Prospective Study of Tardive Dyskinesia Incidence in the Elderly

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Objectives.—To investigate the incidence of tardive dyskinesia in elderly individuals beginning treatment with antipsychotic drugs and to identify risk factors for the development of tardive dyskinesia in the elderly.

Design.—A cohort of previously neuroleptic-naive patients was identified at the time of initiation of antipsychotic drug treatment. Patients were evaluated at baseline and followed up at 3-month intervals for periods ranging from 3 to 119 weeks.

Setting.—Subjects were recruited from the psychiatric and geriatric medical services of two medical centers, a geriatric institute, and three nursing homes in the metropolitan area of New York City, NY.

Patients.—Two hundred fifteen individuals older than 55 years have entered the study thus far. Preliminary data are presented for 160 patients who were followed up for at least 1 month. Their age range was 57 to 99 years (mean, 77 years). Seventy-two percent were women and 87% were white. Sixty-seven percent of patients had a diagnosis of organic mental syndrome and 42% had a psychiatric diagnosis.

Interventions.—A naturalistic, longitudinal, repeated assessment paradigm was employed. Assessments included abnormal involuntary movements, extrapyramidal signs, psychiatric symptoms, and medical and drug treatment histories.

Main Outcome Measure.—The incidence of tardive dyskinesia was determined using a standardized rating instrument and survival analysis.

Results.—The incidence of neuroleptic-induced dyskinesia was 31% (95% confidence interval, 20%, 42%) after 43 weeks of cumulative neuroleptic treatment. Psychiatric (as opposed to organic) diagnosis and presence of extrapyramidal signs early in treatment were associated with increased tardive dyskinesia vulnerability.

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NEUROLEPTIC drugs are frequently used to treat behavioral disturbance and mental illness in elderly patients.[1,2] Previous work indicates that the elderly are more susceptible to problems associated with the side effects of neuroleptic drugs, including tardive dyskinesia (TD). In fact, increasing age has been the most consistently reported risk factor for TD development.[3-13] Published prevalence estimates, which have varied widely due to method and sample differences, range from 0.5% to 56%.[3-14] Jeste and Wyatt[13] reported that the prevalence of TD in patients older than 40 years is nearly three times that of patients younger than 40 years. In a recent survey of 2250 individuals at five sites, which employed the same raters and methods throughout, Woerner et al[15] reported dyskinesia rates varying from 13% in a voluntary psychiatric hospital to 36% in a sample of psychiatric patients at a state hospital. There was a steady rise in prevalence with age, more pronounced for women than for men. The rate was 67% among the geriatric inpatients in the state hospital and 16.5% among nonpsychiatric geriatric inpatients with a relatively brief duration of neuroleptic exposure ($\bar{x}$ = 18 months).[16]

Although these data suggest an increased risk of dyskinesia for elderly patients, prevalence rates based on cross-sectional data are not definitive. Increased incidence and persistence may each contribute to higher prevalence, as may increased severity because of greater likelihood of detection. Both severity and persistence of dyskinesia have been found to increase with age.[11,17,18] Finally, high rates of spontaneous dyskinesia in elderly populations have been reported,[9,10] raising questions about the validity of TD diagnoses.

Results from a prospective study of more than 600 psychiatric patients conducted by our research group indicated an incidence of 18.5% following 4 years of cumulative neuroleptic exposure.[19] These patients were relatively young ($\bar{x}$ = 28 years); nonetheless, age was a risk factor with TD risk increasing dramatically after age 40 years.

We report the findings from the first 3 years of an ongoing prospective study of geriatric patients starting neuroleptic treatment for the first time. The same methods were used throughout and were aimed at assessing incidence of TD among the elderly, and the risk factors contributing to its development.

METHODS

Subjects

Subjects were recruited from the psychiatric and medical geriatric services of two medical centers, a geriatric institute, and three nursing homes in the metropolitan area of New York City, NY. All patients aged 55 years or older and about to start neuroleptic

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treatment for any indication were screened. Those with a previous history of neuroleptic treatment or those with neurological disorders, such as Huntington's or Parkinson's disease for which they were being treated and which may have produced abnormal movements, were excluded.

