. Vitamin E is the third treatment alternative.

Patients with choreiform TD may respond to drugs that influence γ-aminobutyric acid (GABA) neurotransmission such as clonazepam, baclofen, or valproic acid (144). The timing of treatment may be important because some patients with TD progress to a severe dystonic form of the disorder that is usually resistant to pharmacologic treatment (110). Drugs that deplete presynaptic dopamine such as reserpine or tetrabenzamine may be helpful, but they can exacerbate affective illness in vulnerable patients (145,146). Patient response to acetylcholine agonists is variable. Physostigmine provocation has been advocated as a screening procedure to identify patients who will respond to cholinergic precursors (147,148). Clinically, acetylcholine agonist treatment approaches have been disappointing, and side effects have limited their utility (149).

Tardive dystonia differs clinically from idiopathic forms of dystonia, yet it may respond to similar treatments. In dystonia, physostigmine tends to increase the severity of abnormal movements. Anticholinergic drugs have been helpful, but their clinical utility is limited by the occurrence of memory impairment, agitation, and delirium (150). Dopamine-depleting drugs may be helpful in 10% to 12% of patients with dystonia (150). Dopamine agonists such as L-dopa and amantadine may be effective in a similar percentage of patients with dystonia (129). The use of GABAergic drugs has been of limited benefit.

THE COURSE OF THE DISORDER

It is a mistake to classify TD as irreversible because patients with chronic TD may experience remission even after several years. It is better to classify TD as transient or persistent and specify precisely how long the movement disorder has in fact persisted.

What proportion of patients has TD that remits after only a few weeks or a few months, and what proportion persists for years? Although these are important questions, they cannot be answered based on direct research. The persistence of TD may be masked by continued neuroleptic treatment, and most TD studies in populations with psychiatric disorders have been done in patients with schizophrenia who are treated with neuroleptics even after TD is diagnosed.

In elderly patients, TD is usually a persistent disorder, whereas in studies of children treated with neuroleptics, the remission rate is very high (16,151). Although persistent cases are not unknown, they are rare (8). There is an age-dependent decrease in dopamine neurotransmission that may interact with neuroleptic neurotoxicity to cause severe and persistent forms of TD in elderly patients, and this same element could conceivably confer a measure of protection to young people (70). Children usually are treated with low doses of neuroleptics for shorter periods, and they metabolize drugs more efficiently. The relative persistence rates for TD in young and elderly patients may be a pharmacodynamic phenomenon or it may simply be related to prescription habits.

It is possible that even transient TD in early life may set the stage for neurodegenerative changes in later years, admittedly a speculation but one based on some established models of the evolution of neuropsychiatric disorders: postencephalitic parkinsonism, the late neuropathic sequelae of poliomyelitis, late-onset psychosis after traumatic brain injury, and

the putative kindling psychosis of temporal lobe epilepsy (10). These are all models of early central nervous system insult followed by late deterioration in function. It is possible that some patients who have had transient TD in early life will develop encephalopathic changes when they are old.

This is another example of cerebral reserve, a concept that was introduced in Chapter 6 in the discussion of postconcussion effects. It is said that the dopamine system is particularly vulnerable to the effects of insult; postencephalitic parkinsonism, post–*N*-methyl-D-aspartate parkinsonism, and TD are three concrete examples. In the first case, it is youthful exposure to the virus that leads to parkinsonism in middle age. We have no way of knowing whether exposure to neuroleptics in childhood may have a similar effect. TD in children tends to be transient; they have so many extra neurons, even in the dopamine system, that it is hard to confirm the possibility of a late effect, but it is possible, and with time, we may find out.

In mentally retarded people, one of our studies reported TD in 25 of 38 individuals who were withdrawn from neuroleptic treatment, but 13 of 25 had transient TD that remitted within only a few weeks (152). A subsequent study of a subgroup of that original sample who returned to neuroleptic treatment and who were withdrawn from neuroleptics a second time 3 years later demonstrated progressive TD in five patients and TD that had actually decreased in severity in four patients; the former had been treated with high doses of neuroleptics, the latter group with low doses (10). Although this was only a small study, it suggests that patients with TD may continue on neuroleptics if they absolutely have to, as long as the doses are kept low.

Paulson et al. (7) reexamined a group of mentally retarded people 4 years after a neuroleptic withdrawal trial and found that six (of 15) had persistent TD with no change in severity, five had more severe TD, and four had actually improved.

If one can surmise anything from these small studies, it is that TD is persistent in some substantial fraction (one-third or two-thirds) of mentally retarded patients who have the disorder, that persistence is to be measured in years, but that remission may occur with time and judicious management. How do these conjectures correspond with the results of TD research in other patient groups?

