Tardive Dyskinesia

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Abstract

Neuroleptic-induced tardive dyskinesia (TD) continues to be a serious problem in the psychopharmacology of schizophrenia. The overall mean prevalence of TD among chronically neuroleptic-treated patients is approximately 24 percent. The annual incidence in younger adults is 4 to 5 percent. Aging is a major risk factor for TD. Our ongoing prospective study suggests that the annual incidence in patients over age 45 is over 30 percent. Other likely risk factors include female gender, mood disorders, "organic" brain dysfunction or damage, diabetes mellitus, and early extrapyramidal side effects. Metoclopramide, a D_2-receptor blocker commonly used in nonpsychiatric medical patients, can also produce persistent TD. TD can best be assessed for research purposes by a combination of subjective and objective methods. In recent years, several instrumental procedures have been developed to objectively quantify various abnormal movements. The advantages and limitations of the traditional rating scales and the newer instrumental approaches are discussed. The course of TD is variable but often not progressive. The early theory that striatal dopamine receptor supersensitivity causes TD has now given way to the hypothesis of multiple neurotransmitter system involvement. Several animal studies have reported striatal neuronal damage with prolonged neuroleptic treatment, although its relevance to TD remains unclear. Treatments for TD, other than neuroleptic withdrawal, are still experimental.

Neuroleptic-induced tardive dyskinesia (TD) was first reported in 1957 (Schonecker 1957), 5 years after neuroleptic drugs were introduced into psychopharmacology. After years of controversy, there is now general agreement that neuroleptics are indeed a major factor in the development of potentially persistent dyskinesia in treated patients. TD may be defined as a syndrome consisting of abnormal, involuntary movements, usually of choreoathetoid type, sometimes stereotyped, principally affecting the mouth and face, sometimes the limbs, and occasionally the trunk, which occurs relatively late in the course of drug treatment and in the etiology of which the neuroleptic treatment is a necessary factor (Jeste and Wyatt 1982).

Epidemiology

Prevalence. Estimating TD prevalence is important in identifying the size and characteristics of at-risk populations, but collating data from various surveys is difficult. Lack of comparable methodology, dissimilar criteria for defining TD, and differences in patient populations are some of the problems faced by reviewers (Jeste and Wyatt 1981*a*). A common difficulty in determining the prevalence of TD is that, paradoxically, neuroleptics also suppress the symptoms of TD. Hence some false negatives, or patients whose dyskinesia is masked by their medication, must be assumed in any prevalence

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study. Furthermore, many schizophrenia patients need continued neuroleptic treatment and cannot easily be taken off neuroleptics.

Yassa and Jeste (1992) recently analyzed data from 76 published studies on the prevalence of TD. These included a total of 39,187 patients. The reported prevalence ranged from 3 to 62 percent, with a mean of 24.2 percent. The mean prevalence during each of the past three decades was as follows: 13.5 percent during the 1960s, 28.6 percent during the 1970s, and 25.1 percent during the 1980s. The authors also looked at possible cultural differences by comparing results from studies in different continents. Notwithstanding the obvious problems involved in such a comparison, Yassa and Jeste found that Asian patients had lower prevalence of TD than North American, European, or African patients. It is unclear whether such a difference is primarily racial-genetic in origin or is due to external variables such as variations in diagnosis and treatment.

In one study, Woerner et al. (1991) evaluated patients at three institutions: a voluntary hospital with a relatively young patient population; a Veterans Affairs (VA) medical center with an older, more chronic population; and a State facility with mostly elderly and chronic patients. This study showed an overall prevalence of TD symptoms of 23.4 percent among patients treated with antipsychotic drugs. The voluntary hospital had the lowest prevalence, at 13.3 percent, and the State hospital had the highest prevalence of 36.1 percent. The authors estimated the rate of false negatives due to antipsychotic drug masking by withdrawing these medications from a subgroup of those patients displaying no TD symptoms. Of this group, 34 percent exhibited withdrawal-emergent dyskinesia, with the State hospital showing a much higher rate (67%) than the voluntary hospital (18%) or the VA facility (17%).