Assessments

The following assessments were completed at study entry: reviews of medical records and interviews with patients, relatives, and treatment staff to obtain demographic, medical, and psychiatric histories; semistructured interviews with ratings on the Mini-Mental State examination,[20] Brief Psychiatric Rating Scale,[21] and Global Assessment Scale[22]; the Nurse's Observational Scale for Inpatient Evaluation,[23] a standardized examination for abnormal involuntary movements and extrapyramidal side effects with ratings on the modified Simpson Dyskinesia Scale (SDS)[16,23] and the Simpson-Angus Extrapyramidal Side Effect Scale (SAEPS).[24] The SAEPS was repeated weekly for the first 4 weeks, then quarterly; the SDS was repeated at 1 month and then quarterly. The Nurse's Observational Scale for Inpatient Evaluation, and medication history interviews were repeated every 3 months. The remaining scales were repeated every 6 to 12 months thereafter. Psychiatric and medical diagnoses were taken from the clinical records; *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*[25] criteria were employed at the study sites.

The SDS includes 28 items and a six-point global score. In addition, the seven body-area items of the Abnormal Involuntary Movement Scale[22] are rated. Interrater reliability (intraclass correlation coefficient) was .91 on the SDS global rating, for the team of three trained raters.

Patients with a global score of 1 (questionable) or greater were examined by a second rater and, in some cases, a third to confirm the severity level. A global rating of at least 2 (mild TD), determined by two independent examiners, was required to designate a patient with TD. For 97% of the patients with TD, severity criteria according to the Research Diagnosis for Tardive Dyskinesia[26] were also fulfilled; these require Abnormal Involuntary Movement Scale ratings of "mild" movements in two or more body areas, or "moderate" or greater in one. Whenever possible, patients who were presumed to have TD were videotaped. The following evaluations were used to identify possible false-positive results: neurological examination, clinical laboratory testing (complete blood cell count and chemical analysis, VDRL test, erythrocyte sedimentation rate determination, levothyroxine sodium (T_4) radioimmunoassay, determination of serum ceruloplasmin levels, and noncontrast computed tomographic scan). Patients were examined with the SDS and SAEPS monthly for 3 months, then every 3 months thereafter.

No attempt was made to influence patients' treatment regimens; however, discontinuation of neuroleptic therapy was encouraged if TD developed. Actually, a majority of patients, those with TD and those without, were withdrawn from medication periodically, some for long periods, by their clinicians.

Statistical Methods

Survival analysis was used to estimate TD incidence and to assess risk factors for TD development. The analyses of single categorical prognostic factors (eg, gender) used life-table analysis, in which the survival curves were estimated by the Kaplan-Meier method; the equality of the curves was tested by nonparametric Mantel-Cox and Breslow rank tests.[27] The Breslow rank test, which gives more weight to early observations, is reported in the results below. The analyses of continuous prognostic variables (eg, age) and those using sets of prognostic variables simultaneously, employed the Cox proportional hazards regression model.[28]

RESULTS

Sample

Of the 215 patients included here, 99 were seen prior to any neuroleptic treatment and 116 had minimal treatment (median, four doses) prior to baseline. Forty-six of the 215 were later dropped from the database because neuroleptic treatment was never instituted (23 patients), therapy was continued for less than 2 weeks (18 patients), or information indicating substantial prior neuroleptic treatment was later obtained (five patients).

Fourteen patients had abnormal involuntary movements at baseline. Five of these were withdrawn from the study due to prior neuroleptic treatment as noted above. The other nine patients with baseline dyskinesia were excluded from the analyses of incidence and risk factors, but have been followed up to determine the effects of treatment on preexisting "spontaneous" dyskinesias. The remaining 160 subjects were considered at risk for TD development and were included in the analyses.