The research data from studies of adults with schizophrenia are contradictory and hard to interpret. In one study of patients with TD maintained off neuroleptics, no appreciable symptom reduction was noted after 12 months (153). In another, Yassa et al. (154) reported a 2-year follow-up: 66% of the patients with TD showed no change, 18% improved, and 16% grew worse over time. In a 5-year follow-up study by Chouinard et al. (155), the annual, remission rate in patients with TD was 5.5%; this was outweighed by an incidence rate for new cases of 8.4%. In contrast, there have been several reports suggesting that TD remits far more often than it persists (130,156–159), even if neuroleptic treatment is continued. Exactly how substantial the fraction is then of those who have persistent TD remains an area of surmise.

Well-controlled epidemiologic studies of the course of TD are extremely difficult to do because the recruitment of a large number of subjects will necessarily include patients on psychoactive drugs that may influence the course of the disorder, patients who will drop out for one reason or another, and patients with degenerative central nervous system disorders. As a consequence, research attention is turning in the direction of case-control strategies. It is assumed that at least some patients will have long-term persistent TD and that others will remit. The relative proportions are irrelevant; the key to the strategy is accurate assignment to one group or the other. The next step is to identify clinical elements that are associated with persistence and to replicate the finding. This is the difficult part. First, clinical elements from the medical history will be hard to discover, especially in patients with chronic TD who are institutionalized. Second, subject variance will make a successful replication difficult. The strategy, however, is important; if reliable information is attainable, it can be used to guide programs for TD prevention.

A first attempt at this strategy was published by Gardos and Casey (110). They found that generalized dystonic and athetoid movements characterized a more malignant and persistent form of TD. They also reported that patients with severe and persistent TD displayed a variety of axial and centrifugal movements, with buccal-lingual-masticatory choreoathetosis early in the clinical course and a gradual evolution to dystonia as the disorder progressed. Males were more commonly affected with severe and persistent TD, and the duration of treatment was relatively short (less than 1 year). Gardos and Casey concluded that patients who develop severe and persistent TD have a unique vulnerability to neuroleptic-induced movement disorders and that this could be defined in terms of the TD risk factors discussed earlier, especially age, early EPS, and affective disorder.

Malignant Tardive Dyskinesia

The severity of TD is defined in terms of persistence, the nature of the dyskinesia, and the degree to

which it afflicts the patient's behavior and compromises the activities of daily life. The disagreement over relative rates of persistence is mirrored in controversies about relative severity or whether patients with TD are even bothered by their disorder. There is little to be gained from a reiteration of these arguments.

The consensus developing among psychopharmacologists is that TD may sometimes be a malignant disorder, rapid in onset and extreme in its consequences. It seems that some patients are uniquely vulnerable to severe and persistent TD, they can develop the disorder after only a brief course of low-dose neuroleptic treatment, their TD is extraordinarily debilitating, and dystonia and akathisia are its likeliest manifestations. Patients with so-called malignant TD tend to have affective disorders to begin with (110). They are often young, and their disorder is persistent and refractory to treatment. They are rarely if ever anosognosic for the condition. This is a very serious problem (143).

There are only estimates of the relative prevalence of severe forms of TD. The most recent survey, based on 100 TD cases seen at a movement disorder clinic that were probably a seriously afflicted group to begin with, reported 23 severe manifestations of the disorder: persistent bruxism (one case), masseter or lingual hypertrophy (three cases), sustained involuntary tongue protrusion (six cases), incomprehensible speech arising from dysarthria (two cases), spasmodic dysphonia (two cases), anterior cervical spondylolisthesis (one case), palatal dyskinesia with secondary sinus pain (one case), respiratory stridor with laryngospasm (two cases), and disabling dystonic posturing (five cases) (18).

Neuroleptic Nonresponders

It is important to remember that there are even some patients with schizophrenia whose condition grows worse with neuroleptic treatment. In rare cases, psychosis may even occur as an effect of neuroleptic treatment (160). Neuroleptics can cause dysphoria (161), panic (162), phobia (163), and depression (164). Although acute behavioral toxicity to neuroleptic treatment may not be common, it is by no means uncommon. Not only may some patients fail to respond to neuroleptic treatment, but some patients, even those diagnosed with schizophrenia, may actually grow worse with the drugs.