Kane et al. (1988) analyzed the variables related to withdrawal-emergent, or covert, TD and found that patients withdrawn from fluphenazine decanoate had fewer covert symptoms than patients withdrawn from oral medication. Antipsychotic drug dosage did not appear to be related to the development of the disorder, but very high dosages were negatively associated with covert TD. These investigators found a significant positive correlation between withdrawal-emergent TD and age as well as total length of antipsychotic drug treatment.

Although dyskinesia can occur without neuroleptic treatment, such spontaneous dyskinesia is much less common than neuroleptic-induced TD. Owens et al. (1982) initially reported no significant difference in the prevalence of dyskinesia between neuroleptic-treated and untreated schizophrenia patients, but a later analysis (Owens et al. 1985) showed a significant association between neuroleptic use and the prevalence of dyskinesia.

Incidence. A long-term study by Kane et al. (1984, 1988) on over 850 patients suggests that the incidence of TD increases as the length of antipsychotic drug treatment increases, and that for the first several years this progression is linear. The patients in the study had a mean age of 29 years. They were selected without consideration of their psychiatric diagnosis or record of antipsychotic drug treatment. Their median length of lifetime exposure to neuroleptics at baseline was 12 months. The total incidence of TD in this population was 5 percent after 1 year, 10 percent after 2 years, 15 percent after 3 years, and 19 percent after 4 years, with the incidence increasing to 26 percent by the end of the sixth year.

Risk Factors for TD: Patient-Related Variables.

Age. Age appears to be the predominant risk factor for TD. Patients over 40 are three times as likely to develop the disorder as those under 40 (Jeste and Wyatt 1982). Smith and Baldessarini (1980) reported a pronounced linear correlation of the prevalence and severity of TD with age. Older patients also appear to have a less optimistic course of the disease, with fewer instances of spontaneous remission (Kane et al. 1992). The mechanisms for this risk factor remain unclear, but one speculation is that development of TD may be affected by interactions between drug-induced changes in receptors in the striatum and aging-related degenerative effects in the nigrostriatal system. Whether higher plasma levels of antipsychotic drugs due to age-related pharmacokinetic changes (Tran-Johnson et al. 1992) play a role in the predisposition of older patients to TD is entirely unclear. It is also worth stressing that aging is associated with an increased frequency of abnormal movements due to causes other than neuroleptic use (Khot and Wyatt 1991).

Studies of TD in children indicate that they are not immune to persistent TD, and the prevalence

is somewhat higher in older than in younger children (Gualtieri and Hawk 1980; Campbell et al. 1983).

Gender. Gender differences in the prevalence of TD have been reported by a number of researchers. A meta-analysis of the published reports showed that the prevalence was significantly greater in women than in men—the mean values were 26.6 percent and 21.6 percent, respectively (Yassa and Jeste 1992). Furthermore, women tended to have more severe TD and a higher prevalence of spontaneous dyskinesia than men. There appeared to be an interaction between age and gender. Whereas the prevalence of TD seemed to peak in the 50–70-year age group in men, it continued to rise after age 70 in women. It is presently unknown how much these gender differences reflect biological variations and how much they reflect external factors, including differences in neuroleptic treatment.

Psychiatric diagnosis. Casey and Keepers (1988) concluded that schizophrenia patients might be at less risk than patients with other disorders treated with antipsychotics. Kane et al. (1985) reported that the incidence of TD in affective and schizoaffective patients was 26 percent after 6 years, and the rate for schizophrenia patients was 18 percent. Other investigators (Davis et al. 1976; Rosenbaum et al. 1977; Mukherjee et al. 1986; Casey 1988) also have noted that mood disorders, including major depression and bipolar disorder, are risk factors for neuroleptic-induced TD. Even among schizophrenia patients, a history of mood disorders in first-degree relatives may heighten the risk of developing the syndrome (Wegner et al. 1985).

Smoking. Yassa et al. (1987) reported that among neuroleptic-treated psychiatric outpatients, smoking was associated with an increased prevalence of TD. The theoretical rationale for this finding derives from the observation that nicotine stimulates dopamine release from nigrostriatal neurons. Some, but not all, epidemiologic surveys have shown an inverse relationship between smoking and the prevalence of Parkinson disease (which is associated with a central catecholaminergic deficit). The finding of Yassa et al. was replicated by Binder et al. (1987), but not by Menza et al. (1991).

