# Prevalence of Tardive Dyskinesia

STEWART J. TEPPER, M.D.† and JOANNA F. HAAS, M.D.††


## ABSTRACT

**Forty-four epidemiologic studies on tardive dyskinesia were evaluated as to whether they provided information on diagnostic criteria, objective scale and assessment, interobserver reliability, period of observation, and specific interhospital coordination. Studies which met these standards were reviewed for data on class of neuroleptic therapy, dose, duration, continuity of treatment, extrapyramidal toxicity, spontaneous dyskinesias, other drugs and treatment modalities, age and sex. A higher prevalence of tardive dyskinesia has been consistently noted in the elderly and in females. No other predisposing factors for tardive dyskinesia have been conclusively demonstrated thus far. Prevalence of tardive dyskinesia is estimated at 24-56% in chronic neuroleptic users. (J Clin Psychiatry 40:508-516)**


Tardive dyskinesia is an iatrogenic, often unremitting motor disorder characterized by involuntary bucco-lingual-masticatory movements, facial grimaces, blepharospasm, involuntary respiratory grunting, choreoathetoid movements and, occasionally, truncal dystonias. Increase in the use of neuroleptics, the causative agents, has made tardive dyskinesia a serious iatrogenic problem, the magnitude of which has not been fully defined.[1]

The prevalence of tardive dyskinesia in hospitalized psychiatric patients treated with neuroleptics has been estimated from 0.46%[2] to 56%.[3] A critical review was undertaken of studies presenting data on the relationship between patterns of neuroleptic use and development of tardive dyskinesia, emphasizing the methodology of the studies reviewed.

## METHODOLOGIC ISSUES REVIEWED

Three issues were judged to be of special importance in determining the pattern of occurrence of tardive dyskinesia: 1) diagnostic criteria used to define or exclude a possible case of tardive dyskinesia, 2) patterns of neuroleptic use in the population from which cases of tardive dyskinesia were drawn, and, 3) assessment of other factors bearing on the likelihood of developing tardive dyskinesia. In this review, attention will be focused on 44 studies providing information not only on tardive dyskinesia cases but also on the whole population from which such cases were drawn.


† *Cornell University Medical College.*

†† *Assistant Professor of Public Health, Cornell University Medical College.*

*Reprint requests to: Joanna F. Haas, M.D., Cornell Medical Center, 525 East 68th Street, New York, NY 10021.*


## RESULTS

**Diagnostic Criteria for Tardive Dyskinesia.** "The first scientific requirement in any investigation of therapy is a clear, precise statement of diagnostic criteria for the disease under study."[4] This is also the case in investigations of causal relationships. It is important to assure that in every study, tardive dyskinesia is identifiable as a discrete entity and not pooled with other neuroleptic-assocated disorders (specifically extrapyramidal syndromes) which are presently distinguished from tardive dyskinesia.[5] Since this was a factor in selecting papers for review, acceptable definitions were present in most studies included, with 4 exceptions.[6,7,8,9]

**Scale.** Since signs of tardive dyskinesia range from the subtle to the grotesquely obvious, a scale ranking the severity of the disorder was regarded as useful in facilitating comparison between studies. Twenty-two studies[3,10–20] used some form of scale to rank severity of tardive dyskinesia. In general, the presence of a scale led to higher estimates of prevalence of tardive dyskinesia, doubtless because of the inclusion of cases diagnosed on the basis of more subtle signs.

**Objective Measures.** Five investigators attempted to introduce objective methods of assessment of the presence of dyskinesias. These included electroencephalography and film records,[28] a drawing test,[22] electromyography and evoked potentials,[25] polygraph,[3] and film and electromyography.[31]

**Interobserver Reliability.** Nine, for the most part recent, studies instituted measures to assure interobserver agreement.[3,15,16,22,23,25,28,30,31] Greenblatt et al[15] trained 2 observers in recognition of tardive dyskinesia using a standard protocol. These observers independently evaluated each patient for the presence or absence of tardive dyskinesias, and they were reported to have agreed completely in the assessments. Since high levels of diagnostic agreement are possible, adoption of standard protocol with reliability checks appears to be a potentially useful device, particularly for coordinating interinstitutional or long term studies of tardive dyskinesia, thereby permitting survey of larger patient populations.