REFERENCES

1. Lipman RS. The use of psychopharmacological agents in residential facilities for the retarded. In: Menolascino F, ed. *Psychiatric approaches to mental retardation*. New York: Basic Books, 1970:387.
2. Sprague RL, Baxley GB. Drugs used in the management of behavior in mental retardation. In: Wortis J, ed. *Mental retardation & developmental disabilities*. New York: Brunner Mazel, 1978.
3. Hill BK, Balow EA, Bruininckx RH. *A national study of prescribed drugs in institutions and community residential facilities for mentally retarded people*. Minneapolis: University of Minnesota, 1983.
4. Steck H. Le syndrome extrapyramidal et diencephalique au cours des traitements au largactil et au serpasil. *Ann Med Psychol* 1954;112:737–743.
5. Schonecker M. Ein eigentomliches Syndrom in oralen Bereich bei Megaphenapplikation. *Neruenarzt* 1957;28.
6. Uhrbrand L, Faurbye A. Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine, and electroconvulsive therapy. *Psychopharmacologia* 1960;1:408–418.
7. Paulson GW, Rizvi CA, Crane GE. Tardive dyskinesia as a possible sequelae of long-term therapy with phenothiazines. *Clin Pediatr* 1975;14:953–955.
8. Gualtieri CT, Hawk B. Tardive dyskinesia and other drug-induced movement disorders among handicapped children and youth. *J Appl Res Ment Retard* 1980;1:55–69.
9. Kalachnik JE, Harder SR, Kidd-Nielsen P, et al. Persistent tardive dyskinesia in randomly assigned neuroleptic reduction, neuroleptic nonreduction, and no-neuroleptic history groups: preliminary results. *Psychopharmacol Bull* 1984;20:27–31.
10. Gualtieri CT, Barnhill LJ. Tardive dyskinesia in special populations. In: Wolf ME, Mosnaim AD, eds. *Tardive dyskinesia, biological mechanisms & clinical aspects*. Washington, DC: American Psychiatric Press, 1988: 137–154.
11. Kane JM, Smith JM. Tardive dyskinesia, prevalence and risk factors. *Arch Gen Psychiatry* 1982;39:473–481.
12. APA Task Force on Tardive Dyskinesia. *Tardive dyskinesia: a task force report of the American Psychiatric Association*. Washington, DC: American Psychiatric Association, 1992.
13. Saltz BL, Kane JM, Woerner MG, et al. Prospective study of tardive dyskinesia in the elderly. *Psychopharmacol Bull* 1989;25:52–56.
14. Gualtieri CT, Schroeder SR, Hicks RE, et al. Tardive dyskinesia in young mentally retarded individuals. *Arch Gen Psychiatry* 1986;43:335–340.
15. Delwaide PJ, Desseilles J. Spontaneous buccolinguofacial dyskinesia in the elderly. *Acta Neurol Scand* 1977;56:256–262.
16. Perry R, Campbell M, Green WH, et al. Neuroleptic-related dyskinesias in autistic children: a prospective study. *Psychopharmacol Bull* 1985;21:140–143.
17. Baldessarini RJ. Clinical and epidemiologic aspects of tardive dyskinesia. *J Clin Psychiatry* 1985;46:8–13.
18. Davis RJ, Cummings JL. Clinical variants of tardive dyskinesia. *Neuropsychiatry Neuropsychol Behav Neurol* 1988;1:31–38.
19. Rifkin A, Quitkin F, Klein DF. Akinesia: a poorly recognized drug-induced extrapyramidal behavioral disorder. *Arch Gen Psychiatry* 1975;32:672–674.
20. Behrman S. Mutism induced by phenothiazines. *Br J Psychiatry* 1972;121:599–604.
21. Keck PE, Pope HG, McElroy SL. Frequency and presentation of neuroleptic malignant syndrome: a