Ethnicity. In a study of 491 chronic psychiatric patients at a State psychiatric hospital in California, Sramek et al. (1991) found no significant differences in the prevalence of TD among three racial ethnic groups: black, white, and Hispanic. The three groups were similar in the mean neuroleptic dosage used. Yassa and Jeste (1992) noted that, of the four continents they studied, the lowest prevalence of TD was reported in Asia.

Diabetes mellitus. Ganzini et al. (1991) found a higher prevalence of TD in diabetic than in nondiabetic patients. Sewell and Jeste (1992) and Sewell et al. (1992) have suggested diabetes mellitus as a risk factor for metoclopramide-induced TD. The mechanisms underlying the susceptibility of diabetic patients to TD are unclear.

"Organic" brain dysfunction. The presence of organic mental syndromes may be a TD risk factor. A study by Yassa et al. (1984) of over 300 patients treated with antipsychotic drugs who had organic mental disorders found evidence that central nervous system damage was a risk factor for TD, but Gold et al. (1991) failed to support an association between TD and global measures of "organicity" that included psychiatric symptom ratings, some tests of cognitive performance, and ventricular enlargement on CT scans. A number of recent investigations have sought to determine the relationship between brain damage or dysfunction and TD (Manschreck et al. 1990; Mion et al. 1991; Brown and White 1992). The results have been variable. Nonetheless, it would seem useful to assess specific neural damage or dysfunction in relation to TD.

Early onset movement disorders. Numerous studies have reported that patients who react to antipsychotic drug therapy with acute or subacute exrapyramidal symptoms may be at greater risk for developing TD with continued treatment (Kane et al. 1992).

Drug Treatment Variables.

Neuroleptic type. To date, no obvious differences in the risk of TD have been shown among commonly used neuroleptics. A possible exception is the evidence suggesting low susceptibility to TD with sulpiride and clozapine; overall, the data on clozapine are more impressive (Kane et al. 1992).

Neuroleptic dosage. Most studies that have attempted to address this issue (Jeste and Wyatt 1982; Gardos et al. 1988) have been unable to show a definite association between the development of TD and drug variables such as length of treatment, lifetime dosage, or type of drug. Baldessarini et al. (1988) have suggested that the difficulty in finding a relationship between these variables and the appearance of dyskinesia may be

attributed to the relatively high dosage received by many patients.

Drug holidays. Ayd (1966) suggested that reducing cumulative antipsychotic drug exposure might reduce the risk of developing TD. This course was endorsed by the American College of Neuropsychopharmacology–FDA Task Force (1973), but clinical studies in the interim have indicated that interruptions of drug therapy either have no effect or may actually increase the risk of persistent TD as well as the risk of relapse in some patients (Jeste et al. 1979; Goldman and Luchins 1984). Herz and colleagues (1982) proposed intermittent neuroleptic treatment as a means of reducing the risk of TD. Two later studies found, however, that intermittent neuroleptic treatment was associated with significantly higher rates of episodes of both psychotic and dysphoric-neurotic symptoms (Jolley et al. 1989) or of decompensations and hospitalizations, along with more impaired work functioning (Carpenter et al. 1990), than continuous low-dose neuroleptic treatment.

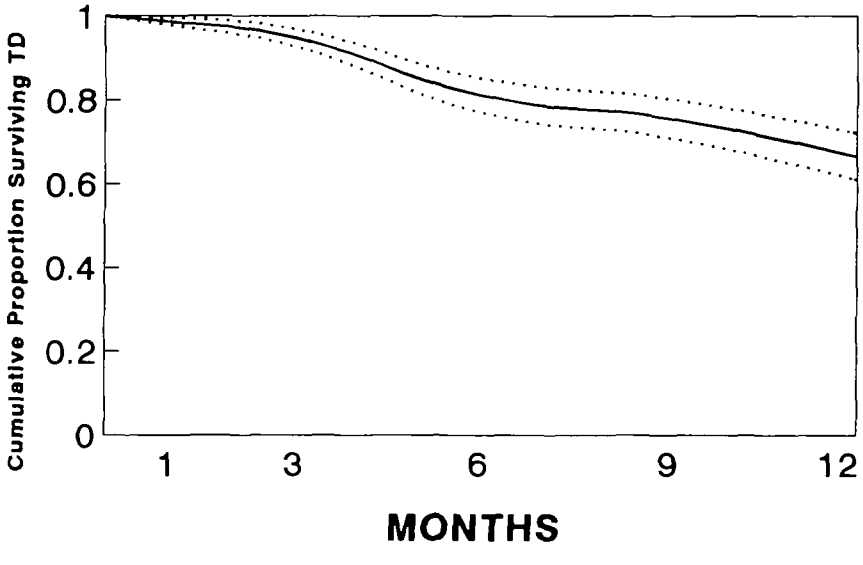
Concomitant medications. Most clinicians have observed that anticholinergic drugs aggravate the symptoms of TD, and withdrawal improves its symptoms. This has led to speculation that these drugs may also promote the development of the disorder, but Gardos and Cole (1983) concluded that there was no increase in the prevalence of TD in patients receiving these medications.