**Hospital Coordination and Period of Observation.** When multiple facilities are involved in a study, or when 1 institution is studied for an extended period, the likelihood of multiple observers having different standards for what constitutes a case of tardive dyskinesia may be a problem, especially if measures have not been taken to assure consistency. Twenty-eight of the studies[3,6–9,11,13,16,19–24,26–29,32–41] were conducted at no more than 3 specified institutions. Fifteen studies[6,7,10,12,14,16,18,20,26,27,29,34,36,37,39] explicitly specified

a discrete time period of less than 5 years during which the observations were collected.

## PATTERNS OF NEUROLEPTIC USE IN THE POPULATION FROM WHICH TARDIVE DYSKINESIA CASES WERE DRAWN

Prevalence, the ratio of cases of a disease to a defined population at a given time, is a measure of the frequency of a disorder. If the prevalence ratio is to be estimated, it is necessary to explicitly enumerate the population which was surveyed in addition to identifying the total number of cases of tardive dyskinesia. It should be noted that prevalence of a condition in a population at a given point in time is a function of both the rate at which new cases occur (incidence) and also of the mean duration of the disorder in question.

Similar considerations apply in establishing relationships between a disorder and possible predisposing factors. In such efforts, not only must the pertinent characteristics of the disease cases be specified but, equally important, those of the population at risk. In reviewing the literature on prevalence of tardive dyskinesia, it was frequently observed that failure to specify the distribution of the characteristic at issue in the study population as a whole made it impossible to evaluate an hypothesized association. For each aspect of neuroleptic use under study, a positive (+) in Table 1 was registered in the numerator if that feature was enumerated for tardive dyskinesia cases; a separate positive was given for the denominator if the distribution of that characteristic was provided for the entire population at risk. Correspondingly, a minus (−) denotes that this information was not recorded for the cases or the population.

**Primary Type of Neuroleptic Treatment.** Primary treatment with neuroleptics is, of course, the most important etiological consideration in tardive dyskinesia. Although neuroleptics vary in potency and acute side effects, there is no firm evidence that any one of these agents is therapeutically more effective than any other for any neuroleptic use. Whether these agents are equally likely to induce tardive dyskinesia is controversial. A +/+ for each of these categories under "neuroleptic type" in Table 1 indicates that information on treatment was presented for all patients, not only for those with tardive dyskinesia.

Thirteen studies described type of neuroleptic use for tardive dyskinesia patients, as well as the treatment patterns by nature of agent in the remainder of the study population.[6,16,18,20–22,25,26,32,33,42–44] None of these 13 studies was able to document a higher occurrence of tardive dyskinesia with any agent or class of agents. Neither was any agent or class of agent exculpated as a cause of tardive dyskinesia.

**The Relationship of Dose of Neuroleptic to Prevalence of Tardive Dyskinesia.** Whether a dose-effect relationship exists between neuroleptic drug usage and the development of tardive dyskinesia is a matter of dispute. Four studies found that prevalence of tardive dyskinesia was not associated with either mean daily dose[8,33,34] or total lifetime drug intake.[14] The decision of Fann et al[33] to include all movements except 10-20 Hz tremors leaves open the possibility that some acute extrapyramidal syndromes may have been included in the tardive dyskinesia group. Jus et al[3] found no relationship between the presence of tardive dyskinesia and mean total amount of neuroleptics taken by patients treated with single neuroleptic agent regimens. However, mean total amount of neuroleptics in a multiple agent regimen was significantly lower for patients with tardive dyskinesia than for non-dyskinetic patients, raising the specter of synergistic toxicity. In another group of heavily treated patients (average daily dose, 510 mg. equivalents of chlorpromazine), Crane[18] reported a somewhat higher frequency of tardive dyskinesia compared to a group with lower average treatment levels (250 mg. chlorpromazine equivalents daily). Our statistical evaluation of Crane's 1970[18] data suggests, however, that this difference could be readily explained by chance alone ($\chi^2 = 1.19$; d.f., 1).

Crane and Paulson[32] observed a negative association between the dose level of neuroleptics at the time of examination (expressed in chlorpromazine equivalents) and the prevalence of tardive dyskinesia. Kennedy et al.[22] found that prevalence of choreiform dyskinetic movements of the oral region was significantly associated with lower doses of trifluoperazine for male, but not for female patients.