prospective study. *Am J Psychiatry* 1987;144: 1344–1346.
22. Guze BH, Baxter LR. Neuroleptic malignant syndrome. *N Engl J Med* 1985;313:163–166.
23. Keck PE, Pope HG, Cohen BM, et al. Risk factors for neuroleptic malignant syndrome. *Arch Gen Psychiatry* 1989;46:914–921.
24. Levenson JL. Neuroleptic malignant syndrome. *Am J Psychiatry* 1985;142:1137–1145.
25. Haskovec L. Akathisie. *Arch Boheme Med Clin* 1902; 3:193–200.
26. Bing R. Uber Einige Bemerkenswerte Begleiterscheinungen der Exrapyramidalen Rigiditat (Akathesie–Mikrographie–Kinesia paradoxica). *Schweiz Med Wochenschr* 1923;53:167–171.
27. Bing R. *Textbook of nervous diseases*, 5th ed. London: Henry Kimpton Press, 1939.
28. Ayd FJ. A survey of drug-induced extrapyramidal reactions. *JAMA* 1961;175:1054–1060.
29. Kruse W. Persistent muscular restlessness after phenothiazine medication: report of 3 cases. *Am J Psychiatry* 1960;117:152–153.
30. Barnes TRE, Braude WM. Akathisia variants and tardive dyskinesia. *Arch Gen Psychiatry* 1985;42:874–878.
31. Demars JCA. Neuromuscular effects of long-term phenothiazine medication, electroconvulsive therapy and leukotomy. *J Nerv Ment Dis* 1966;143:73–79.
32. Faurbye A, Rasch P-J, Petersen PB. Neurological symptoms in pharmacotherapy of psychosis. *Acta Psychiatr Scand* 1964;40:10–27.
33. Brandon S, McClelland MA, Protheroe C. A study of facial dyskinesia in a mental hospital population. *Br J Psychiatry* 1971;118:171–184.
34. Chouinard G, Annable L, Ross-Chouinard A. Fluphenazine enanthate and fluphenazine decanoate in the treatment of schizophrenic outpatients: extrapyramidal symptoms and therapeutic effect. *Am J Psychiatry* 1982;139:312–318.
35. Kennedy PF, Hershon HI, McGuire RJ. Extrapyramidal disorders after prolonged phenothiazine therapy. *Br J Psychiatry* 1971;118:509–518.
36. Mukherjee S, Rosen AM, Cardenas C, et al. Tardive dyskinesia in psychiatric outpatients. *Arch Gen Psychiatry* 1982;39:466–469.
37. Wojcik JD, Gelenberg AJ, LaBrie RA, et al. Prevalence of tardive dyskinesia in an outpatient population. *Compr Psychiatry* 1980;21:370–380.
38. Ganesh S, Rao JM, Cowie VA. Akathisia in neuroleptic medicated mentally handicapped subjects. *J Ment Defic Res* 1989;33:323–329.
39. Gualtieri CT. *Neuropsychiatry and behavioral pharmacology*. Berlin: Springer-Verlag, 1990.
40. Keckich WA. Neuroleptics. Violence as a manifestation of akathisia. *JAMA* 1978;240:2185.
41. Drake RE, Ehrlich J. Suicide attempts associated with akathisia. *Am J Psychiatry* 1985;142:499–501.
42. Mikkelsen E, Detlor J, Cohen D. School avoidance and social phobia triggered by haloperidol in patients with Tourette's disorder. *Am J Psychiatry* 1981;138:1572.
43. Carter G. The abrupt withdrawal of antiparkinsonian drugs in mentally handicapped patients. *Br J Psychiatry* 1983;142:166–168.
44. Decina P, Caracci G, Harrison K, et al. *Painful sensory symptoms in neuroleptic-induced extrapyramidal syndromes*. New York, 1990.