Prospective Study of the Incidence in Patients Over Age 45. We have been studying the incidence of TD in psychiatric outpatients over the age of 45. The patients are enrolled early in the course of their neuroleptic treatment—many with less than 90 days of lifetime treatment with neuroleptics when they enter the study. All the patients receive a comprehensive psychiatric, neurologic, medical, and neuropsychologic evaluation as well as an instrumental assessment of tremor, rigidity, bradykinesia, and dyskinesia. Details of the evaluation and treatment are described elsewhere (Harris et al. 1992). Patients are treated with the lowest effective doses of neuroleptics—usually less than 300 mg chlorpromazine equivalent daily. The treatment strategy is individualized to suit each patient's needs except that, where possible, the patients are assigned randomly to either haloperidol or thioridazine. To the extent clinically feasible, use of any medications is kept to a minimum. Patients are followed at 1 month, 3 months, and every 3 months thereafter.

Preliminary results of our study based on 68 patients were published previously (Harris et al. 1992). Below we present findings from a subsequent analysis of the data on 204 patients, including the original 68. The mean age of our patients was 66 (standard deviation 12) years, and 83 percent were men. The three most common psychiatric diagnoses were dementia (26%), schizophrenia (21%), and mood disorder (17%). Figure 1 shows a survival curve for TD. The criteria for TD were similar to those of Schooler and Kane (1982), except that the required minimum duration of total neuroleptic exposure was 1 month instead of 3 months, and we assessed right and left limbs separately.

The total incidence of TD after 12 months of study-treatment (i.e.,

Figure 1. Proportion of patients surviving tardive dyskinesia (TD) (i.e., not having TD) at the beginning of specified time intervals



Note.—Dotted lines indicate 95-percent confidence intervals.

the total number of patients who manifested TD for the first time during this 12-month period) was 33.3 percent (standard error 5.6%) using the Life Tables analysis (Cutler and Ederer 1958). The incidence was over 40 percent using somewhat more lenient criteria. These lenient criteria differed from those mentioned above only in that they required a minimum of one score of 2 on any of the first seven AIMS (Abnormal Involuntary Movement Scale; National Institute of Mental Health 1975, 1976) items instead of a minimum of two scores of 2 or one score of 3 (Jeste and Yassa, in press). We should mention that, in our earlier analysis of the data on 68 patients, the incidence of TD after 6 months of study-treatment was 27 percent, using the lenient criteria for TD (Harris et al. 1992).

Cox regression (proportional hazards; survival analysis with covariates) on one predictor at a time yielded trends for significant relationship ($p < 0.1$) between TD risk and each of the following measures at baseline: Dementia Rating Scale (Mattis 1976), total score; Rockland TD Scale (Simpson et al. 1979), total score; and the instrumental measure of hand tremor. Interestingly, the risk of TD was not predicted by certain expected variables such as age, gender, diagnosis of mood disorder, severity of depression, or severity of overall psychopathology.

Our results are comparable to those of Saltz et al. (1991), who reported a 31 percent incidence of TD after 43 weeks of cumulative neuroleptic treatment. This similarity in findings is notable, considering that the patients in that study were older (mean age 77 years), were predominantly female (72%), and included many patients in nursing homes and other geriatric inpatient services. Taken together, these two studies clearly point to a markedly elevated risk of neuroleptic-induced TD among patients over age 45.