Four studies concluded that higher cumulative doses of neuroleptics were associated with development of tardive dyskinesia.[16,26,27,35] Crane found that tardive dyskinesia prevalence increased abruptly in patients over age 55 receiving more than 200 mg. chlorpromazine equivalents daily for greater than 6 months, and increased again when duration of treatment was over 2 years.[27]

To summarize, of 13 studies providing data from which the relationship between dose of neuroleptic and prevalence of tardive dyskinesia could be assessed, 4 showed a positive association between dose and tardive dyskinesia, and 7 were unable to detect a significant relationship between magnitude of dose and occurrence of tardive dyskinesia. However, at least 2 distinct measures of dose were used, current dose at the time of evaluation, and cumulative lifetime intake. In addition, high dose neuroleptics being administered at the time of observation may have masked underlying tardive dyskinesia.

**Duration of Neuroleptic Treatment and Prevalence of Tardive Dyskinesia.** Once again, varied conclusions are drawn when duration of treatment is correlated with

**Table 1**
**Summary of methods used and issues addressed in selected studies of the frequency of tardive dyskinesia**
**Factors Affecting the Prevalence of Tardive Dyskinesia**

| Study | Neuroleptic Type | Dose | Duration | Acute EPS Toxicity | Other Drugs | Other Treatment | Structural Brain Disease | Age | Sex | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Hall *et al.* (1956) | +/+ | — | +/+ | — | — | — | | | | |
| Uhrbrand and Faurbye (1960) | — | — | — | — | — | — | +/− | +/− | 1** | [1]All patients were female. |
| Faurbye *et al.* (1964) | 2 | — | 2 | — | 2 | 2 | — | 2 | 3 | [2]Data on neuroleptic type, duration of exposure, ECT and other therapy, and age of patients were given for schizophrenic patients only. [3]All patients were female. |
| Hunter *et al.* (1964) | +/− | +/− | — | — | −/+ | +/− | 4 | — | +/+ | [4]All patients were brain damaged. |
| Pryce and Edwards (1966) | +/− | +/− | +/− | — | — | +/+ | +/− | — | 5 | [5]All patients were female. |
| Demars (1966) | +/− | 6 | 6 | −/+ | — | +/+ | +/+ | 6 | 6 | [6]Case-control group. |
| Degkwitz and Wenzel (1967) | — | — | — | +/− | +/− | +/− | +/− | +/+ | +/+ | |
| Hoff and Hoffman (1967)[7] | — | — | — | — | — | — | — | — | — | [7]Questionnaire survey; patients were not observed by authors. |
| Crane and Paulson (1967) | +/+ | +/+ | — | −/+ | −/+ | — | +/+ | +/+ | −/+ | |
| Turunen and Achtè (1967)[8] | +/− | +/− | +/− | — | +/− | +/− | +/− | +/− | +/+ | [8]Chart review with no personal observation of patients by investigators. |
| Siede and Muller (1967)[9] | — | — | — | +/− | — | — | +/− | +/+ | +/+ | [9]Geriatric population. |
| Crane (1968a) | — | 10 | 10 | — | — | — | 11 | +/+ | +/+ | [10]+/+ for experimental period only. [11]All patients were schizophrenic. |
| Crane (1968b) | −/− | +/− | — | — | +/− | — | −/+ | — | 12 | [12]All patients were male. |
| Greenblatt *et al.* (1968)[13] | — | — | — | — | — | — | +/+ | — | — | [13]Geriatric population. |
| Paulson (1968)[14] | — | −/− | — | — | — | — | +/− | +/− | +/− | [14]Population selection was not systematic. |
| Eckmann (1967) | — | — | — | — | — | — | — | — | — | |
| Heinrich *et al.* (1968) | 15 | 15 | 15 | +/− | 15 | 15 | 15 | +/+ | 15 | [15]Case-control study. |
| Villeneuve *et al.* (1969)[16] | — | — | — | — | +/− | +/− | +/− | +/− | +/+ | [16]Questionnaire sent to clinicians. |