45. Ford BM, Greene PM, Fahn SM. Oral and genital tardive pain syndromes. *Neurology* 1994;44:2115–2119.
46. Koller WC. Sensory symptoms in Parkinson's disease. *Neurology* 1984;34:957–959.
47. Deniker P. From chlorpromazine to tardive dyskinesia (brief history of the neuroleptics). *Psychiatry J Univ Ottawa* 1989;14:253–259.
48. Walters A, Hening W, Chokroverty S, et al. Opioid responsiveness in patients with neuroleptic-induced akathisia. *Mov Disord* 1986;1:119–127.
49. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995;47:575–604.
50. Ekbom DA. Asthenia crurum paraesthetica ("irritable legs"). *Acta Med Scand* 1944;118:197–209.
51. Walters AS, Hening W. Clinical presentation and neuropharmacology of restless legs syndrome. *Clin Neuropharmacol* 1987;10:225–237.
52. Yassa R, Iskandar H, Nastase C. Propranolol in the treatment of tardive akathisia: a report of two cases. *J Clin Psychopharmacol* 1988;8:283–285.
53. Ratey JJ, Sorgi P, Polakoff S. Nadolol as a treatment for akathisia. *Am J Psychiatry* 1985;142:640.
54. Zubenko GS, Cohen BM, Lipinski JF, et al. Use of clonidine in the treatment of akathisia. *Psychiatry Res* 1984;13:253–259.
55. Adler L, Angrist B, Peselow E, et al. Clonidine in neuroleptic-induced akathisia. *Am J Psychiatry* 1987;144: 235–236.
56. De Keyser J, Ebinger G, Herregodts P. Pathophysiology of akathisia. *Lancet* 1987;2:336.
57. Borison RL, Diamond BI. Treatment of extra-pyramidal side effects: amantadine versus benzotropine. *World J Psychosynthesis* 1984;16:40–43.
58. D'Mello DA, McNeil JA, Harris W. Buspirone suppression of neuroleptic-induced akathisia: multiple case reports. *J Clin Psychopharmacol* 1989;9:151–152.
59. Gualtieri CT. The problem of tardive akathisia. *Brain Cognition* 1993;23:102–109.
60. Gualtieri CT, Guimond M. Tardive dyskinesia and the behavioral consequences of chronic neuroleptic treatment. *Dev Med Child Neurol* 1981;23:255–259.
61. Famuyiwa OO, Eccleston D, Donaldson AA, et al. Tardive dyskinesia and dementia. *Br J Psychiatry* 1979; 135:500–504.
62. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. *Am J Psychiatry* 1980;137:16–21.
63. Sale I, Kristall H. Schizophrenia following withdrawal from chronic phenothiazine administration: a case report. *Aust N Z J Psychiatry* 1978;12:73–75.
64. Caine ED, Margolin DI, Brown GL, et al. Gilles de la Tourette's syndrome, tardive dyskinesia and psychosis in an adolescent. *Am J Psychiatry* 1978;135:241–243.
65. Edwards H. The significance of brain damage in persistent oral dyskinesia. *Br J Psychiatry* 1970;116:271–275.
66. Wilson IC, Garbutt JC, Lanier CF, et al. Is there a tardive dysmentia? *Schizophr Bull* 1983;9:187–192.
67. Struve FA, Willner WA. Cognitive dysfunction and tardive dyskinesia. *Br J Psychiatry* 1983;143:597–600.
68. Wolf ME, Ryan JJ, Mosnaim AD. Cognitive functions in tardive dyskinesia. *Psychol Med* 1983;13:671–674.
69. Collerton D, Fairbairn A, Britton P. Cognitive performance of medicated schizophrenics with tardive dyskinesia. *Psychol Med* 1985;15:311–315.