TD in Nonpsychiatric Patients Treated With Metoclopramide. Metoclopramide is a dopamine D_2-receptor blocker, commonly used in medicine to treat vomiting, gastroesophageal reflux, gastric stasis following vagotomy, and diabetic gastroparesis. Although it has reportedly been found useful in treating psychotic symptoms (Stanley et al. 1980), the doses needed are quite high. There have been published cases of metoclopramide-associated TD (Sewell et al. 1992). Sewell and Jeste (1992) reviewed the literature and found 67 such case reports. Although there are no published studies of its incidence or prevalence, metoclopramide-induced TD is not rare. In the case reports reviewed, the mean length of treatment with metoclopramide before the onset of TD was 20 months. In 71 percent of the patients followed long-term, the dyskinesia was still present at least 6 months after metoclopramide had been discontinued. Unfortunately, there is much less awareness of the risk of persistent TD with metoclopramide than with the neuroleptics used in psychiatric patients.

Assessment of TD

Gardos et al. (1977) reviewed the state of TD assessment and concluded that an absence of reliable and precise assessment methods might have been partly responsible for our inability to delineate the syndrome, determine its prevalence, and evaluate the efficacy of putative treatments. The assessment methods have improved during the past 15 years.

Many patients undergoing treatment with neuroleptics also develop tremors, tics, dystonia, and myoclonus (Jeste and Wyatt 1982). There is ample evidence supporting the notion that TD and drug-induced parkinsonism frequently coexist (Caligiuri et al. 1991*a*). Differentiating dyskinesia from other hyperkinetic movement disorders is difficult, but critical to effective diagnosis and management of the disorder.

Factors Influencing Assessment. Certain factors may also influence the diagnosis and assessment of TD. They include, but are not limited to, voluntary suppression, motor activation, stress, and masking by neuroleptics.

Voluntary suppression. A patient may consciously suppress the involuntary movements temporarily. Clinicians' attempts to divert the patient's attention may be problematic because such diversionary strategies are nonstandard and may induce additional variation in the intensity of dyskinesia.

Motor activation. Ancillary motor activity can either increase or decrease the severity of TD. Voluntary movements of the dyskinetic part tend to suppress dyskinesia; those of unaffected parts of the body may increase the TD.

Stress. Psychological stress has been shown to increase dyskinetic movements. Conversely, relaxation and sedation reduce the severity of TD.

Masking of TD by neuroleptics. Neuroleptic withdrawal may initially aggravate the intensity of dyskinesia; restarting or increasing

the dose of neuroleptics may suppress it for at least a few days.

Measurement of TD. The measurement of dyskinesia may take various forms, and no single measurement tool is considered ideal. The overall usefulness of a particular assessment procedure is determined by the goal of assessment, whether the procedure will be used for clinical or research purposes, and careful consideration of the advantages and limitations of the procedure.

Self-reports. The reliability of self-rating among psychiatric patients may be open to question. Nevertheless, if reliable, and when monitored over a 24-hour period, self-ratings of TD may be useful in assessing the variability of the disorder, diurnal patterns, and the effects of environmental stress.

Observer ratings. Traditionally the assessment of TD has involved using one of several available rating scales, including the AIMS and the Rockland Dyskinesia Rating Scale (Simpson et al. 1979). For a more complete listing of rating scales, see Kane et al. (1992). The AIMS is the most frequently used TD scale. It identifies seven areas of the body and their most common abnormal movements and assesses each such movement on a scale of 0 to 4. It also allows for a global severity rating. The AIMS is a reliable rating scale for trained raters, but it does not distinguish between TD and other movement disorders. The Rockland scale differs from the AIMS in that it uses a 34-item scale with a scoring range of 1 to 6 that includes definitions of each scoring point. It is designed to be more specific for TD than the AIMS (although it does contain some items not specific to TD, such as restless legs and akathisia), and is also considered a reliable rating system when used by trained staff.

The use of standardized rating scales is beneficial in the initial assessment of TD, but their follow-up value is also important. When administered at regular intervals, these scales can assist clinicians in judging the progression of symptoms in a diagnosed patient, in detecting sudden changes in the severity of symptoms, and in assessing response to treatments. We should point out, however, that the rating scales are not diagnostic instruments.