Abnormal Movements at Baseline

Of the nine patients with baseline dyskinesia, four had taken neuroleptics for one to 14 days prior to examination, and five had never been treated with neuroleptics. When calculating prevalence using only patients with TD with no treatment prior to baseline, the rate of "spontaneous" dyskinesia is 5% (five of 99 patients). If we include subjects with minimal prior exposure, the rate is 4.3% (nine of 210 patients). Movements were predominantly orofacial; eight patients' dyskinesias were mild in severity and one patient's condition was rated moderate. A complete blood cell count and chemical analysis were obtained for eight of the nine patients; neurological examinations, computed tomographic scans, and T_4 radioimmunoassays were obtained for six patients; VDRL tests and erythrocyte sedimentation rate determinations for four patients; and determination of serum ceruloplasmin levels for two patients. No definitive explanation for the abnormal movements was derived from these tests, except for one patient with sensory deficit secondary to tumor resection. This was judged by the neurologist to be definitely implicated in the movement disorder. Six of the nine patients with baseline dyskinesia had conditions that could result in abnormal movements. These were stroke (three patients), multi-infarct dementia (two patients), and Alzheimer's disease (one patient). The movements persisted for at least 3 months (range, 3 to 21 months) in five patients, fluctuated over time in one patient, and were masked by the institution of neuroleptic treatment in one patient. Two patients have not been followed up for 3 months.

Characteristics of the At-Risk Sample

As shown in the Table, the at-risk subjects' ages ranged from 57 to 99 years (mean ± SD, 77 ± 9.0) and they were predominantly white (87%) and female (72%). One hundred seven (67%) had an organic mental syndrome diagnosis and 67 (42%) a psychiatric diagnosis (primarily major affective disorder). Subjects were a mean of 74 ± 12.4 years old at first neurological or psychiatric treatment and had had 5.6 ± 16.3 months of inpatient treatment at study entry.

Patients' medical histories revealed cardiovascular disease in 107 (67%), neurological disease in 69 (43%), connective tissue disease in 46 (29%), cancer in 21 (13%), endocrine disorder in 37 (23%), gastrointestinal disorder in 43 (27%), and genitourinary disorder in 29 (18%). Prior to study entry, 48 (30%) had been treated with antidepressants

Subject Characteristics at Study Entry (N = 160)	
Age, y	
Mean	77
SD	8.9
Range	57-99
Education, y	
Mean	10.0
SD	3.8
Range	0-19
Organic mental syndrome diagnosis	
None	33%
Dementia (senile dementia of Alzheimer's type and multi-infarct dementia)	29%
Organic affective syndrome	4%
Organic delusional syndrome	15%
Other delirium or substance-related syndromes	18%
Age at onset of neurological or psychiatric treatment, y	
Mean	73
SD	12.8
Range	16-98
Gender	
Male	28%
Female	72%
Race	
White	87%
Black	8%
Hispanic	4%
Asian	1%
Psychiatric diagnosis	
None	58%
Schizophrenia or schizoaffective disorder	2%
Major affective disorder	31%
Other	9%
Total inpatient months	
Mean	5.6
SD	16.5
Range	0-108

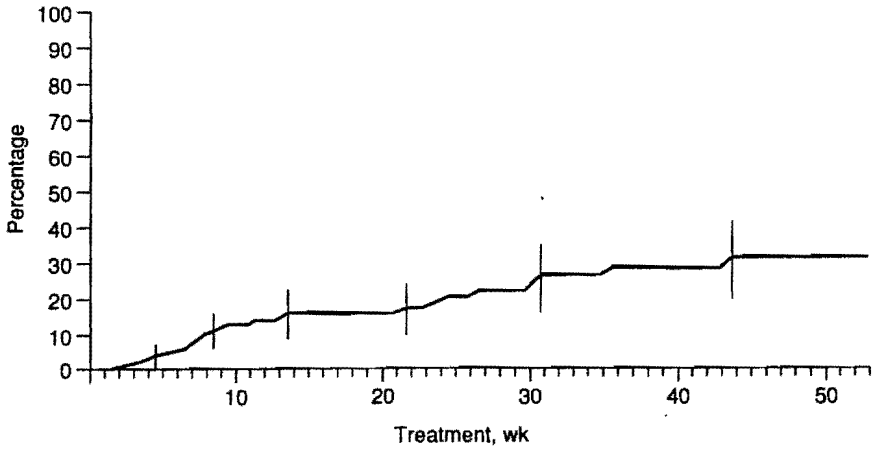

Fig 1.—Percentage of patients developing tardive dyskinesia by weeks of neuroleptic treatment. Vertical bars indicate 95% confidence intervals.