70. Waddington JL, Youssef HA, Mooloy AG, et al. Association of intellectual impairment, negative symptoms, and aging with tardive dyskinesia: clinical and animal studies. *J Clin Psychiatry* 1985;46:29–33.
71. Wegner JT, Catalano F, Gibralter J, et al. Schizophrenics with tardive dyskinesia. *Arch Gen Psychiatry* 1985; 42:860–865.
72. Thomas P, McGuire R. Orofacial dyskinesia, cognitive function and medication. *Br J Psychiatry* 1986;149: 216–220.
73. Gilleard CJ, Vaddad KS. Mood, memory, and performance and the severity of tardive dyskinesia. *Percept Mot Skills* 1986;63:1037–1038.
74. Goldberg E. Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. *Schizophr Bull* 1985; 11:255–263.
75. Szechtman H, Nahmias C, Garnett ES, et al. Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. *Arch Gen Psychiatry* 1988;45: 523–532.
76. Stahl SM. Akathisia and tardive dyskinesia: changing concepts. *Arch Gen Psychiatry* 1985;42:915–917.
77. Christensen E, Miller JE, Faurbye A. Neuropathological investigation of 28 brains from patients with dyskinesia. *Acta Psychiatr Scand* 1970;46:14–23.
78. Hunter R, Blackwood W, Smith MC, et al. Neuropathological findings in three cases of persistent dyskinesia following phenothiazine medication. *J Neurol Sci* 1968;7:263–273.
79. Bartzokis G, Garber HJ, Marder SR, et al. MRI in tardive dyskinesia: shortened left caudate T2. *Biol Psychiatry* 1990;28:1027–1036.
80. Mion CC, Andreasen NC, Arndt S, et al. MRI abnormalities in tardive dyskinesia. *Psychiatry Res Neuroimag* 1991;40:157–166.
81. Mayeux R, Stern Y. Intellectual dysfunction and dementia in Parkinson's disease. In: Mayeux R, Rosen WG, eds. *The dementias*. New York: Raven Press, 1983:211–227.
82. Mayeux R, Stern Y, Rosen J, et al. Depression, intellectual impairment and Parkinson disease. *Neurology* 1981;31:645–650.
83. Taylor AE, Saint-Cyr JA, Lang AE, et al. Parkinson's disease and depression: a critical re-evaluation. *Brain* 1986;109:279–292.
84. Brandt J, Strauss ME, Larus J, et al. Clinical correlates of dementia and disability in Huntington's disease. *J Clin Neuropsychol* 1984;6:401–412.
85. Dening TR, Berrios GE. Wilson's disease: psychiatric symptoms in 195 cases. *Arch Gen Psychiatry* 1989;46: 1126–1134.
86. Folstein SE, Leigh J, Parhad IM, et al. The diagnosis of Huntington's disease. *Neurology* 1986;36:1279–1283.
87. Sax DS, O'Donnell B, Butters N, et al. Computed tomographic, neurologic, and neuropsychological correlates of Huntington's disease. *Int J Neurosci* 1983; 18:21–36.
88. Starosta-Rubinstein S, Young AB, Kluin K, et al. Clinical assessment of 31 patients with Wilson's disease: correlations with structural changes on magnetic resonance imaging. *Arch Neurol* 1987;44:365–370.
89. Chui HC, Mortimer JA, Slager U, et al. Pathologic correlates of dementia in Parkinson's disease. *Arch Neurol* 1986;43:991–995.
90. Stern Y, Tetrud JW, Martin WRW, et al. Cognitive change following MPTP exposure. *Neurology* 1990; 40:261–264.
91. Medalia A, Isaacs-Glaberman K, Scheinberg H. Neuropsychological impairment in Wilson's disease. *Arch Neurol* 1988;45:502–504.
92. Rapoport JL, Wise SP. Obsessive-compulsive disorder: evidence for basal ganglia dysfunction. *Psychopharmacol Bull* 1988;24:380.
93. Trautner RJ, Cummings JL, Read SL, et al. Idiopathic basal ganglia calcification and organic mood disorder. *Am J Psychiatry* 1988;145:350–353.
94. Bowen FP. Behavioral alterations in patients with basal ganglia lesions. In: Yahr MD, ed. *The basal ganglia*. New York: Raven Press, 1975:169–180.
95. Buchwald NA, Hull CD, Levine MS, et al. The basal ganglia and the regulation of response and cognitive sets. In: Brazier MAB, ed. *Growth and development of the brain*. New York: Raven Press, 1975:171–189.
96. Hassler R. Striatal control of locomotion, intentional actions and of integrating and perceptive activity. *J Neurol Sci* 1978;36:187–224.
97. Teuber H, Proctor F. Some effects of basal ganglia lesions in subhuman primates and man. *Neuropsychologia* 1964;2:85–93.
98. Divac I. Functions of the caudate nucleus. *Acta Biol Exp* 1968;2:107–120.
99. Villablanca JR, Olmstead CE. The striatum: a fine tuner of the brain. *Acta Neurobiol Exp* 1982;42:227–299.
100. Rosvold HE, Mishkin M, Swarcbart MK. Effects of subcortical lesions in monkeys on visual- discrimination and single-alternation performance. *J Comp Physiol Psychol* 1958;51:437–444.
101. Rosvold HE, Szwarcbart MK. Neural structures involved in delayed response performance. In: Warren JM, Abert K, eds. *The frontal granular cortex and behavior*. New York: McGraw-Hill, 1964:1–15.
102. Delgado JMR. Inhibitory functions of the neostriatum. In: Divac I, Oberg RGE, eds. *The neostriatum*. Oxford: Pergamon Press,1979:241–262.
103. Iversen SD. Behavior after neostriatal lesions in animals. In: Divac I, Oberg RGE, eds. *The neostriatum*. Oxford: Pergamon Press, 1979:195–210.
104. Oberg RGE, Divac I. "Cognitive" functions of the neostriatum. In: Divac I, Oberg RGE, eds. *The neostriatum*. Oxford: Pergamon Press, 1979:291–313.
105. Walker-Batson D, Unwin H, Curtis S, et al. Use of amphetamine in the treatment of aphasia. *Restor Neurol Neurosci* 1992;4:47–50.
106. Hruska RE, Silbbergeld EK. Increased dopamine receptor sensitivity after estrogen treatment using the rat rotation model. *Science* 1980;208:1466–1468.
107. Yassa R, Lal S, Korpassy A, et al. Nicotine exposure and tardive dyskinesia. *Biol Psychiatry* 1987;22:67–72.
108. Olivera AA. Tardive dyskinesia in psychiatric patients with substance use disorders. *Am J Alcohol Abuse* 1990;16:57–66.
109. Zaretsky A, Rector NA, Seeman MV, et al. Current cannibus use and tardive dyskinesia. *Schizophr Res* 1993;11:3–8.
110. Gardos G, Casey DE. *Clinical insights monograph: tardive dyskinesia and affective disorders*. Washington, DC: American Psychiatric Press, 1984.
111. Gualtieri CT. Pharmacotherapy and the neurobehavioral sequelae of closed head injury. *Brain Inj* 1988;2: 101–129.