As noted by Bartzokis et al. (1989), the quality of scoring on rating scales is subject to the experience of the examiner. Most rating scales provide criteria for scaling the severity of movements, but these criteria differ. For example, the severity of choreoathetoid movements may be rated based on (1) their frequency of occurrence throughout the observation period, (2) the amplitude of movement or distance the limb or body region travels, (3) the speed or acceleration of movement, (4) the distribution of movements across body regions, (5) the bizarre quality of movement, (6) how disturbing the movement is to the patient, and/or (7) whether the movement disrupts purposeful function. Any of these attributes is likely to be the focus of an observer, and more important, the focus may change as the clinician becomes more familiar with the patient.

Videotaping the patient while rating the distribution and severity of TD is useful for increasing the validity and reliability of TD assessment. Valuable data may be stored and retrieved for longitudinal studies. Videotapes may be used for training purposes and for evaluating reliability of individual raters and the variation among raters.

Objective instrumental procedures. Objective instrumental procedures for quantifying tremor were initially reported over 100 years ago (Peterson 1889). Although TD was recognized as a clinical problem in psychiatry in the late 1950s, instrumental procedures for assessing TD did not appear until 1973 (Jus et al. 1973). Instrumental assessments are designed to enhance our understanding of TD and thereby help us prevent and treat it (Lohr and Caligiuri 1992). Instrumental procedures for objectively quantifying dyskinesia have been slow in developing; however, with recent advances in computer technology and ease of utilization, movement quantification is likely to become more widely accessible.

Certain essential requirements must be fulfilled when considering the use of an objective instrumental measurement of abnormal movements. The technique should provide data that are reliable, sensitive, and valid for the pathology being measured. The apparatus should be relatively easy to use, the machine-patient interface should be uncomplicated, and the transduction system should be easy to maintain. Finally, the measurement system should be portable so that its use is not confined to an instrumentation laboratory. Below we describe three commonly used instrumental procedures.

Accelerometry. Accelerometers are widely used to quantify involuntary movements such as tremor and dyskinesia. An accelerometer is a miniature piezoelectric or strain gauge device that responds to acceleration in a single plane.

The device may be attached to the finger, hand, foot, or leg without obstructing natural movement. Acceleration due to motion in a particular vector is transduced. Accelerometry, in general, has high sensitivity and concurrent validity with observer ratings (Alpert et al. 1976; Chien et al. 1977; Fann et al. 1977; Tryon and Pologe 1987; Lohr et al. 1990).

Force procedures. Force gauges or load cells may be used to evaluate dyskinesia. The basic assumption underlying isometric force procedures is that dyskinetic movements are a direct consequence of random muscle contractions and that these muscle contractions produce changes in measurable force over time (Caligiuri and Lohr 1989, 1990; Caligiuri et al. 1991*b*).

Ultrasound. Ultrasonic transduction of movement involves the Doppler or pulse echo technique (McClelland et al. 1987; Bartzokis et al. 1989; Kern et al. 1991). The ultrasound procedures are suitable for both brief screening and clinical monitoring of TD in a naturalistic setting, and the procedure is noninvasive. Ultrasound has not attained wide usage, however, because of the costs of purchase and maintenance, difficulties in calibration, and lack of anatomic specificity.

Several currently available quantitative instrumental measures appear to correlate significantly with rating scales, and in some cases may be able to detect subclinical dyskinesia and help differentiate TD from other movement disorders. The combination of subjective ratings and objective measurements of TD can frequently yield more information about the disorder than a single procedure (Gardos et al. 1977).

Course

One study found no change in the prevalence rate in a 4-year period because the number of new TD cases matched the number of patients who no longer manifested symptoms (Richardson and Casey 1988). Barron and McCreadie (1983) reported that of 103 patients assessed at a 1-year interval, 55 percent did not display TD symptoms in either examination, 18 percent had TD at both examinations, 9 percent developed TD de novo, and 18 percent no longer had the condition. A 3-year followup described by Barnes et al. (1983) on 99 of the original 182 patients showed that the point prevalence for TD increased from 39 to 47 percent. Of the 60 patients who did not have TD in the original assessment, 22 developed the condition, while 14 of the 39 patients with symptoms had a remission.