(13 [8%] for more than 6 months), 58 (36%) with anxiolytics, 16 (10%) with hypnotics, 8 (5%) with lithium, 10 (6%) with anticonvulsants, 5 (3%) with stimulants, and 8 (5%) with electroconvulsive therapy. In addition to neuroleptics, during the course of the study 66 patients (41%) were treated with anxiolytics, 62 (39%) were treated with antidepressants, 34 (21%) were treated with anticholinergics, and 8 (5%) were treated with lithium.

Indications for Neuroleptic Therapy

According to medical record review, clinical indications for neuroleptic use were psychosis and agitation associated with a variety of conditions, ranging from Alzheimer's disease to delusional depression. According to our behavioral ratings at baseline, of the 160 subjects, 106 (66%) exhibited psychotic symptoms with or without agitation or dementia; 42 (26.3%) exhibited agitation alone or with dementia; 8 (5.0%) showed dementia alone; and 4 (2.5%) did not exhibit dementia, psychosis, or agitation.

Cases of Dyskinesia Identified During Follow-up

Follow-up ranged from 3 to 119 weeks for the 160 subjects. Twenty-eight patients with dyskinesia were identified during follow-up, all but one case were mild in severity; orofacial movements predominated. Computed tomographic scans and complete blood cell counts were obtained for 23 of the 28 patients; chemical analyses of the blood for 20; neurological examinations for 19; T_4 radioimmunoassays and VDRL tests for 15; erythrocyte sedimentation rate determinations for 12; and determinations of serum ceruloplasmin levels for nine patients. No clear false-positive results were identified by these tests. Sixteen patients (57%) had preexisting conditions that could cause abnormal movements, although movements were not evident at baseline. These were stroke with or without dementia in 11 patients, Alzheimer's disease in two patients, estrogen treatment in two patients, and delirium in one patient. Twenty-three patients were followed up for at least 3 months after TD was diagnosed; for 18 patients, movements persisted for at least 3 months (range, 3 to 25 months). Seventeen patients were not taking neuroleptics at the time of TD diagnosis.

Incidence of Dyskinesia.—Since neuroleptic treatment was intermittent for most patients, survival analyses were conducted in two ways, calculating incidence as a function of time while the patient was taking neuroleptics and of real (calendar) time under observation.

The mean time (±SD) in follow-up was 35.3 (±29.8) weeks (range, 3 to 119 weeks); the mean cumulative time while taking neuroleptics was 22.7±25.2 weeks (range, 2 to 121 weeks). The incidence of dyskinesia was 31% (95% confidence interval [CI], 20%, 42%) at the end of 43 weeks of cumulative neuroleptic exposure (Fig 1). At the end of 55 calendar weeks, the incidence of TD was 27% (95% CI, 17%, 37%). Both survival curves appear to plateau at the end. No cases of TD have developed after 43 weeks of treatment, although 23 subjects were followed up beyond this point. Similarly, no TD cases developed after 55 calendar weeks of follow-up, although 35 subjects were followed up beyond this point.

Risk Factors.—Survival analyses to identify risk factors included the 160 patients described above. Since the results were essentially the same for analyses using time on medication and calendar time, only the former are presented.

Gender.—The incidence of TD was not significantly related to gender; rates were slightly higher for men despite the fact that men were significantly younger than women (74 ± 9.1 vs 78 ± 8.7 years; $t=2.4$; $df=158$; and $P=.02$).

Age and Diagnosis.—The incidence of TD was found to decrease significantly with increasing age by survival analysis using the Cox proportional hazards regression model ($\chi^2=5.99$; $df=1$; and $P=.01$). Stratification by gender does not affect this relationship but diagnosis is a factor. As shown in Fig 2, patients who were given a nonorganic psychiatric diagnosis (mainly affective disorder) (n = 50) by treating clinicians showed increased vulnerability to TD, compared with those with a diagnosis of organic mental syndrome (n = 90; subjects with both diagnoses were excluded from these analyses) (Breslow statistic = 6.7; $df=1$; and $P=.01$). Subjects with psychiatric diagnoses were significantly younger than those with organic diag-