112. Kane JM, Woerner M, Weinhold P, et al. Incidence of tardive dyskinesia: five year data from a prospective study. *Psychopharmacol Bull* 1984;20:39–40.
113. Jeste D, Karlson CN, Wyatt RJ. Movement disorders and psychopathology. In: DV JESTE, Wyatt RJ, eds. *Neuropsychiatric movement disorders.* Washington, DC: APA Press, 1984.
114. Gualtieri CT, Sprague RL, Cole JO, et al. Tardive dyskinesia litigation and the dilemmas of neuroleptic treatment. *J Psychiatry Law* 1986;14:187–216.
115. Munyon WH, Salo R, Briones DF. Cytotoxic effects of neuroleptic drugs. *Psychopharmacology* 1987;91: 182–188.
116. Tkacz C, Hawkins DR. A preventive measure for tardive dyskinesia. *J Orthomol Psychol* 1981;10:119–123.
117. Lohr JB, Kuczenski R, Bracha HS, et al. Increased indices of free radical activity in the cerebrospinal fluid of patients with tardive dyskinesia. *Biol Psychiatry* 1990;28:535–539.
118. Peet M, Laugharne J, Rangarajan N, et al. Tardive dyskinesia, lipid peroxidation, and sustained amelioration with vitamin E treatment. *Int Clin Psychopharmacol* 1993;8:151–153.
119. Gattaz WF, Emrich A, Behrens S. Vitamin E attenuates the development of haloperidol-induced dopaminergic hypersensitivity in rats: possible implications for tardive dyskinesia. *J Neural Transm* 1993;92:197–201.
120. Tariq M, al-Deeb S, al-Moutairy K, et al. Effect of selenium and vitamin E on iminodipropionitrile induced dyskinesia in rats. *Int J Neurosci* 1994;78:185–192.
121. Adler LA, Peselow E, Duncan E, et al. Vitamin E in tardive dyskinesia: time course of effect after placebo substitution. *Psychopharmacol Bull* 1993;29: 371–374.
122. Akhtar S, Jajor TR, Kumar S. Vitamin E in the treatment of tardive dyskinesia. *J Postgrad Med* 1993;39: 124–126.
123. Dabiri LM, Pasta D, Darby JK, et al. Effectiveness of vitamin E for treatment of long-term tardive dyskinesia. *Am J Psychiatry* 1994;151:925–926.
124. Lohr JB, Caligiuri MP. A double-blind placebo-controlled study of vitamin E treatment of tardive dyskinesia. *J Clin Psychiatry* 1996;57:167–173.
125. Ananth J. Current psychopathological theories of tardive dyskinesia and their implications for future research. *Neuropsychobiology* 1982;8:210–222.
126. Creese I, Burt DR. Dopamine receptor binding enhancement accompanies lesion-induced behavioral supersensitivity. *Science* 1977;197:596–598.
127. Fjalland B, Nielson IM. Enhancement of methylphenidate-induced stereotypies by repeated administration of neuroleptics. *Psychopharmacologia* 1974; 34:105–109.
128. Weiss B, Santelli S. Dyskinesias evoked in monkeys by weekly administration of haloperidol. *Science* 1978;200:799–801.
129. Stahl SM, Davis KL, Berger PA. The neuropharmacology of tardive dyskinesia, spontaneous dyskinesia, and other dystonias. *J Clin Psychopharmacol* 1982;2: 321–328.
130. Casey DE, Povisen UJ, Meidahl B, et al. Neuroleptic-induced tardive dyskinesia and parkinsonism: changes during several years of continuing treatment. *Psychopharmacol Bull* 1986;22:250–253.
131. Waddington JL. Tardive dyskinesia: a critical re-evaluation of the causal role of neuroleptics and of the dopamine receptor supersensitivity hypothesis. In: Callaghan N, Galvin R, eds. *Recent research in neurology.* London: Pitman Books, 1984.
132. Tarsy D, Baldessarini RJ. The pathophysiologic basis of tardive dyskinesia. *Biol Psychiatry* 1977;12:431–450.
133. Fahn S. Therapeutic approach to tardive dyskinesia. *J Clin Psychiatry* 1985;46:19–24.
134. Hershey T, Bhargava N, Sadler M, et al. Conventional versus intensive diabetes therapy in children with type 1 diabetes: effects on memory and motor speed. *Diabetes Care* 1999;22:1318–1324.
135. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol and experience interact to affect rate of recovery after motor cortex surgery. *Science* 1982;217: 855–857.
136. Tsai G, Goff DC, Chang RW, et al. Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. *Am J Psychiatry* 1998; 155:1207–1213.
137. Pandurangi AK, Devi V, Channabasavanna SM. Caudate atrophy in irreversible tardive dyskinesia. *J Clin Psychiatry* 1980;41:229–231.
138. Nielson EB, Lyon M. Evidence for cell loss in corpus striatum after long-term treatment with a neuroleptic drug flupenthixol in rats. *Psychopharmacology* 1978; 59:85–90.
139. Chadwick DREH, Marsden CD. Anticonvulsant-induced dyskinesias: a comparison with dyskinesias induced by neuroleptics. *J Neurol Neurosurg Psychiatry* 1976;39:1210–1218.
140. Jacome D. Carbamazepine-induced dystonia. *JAMA* 1979;241:2263.
141. Muenter MD, Whisnant JP. Basal ganglia calcification, hypoparathyroidism, and extrapyramidal motor manifestations. *Neurology* 1968;18:1075–1083.
142. Cummings JL, Gosenfeld LF, Houlihan JP, et al. Neuropsychiatric disturbances associated with idiopathic calcification of the basal ganglia. *Biol Psychiatry* 1983;18:591–599.
143. Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: late-onset & persistent dystonia caused by antipsychotic drugs. *Neurology* 1982;32:1335–1346.
144. Fahn S. Drug treatment of hyperkinetic movement disorders. *J Clin Psychiatry* 1987;7:192–207.
145. Fahn S. Treatment of tardive dyskinesia: use of dopamine depleting agents. *Clin Neuropharmacol* 1983; 6:151–158.
146. Asher SW, Aminoff MJ. Tetrabenzamine and movement disorders. *Neurology* 1981;31:1051–1054.
147. Casey DE, Denney D. Pharmacologic characterization of tardive dyskinesia. *Psychopharmacology* 1977; 54:1–8.
148. Moore DC, Bowers MB. Identification of a subgroup of tardive dyskinesia by pharmacological probes. *Am J Psychiatry* 1980;137:1202–1205.
149. Gelenberg AJ, Doller-Wojcik JC, Growden JH. Choline and lecithin in the treatment of tardive dyskinesia. *Am J Psychiatry* 1979;136:772–775.
150. Kang UJ, Burke RE, Fahn S. Natural history and treatment of tardive dyskinesia. *Mov Disord* 1986;1: 193–208.
151. Gualtieri CT, Hicks RE, Patrick K, et al. Clinical correlates of methylphenidate blood levels. *Ther Drug Monit* 1984;6:379–392.