Glazer et al. (1990) reported that the predictors of improvement in TD after neuroleptic discontinuation included diagnosis of affective or schizoaffective disorders, duration of psychiatric illness, being employed, younger age, and higher neuroleptic dose before withdrawal. Conversely, the most important predictors of persistence of TD among patients continued on neuroleptics were older age and the presence of non-orofacial TD at baseline (Glazer et al. 1991).

Time appears to be a critical factor in the outcome of TD patients. The lessening or disappearance of symptoms seems to be positively correlated with the length of followup: Those studies with followups of more than 5 years show the most patients with resolving symptoms. Casey and Gerlach (1986) found that TD improved in 50 percent of patients whether or not antipsychotics were used. These findings challenge the conventional wisdom that continued use of neuroleptics in patients with TD always makes TD more severe and persistent.

In most studies it also appears that TD gradually improves or stabilizes over a period of years rather than within the first year of followup. It may be that the TD improves as slowly as it tends to develop, so rather than seeing it as a reversible or irreversible condition, it may be more helpful to view it as being on a continuum from resolution to persistence.

Complications

The development of TD in patients treated with neuroleptics may be accompanied by both physical and psychosocial complications that can have serious consequences.

Among the most common physical complications of the oral manifestations of TD are dental and denture problems. Oral dyskinesia may also result in traumatic ulceration and even infection of the tongue, cheeks, and lips of patients. Oral dyskinesia can result in muffled speech, which may become unintelligible as the patient's diction is interrupted by continual movements of the tongue and lips (Portnoy 1979). Swallowing disorders are another, although uncommon, complication of oropharyngeal dyskinesia. Respiratory disturbances in the form of irregularities in rate, depth, and rhythm of respiration accompanied by reflexive grunting, snorting, and gasping as well as shortness of breath have also been reported. Casey and Rabins (1978) described a severe case in a patient whose symptoms included frequent vomiting, retching, aerophagia, and

the paroxysmal contraction and distension of the abdominal wall related to irregular respiration. Weight loss is an uncommon complication of severe TD.

Patients with TD may also be more vulnerable to falls and injuries resulting from gait disturbances. A study of life expectancy of TD patients by Mehta et al. (1978) found that 19 dyskinetic patients had died after 5 years compared with 12 patients in the control group. However, such an association with shortened longevity was not found by Kucharski et al. (1979).

The abnormal involuntary body movements that characterize TD can produce serious psychosocial problems in patients suffering from this disorder. These patients may be stigmatized. Particularly among outpatients, the shame, guilt, anxiety, and anger that these symptoms can cause may result in depression.

Pathophysiology

Supersensitivity of striatal dopamine (DA) receptors was previously thought to be the mechanism involved in the development of TD. A number of studies have pointed to the shortcomings of this hypothesis (Jeste and Wyatt 1981*b*). Briefly, this supersensitivity may be a normal consequence of neuroleptic treatment and does not explain why TD develops and persists only in some patients. It now seems that several neurotransmitter systems may be affected. These include dopaminergic, noradrenergic, gamma-amino-butyric acid (GABA)ergic, cholinergic, and peptidergic pathways. The literature suggests that TD may be associated with increased central dopaminergic and noradrenergic activity and reduced GABAergic and cholinergic activity. It is possible, though unproven, that there are subtypes of TD, each with a somewhat different profile of neurochemical alterations.

In recent years, interest has also focused on neuroleptic-induced neuronal pathology. Jeste et al. (1991) reported that rats treated with fluphenazine for 8 months had a significantly lower density of large striatal neurons than vehicle-treated rats or rats treated with fluphenazine for 4 months. The results of 12-months' treatment seemed to be confounded by effects of aging—that is, the aged controls (vehicle-treated rats) also had very low values. Benes et al. (1983) and Meshul and Casey (1989) have reported electron microscopic changes in the rat striatal neurons with haloperidol treatment. It is unclear whether such neuroleptic-induced striatal pathology is relevant to persistent TD.