| Jones and Hunter (1969) | — | — | — | — | — | — | −/+ | +/+ | +/+ | |
| Degkwitz (1969) | — | — | — | −/+ | — | — | — | — | +/+ | |
| Degkwitz *et al.* (1970) | — | +/+ | +/+ | +/+ | — | — | — | +/+ | +/+ | |
| Crane (1970)[17] | +/− | +/− | +/− | — | — | — | — | +/+ | −/+ | [17]Experimental study of 2 dose levels of trifluoperazine. |
| Edwards (1970) | — | 18 | 18 | — | — | 18 | 18 | 18 | +/+ | [18]Case-control study method for total neuroleptic intake and age. |
| Lehmann *et al.* (1970) | — | +/+ | +/+ | — | −/+ | −/+ | −/+ | — | +/+ | |
| Dynes (1970) | — | — | — | — | — | — | 19 | 19 | 19 | [19]Population not systematically selected. |
| Roxburgh (1970)[20] (Ref. 45) | — | — | — | — | — | — | — | — | — | [20]Clinical study, not a cross-sectional study. |
| Hippius and Lange (1970) | — | +/+ | — | — | — | — | — | +/+ | +/+ | |
| Ettinger and Curren (1970) | +/+ | — | — | — | — | — | — | — | — | |
| Kennedy *et al.* (1971) | +/+ | +/+ | +/+ | — | +/+ | — | — | +/+ | +/+ | |
| Brandon *et al.* (1971) | — | — | — | — | +/+ | +/+ | +/+ | +/+ | +/+ | |
| Crane (1972) | — | — | — | +/+ | — | — | — | — | — | |
| Fann *et al.* (1972) | — | +/+ | — | — | — | — | — | +/+ | +/+ | |
| Polizos *et al.* (1973)[21] | +/+ | — | — | — | — | — | — | — | — | [21]Pediatric study. |
| Elie *et al.* (1973)[22] | +/+ | 23 | 23 | — | — | — | — | — | — | [22]Evaluated objective measure for diagnosis of Tardive Dyskinesia. [23]Positive for experimental study only. |
| Crane (1973) | — | — | — | — | — | — | — | — | — | |
| Crane and Smeets (1974)[24] | +/+ | +/+ | +/+ | — | — | — | — | −/+ | — | [24]Geriatric study. |
| Englehardt *et al.* reported by Ayd (1974)[25] | +/+ | — | — | +/+ | — | — | — | — | — | [25]Pediatric study. |
| Crane (1974) | −/+ | +/+ | +/+ | — | +/+ | — | −/+ | +/+ | +/+ | |
| Paulson *et al.* (1975) | — | — | — | — | — | — | — | — | — | |
| Yagi *et al.* (1976) | — | — | +/− | +/+ | — | — | +/− | +/− | — | |
| Jus *et al.* (1976) | +/+ | +/+ | +/+ | +/+ | +/+ | +/+ | +/+ | +/+ | +/+ | |
| Bourgeois *et al.* (1976) | −/+ | — | — | — | — | +/− | +/+ | −/+ | +/− | |
| Delwaide and Desseilles (1977)[26] | — | — | — | — | — | — | +/+ | +/+ | +/+ | |
| Bell and Smith (1978) | — | — | — | +/+ | — | +/+ | — | +/+ | +/+ | [26]Study of spontaneous dyskinesia in the elderly. |

prevalence of tardive dyskinesia. No effects of duration of treatment on tardive dyskinesia prevalence was discerned in 4 studies.[3,22,33,24] However, Heinrich et al[16] found significantly greater prevalence of tardive dyskinesia in patients treated longer than 1 year. Lehmann et al[35] used length of hospitalization as a measure of duration of treatment and found that it was also associated with higher cumulative dose and higher dosage at the time of evaluation. In a group of geriatric patients,[26] the prevalence of tardive dyskinesia was significantly higher among patients having received neuroleptic agents for greater than 6 months than among patients treated for shorter periods. It is important to note the occurrence in that group of a case of tardive dyskinesia in a patient who had been treated with modest doses of thioridazine for only 2.5 months. In a cross-sectional survey of psychiatric patients in a single hospital, Crane[27] noted a significant correlation between duration of treatment and risk of tardive dyskinesia even after controlling for age and maximum dose.

Thus, 4 of 8 studies suggested higher risk of tardive dyskinesia with a longer duration of treatment, while 4 were unable to demonstrate such an association.