152. Gualtieri CT, Keppel JM, Schroeder SR. Tardive dyskinesia: new facts and new recommendations. *Psychiatr Aspects Ment Retard Rev* 1986;5:1–6.
153. Glazor W, Moore DC, Schooler NR, et al. Tardive dyskinesia: a discontinuation study. *Arch Gen Psychiatry* 1984;41:623–627.
154. Yassa R, Nair V, Schwartz G. Tardive dyskinesia: a two-year follow-up study. *Psychosomatics* 1984;25.
155. Chouinard G, Annable L, Mercier P, et al. A five-year follow-up study of tardive dyskinesia. *Psychopharmacol Bull* 1986;22:259–263.
156. Casey DE. Tardive dyskinesia: reversible and irreversible. In: Casey DE, Chase TN, Christensen AV, et al., eds. *Dyskinesia—research and treatment*. Berlin/Heidelberg: Springer-Verlag, 1985.
157. Yagi G, Itoh H. Follow-up study of 11 patients with potentially reversible tardive dyskinesia. *Am J Psychiatry* 1987;144:1496–1498.
158. Quitkin F, Rifkin A, Gochfeld L, et al. Tardive dyskinesia: are first signs reversible? *Am J Psychiatry* 1977; 134:84–87.
159. Kane JM, Weinhold P, Kinon B, et al. Prevalence of abnormal involuntary movements ("spontaneous dyskinesias") in the normal elderly. *Psychopharmacology* 1982;77:105–108.
160. Chaffin DS. Phenothiazine-induced acute psychotic reaction: the "psychotoxicity" of a drug. *Am J Psychiatry* 1964;121:26–32.
161. Singh MM, Kay SR. Dysphoric response to neuroleptic treatment in schizophrenia: its relationship to autonomic arousal and prognosis. *Biol Psychiatry* 1979;14: 277–294.
162. Bachmann KM, Modestin J. Neuroleptic-induced panic attacks in a patient with delusional depression. *J Nerv Ment Dis* 1987;175:373–375.
163. Mikkelsen EJ, Detlor J, Cohen DJ. School avoidance and social phobia triggered by haloperidol in patients with Tourette's syndrome. *Am J Psychiatry* 1981;138: 1572–1576.
164. Moller H, von Zerssen D. Depressive states occurring during the neuroleptic treatment of schizophrenia. *Schizophr Bull* 1982;8:109–117.