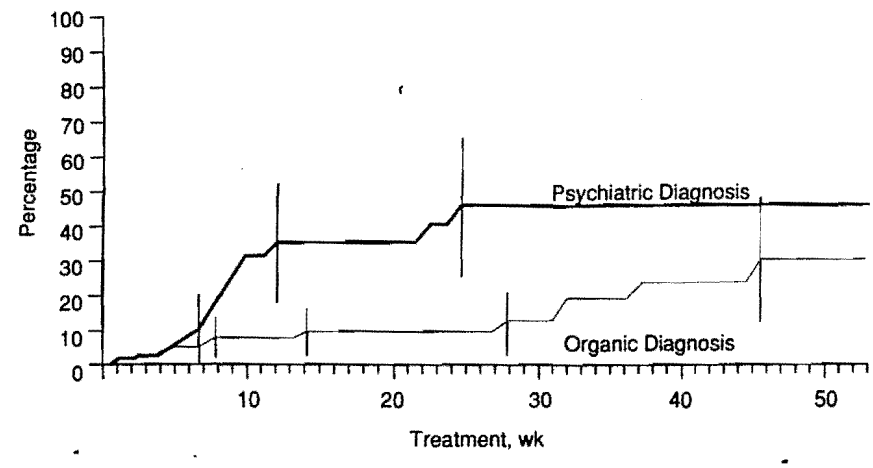

Fig 2.—Percentage of patients developing tardive dyskinesia by psychiatric diagnosis and by weeks of neuroleptic treatment. Vertical bars indicate 95% confidence intervals.

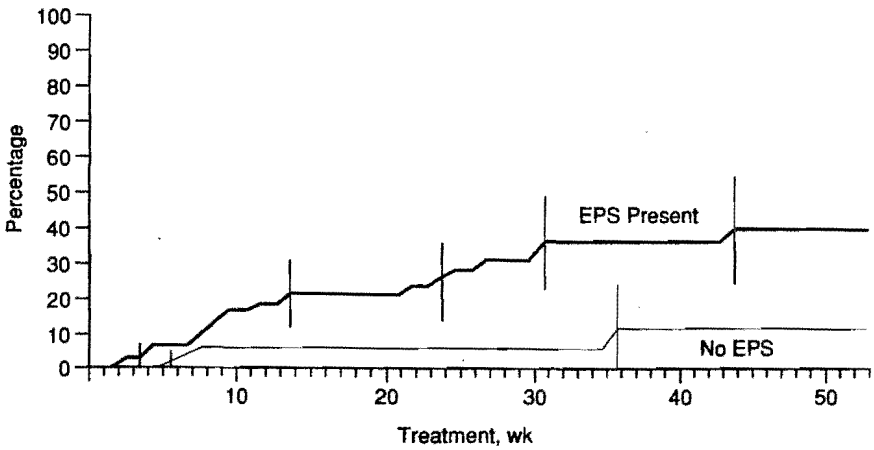

Fig 3.—Percentage of patients developing tardive dyskinesia by presence of extrapyramidal signs (EPS) and by weeks of neuroleptic treatment. Vertical bars indicate 95% confidence intervals.

noses ($\bar{x} \pm SD = 71 \pm 8.4$ vs 80 ± 8.1 years; $t = 5.9$; $df = 138$; and $P < .01$). When the effect of diagnosis is statistically controlled, the relationship of age to TD incidence is no longer significant.

Electroconvulsive Therapy.—The incidence of TD was higher among patients with a history of electroconvulsive therapy (n = 8) than among those with no such history (Breslow statistic = 4.6; $df = 1$; and $P = .03$). This effect remained at the trend level ($P < .08$) when the effect of psychiatric diagnosis was partialled out.

Dose.—The incidence of TD was not significantly related to neuroleptic dose, when this was examined as starting dose or dose at the time closest to TD development. Mean ± SD dose in chlorpromazine–milligram equivalents at time closest to outcome was 48 ± 148 for patients with TD vs 80 ± 108 for patients without TD ($t = 1.08$; $df = 157$; and $P = .28$). The initial treatment for 62% of patients was with haloperidol, 16% were treated with perphenazine, 12% with either chlorpromazine or thioridazine, and the remainder with fluphenazine, loxapine, thiothixene, or molindone. The TD vulnerability was not related to drug class.