Treatment of TD

Despite the efforts of researchers, as yet there appear to be no consistently reliable therapies for patients who develop the syndrome. There has been some methodologic progress in the quality of recent investigations, with more studies using double-blind design and standardized rating scales such as the AIMS or the Rockland TD Scale. Yet, analysis of treatment results for this disorder is still frustrated by other methodological problems such as small sample sizes and short durations of treatment trials (Jeste et al. 1988).

Neuroleptic Withdrawal. This is the most logical treatment of neuroleptic-induced TD. In many chronic schizophrenia patients, however, a discontinuation of neuroleptics may not be immediately feasible because of a risk of relapse or exacerbation of psychotic symptoms. Nonetheless, at least an attempt at a dosage reduction is warranted in most cases.

Neuroleptics. Ironically, neuroleptics have proved to be the most effective suppressors of TD symptoms. Because symptoms quickly return when treatment is withdrawn, however, this suppression almost certainly represents a masking effect rather than a cure, and except in the more severe cases, neuroleptics should not be used as a treatment. A compilation of the results of studies on the effectiveness of neuroleptics in suppressing TD shows that approximately 66 percent of patients experience an improvement in symptoms of 50 percent or more. Because this improvement is greater than that with most other sedative drugs or a placebo, these results indicate that neuroleptics probably have an intrinsic ability to suppress TD symptoms (Jeste et al. 1988).

In recent years, there has been a growing interest in the use of atypical neuroleptics for the treatment of TD. Lieberman et al. (1991) reviewed eight published studies on the effects of clozapine on TD. Overall, clozapine had a beneficial effect (50% or greater reduction in symptom severity) in approximately 43 percent of patients with TD. Given the elevated risk of potentially fatal agranulocytosis and the consequent need for a weekly monitoring of white blood cell counts, the use of clozapine for the treatment of TD should be restricted to patients with severe TD, especially tardive dystonia.

Other treatments. A large number of experimental treatments have been used in TD patients with variable success. Prominent among these are noradrenergic antagonists such as clonidine and propranolol and GABAergic agents such as the benzodiazepines. For a detailed review of the studies of such treatments, the reader may refer to Jeste et al. (1988). While considering the use of any pharmacologic agents in the treatment of TD, one must consider their risk-benefit ratio in a given patient. These drugs benefit only some patients with TD and, furthermore, can have their own side effects. Below we consider one experimental treatment strategy as an example.

Vitamin E. Lohr et al. (1988) suggested that chronic use of neuroleptics may lead to an excessive production of free radicals, which in turn may damage catecholaminergic and other neurons. Such structural changes may underlie the development of persistent TD. The authors, therefore, tested the efficacy of vitamin E (alpha-tocopherol), a safe but highly potent scavenger of free radicals, in the treatment of TD. Fifteen patients with persistent TD were treated with vitamin E and placebo in a randomized crossover trial. Vitamin E (400–1,200 I.U./day) was more effective than placebo, with the greatest improvement occurring in patients with a short duration of TD. This finding was replicated by Elkashef et al. (1990) and Adler et al. (1992). Egan et al. (1992) did not find a significant difference between vitamin E and placebo; however, in patients with a relatively short duration of TD, vitamin E was more effective than placebo, and this effect was not due to an increase in the blood levels of neuroleptics. Overall, the amount of published data on vitamin E is too limited to allow generalizable recommendations. Nonetheless, this relatively nontoxic agent may be tried in moderately severe or severe TD of relatively short duration.

Prevention of TD. There is no known definitive means of preventing TD in patients in whom neuroleptic maintenance is indicated. As mentioned under "Risk Factors," the value of drug holidays or intermittent treatment is questionable. The incidence of TD may be lower with atypical neuroleptics such as clozapine, although these agents have other adverse effects. The best strategy to reduce the risk of TD is to restrict the long-term use of neuroleptics to well-defined indications, to employ these drugs in the lowest effective doses, and to evaluate patients at frequent intervals for early signs of TD.

Future Directions

Future investigations should seek to clarify a number of issues. For example, what is the relative contribution of each known risk factor to the development and persistence of TD? What are the exact mechanisms underlying persistent TD? It is likely that we will see further evolution of objective methods for assessing TD. There is a critical need to study strategies for the treatment and, even better, the prevention of TD. Alternatives to the traditional neuroleptic treatment of schizophrenia must be developed.

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