Extrapyramidal Signs.—Patients were categorized as parkinsonian-positive or parkinsonian-negative based on SAEPS ratings during the first 4 weeks of neuroleptic treatment. Parkinsonian signs were identified without respect to cause (eg, parkinsonism secondary to neuroleptic therapy or secondary to other causes such as Alzheimer's disease). Parkinsonian-positive was defined as a score of 2 (moderate) or greater at any of the four rating points on any of the following items: rigidity (muscle resistance to passive motion at the wrist, elbow, or shoulder); tremor (at rest or on intention); akinesia (reduction in spontaneous motor or verbal activity); or akathisia. As Fig 3 illustrates, those with parkinsonian signs (n = 103) developed TD at a faster rate. The TD rates (± SE) were 40% ± 7.4% vs 12% ± 6.6% after 43 weeks of treatment (Breslow statistic = 5.5; $df = 1$; and $P = .02$). Subjects with and without concurrent antiparkinsonian medication during the follow-up period were equally likely to develop TD.

COMMENT

The incidence of TD in 31% of patients after 43 weeks of neuroleptic treatment confirms reports in the literature indicating increasing age as a risk factor for TD. It represents more than a sixfold increase over the incidence rate of 4% to 5% per year of exposure found for the sample of nongeriatric psychiatric patients followed up prospectively using the same methods by our research group.[19]

Although not particularly high compared with prevalence rates reported for neuroleptic-treated elderly patients,[11-18] the fact that these patients developed abnormal movements with so little treatment is surprising. Some may question whether many of these should in fact be considered TD cases, since they have emerged following less than 3 months of neuroleptic treatment.[26]

Validity of TD diagnoses among elderly patients is an issue of considerable importance, given the high rate of neuromedical conditions that may be associated with abnormal movements resembling TD and the high incidence of spontaneous dyskinesia among elderly patients reported in the literature. The 5% rate of spontaneous dyskinesia in our sample is low compared with some earlier surveys.[5,29] When movements emerge in the course of neuroleptic treatment among subjects free of movements prior to treatment, one may infer that the movements are not solely the result of a preexisting neuromedical condition. It is possible that short-term neuroleptic treatment alone may be insufficient to induce TD, but may con-

tribute to provoking movements in neurologically predisposed individuals.

The fact that an organic diagnosis was associated with less TD vulnerability than was a psychiatric diagnosis would suggest that coarse brain disease is not the most salient predisposing factor in this population. Although puzzling, this finding is consistent with a recent report by Karson et al[30] of lower TD prevalence for elderly patients with organic mental syndromes and frontal lobe injuries.

The plateau in the incidence curve toward the end of the first year of neuroleptic exposure suggests a period of maximum risk, consistent with Toennissen et al,[12] who reported the greatest increase in TD prevalence in an elderly sample occurring within the first 2 years of drug therapy. The plateau effect in our data must be interpreted with caution due to the small number of cases followed up for more than a year.

One explanation for the early development of TD may be the reduction in the number and plasticity of dopamine neurons in the brains of the elderly.[31] A system with marginal functional reserve may be more susceptible to perturbation by dopamine blocking agents.

The increased risk associated with psychiatric diagnosis (primarily affective disorder) is consistent with our results for younger patients[19] and other reports of increased risk of TD for affective disorders compared with other diagnoses.[32] Similarly, the predictive validity of acute extrapyramidal effects seen early in treatment is consistent with our earlier study,[19] where subjects showing acute extrapyramidal signs were more than twice as likely to develop TD as those not selected for extrapyramidal signs.

Treatment recommendations based on the high risk of TD in this population cannot properly be made without assessment of the benefits of the neuroleptic treatment. Analysis of efficacy within this study is complicated by its naturalistic design, and is being deferred until the sample is complete. Nonetheless, the finding of increased risk associated with a diagnosis of affective disorder would seem to merit clinical application. The literature suggests that while neuroleptic treatment is effective for the majority of patients with late-onset schizophrenia,[33,34] this may not be true for psychotic depression[35]; electroconvulsive therapy may be an alternative for the latter.[35,36] In view of the evidence of increased risk for those with early parkinsonian signs, alternative treatments should be considered for these patients as well. Although almost all our TD cases were mild, some can be severe, even debilitating,[37] and there is no way to predict who will develop the more severe form.

These findings should help inform risk–benefit assessments of neuroleptic treatment for the elderly. In addition, further research in this vulnerable population may contribute to our understanding of the pathophysiology of TD.

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