**Continuity of Treatment.** It has been suggested that prevalence of tardive dyskinesia may be decreased with "drug vacations" or drug free periods.[46] Jus et al,[43] in the only study addressing this issue directly, found that in patients treated with piperazine phenothiazines and/or butyrophenones, the mean duration of drug free intervals was significantly shorter in patients who developed tardive dyskinesia than in those who did not. This relationship was not demonstrated in patients treated with other classes of neuroleptics.

**Acute Extrapyramidal Toxicity.** The extrapyramidal syndrome, including drug-induced parkinsonism, akathisias, and acute dystonic reactions with oculogyric crisis has been proposed as a predictor for tardive dyskinesia. Two studies[3,34] found no increased prevalence of tardive dyskinesia in patients with histories of extrapyramidal syndrome. Crane[24] noted that similar proportions of patients with and without pseudoparkinsonian manifestations while taking neuroleptics go on to develop tardive dyskinesia when neuroleptic drug dose is reduced. However, mean scores reflecting both frequency and severity of tardive dyskinesia were higher in the group with prior parkinsonian signs. In a study confined to schizophrenic children, Englehardt et al found "no relationships between the occurrence of extrapyramidal syndrome during treatment and subsequent development of withdrawal emergent syndrome of childhood."[42] In a study of 259 Japanese psychiatric outpatients, Yagi et al[37] observed that of 19 patients with tardive dyskinesia, 18 had concomitant extrapyramidal signs, while another 123 patients who exhibited extrapyramidal signs did not have tardive dyskinesia. Bell and Smith[30] showed a low ($r=0.15$ to 0.18) but significant level of correlation between the presence of tardive dyskinesia and extrapyramidal syndrome. Thus, of 6 studies addressing the relationship between tardive dyskinesia and neuroleptic-induced extrapyramidal syndrome, 3 showed no association, 2 showed an association between the 2 disorders, and 1 was inconclusive.

**Spontaneous Dyskinesias.** A further source of difficulty in interpreting relationships between tardive dyskinesia and neuroleptic treatment is the spontaneous occurrence of signs indistinguishable from some cases of tardive dyskinesia. Failure to take into account the frequency of the spontaneous disorder might lead to incorrect conclusions concerning prevalence of the neuroleptic-induced syndrome.

Table 2 summarizes studies from which prevalence of spontaneous dyskinesias can be estimated (i.e., dyskinesias occurring in patients not treated with neuroleptics). Those studies which include high proportions of elderly patients tend to report the highest rates of spontaneous dyskinesias, suggesting that spontaneous dyskinesia is an age related phenomenon. It is possible that the greater risk of neuroleptic-induced tardive dyskinesia in older persons, discussed below, might partially reflect an increased rate of the spontaneous disorder.

## OTHER FACTORS WHICH MAY AFFECT THE FREQUENCY OF TARDIVE DYSKINESIA

While the primary issue remains explaining how the neuroleptic treatment pattern (nature of agent, duration and dosage, continuity of treatment) affects the likelihood of developing tardive dyskinesia, other factors, such as characteristics of the patient, have been thought to influence the risk of developing this disorder in the presence of neuroleptic treatment. Various studies have attempted to evaluate the impact of such factors, including age, sex, presence of organic brain disease, prior exposure to other treatments (ECT, insulin shock, leucotomy) and concurrent treatment with other drugs, particularly antiparkinsonian agents.

Some of these factors may operate independent of neuroleptic treatment patterns; others, like age and diagnosis, are related to the pattern of treatment with neuroleptic agents and could be either secondary confounding factors, or independent risk factors. For example, increasing patient age may be associated with greater likelihood of developing tardive dyskinesia. On the other hand, patients who are older at the time of an evaluation may have a longer history of psychiatric disorder, with longer duration of exposure and higher cumulative dose of neuroleptic than younger patients. Again, for purposes of this critique, in Table 1 a positive (+) is given in the numerator when this information is available on cases, and a positive (+) in the denominator when it is also given for the full population under study.

Table 2
Prevalence of Spontaneous Dyskinesias

| Study and Year | No. of patients not treated with neuroleptics | No. of these patients developing dyskinesia | Percent |
|---|---|---|---|
| Demars[31]* | 117 | 11 | 9.4% |
| Degkwitz and Wenzel[34]* | 525 | 7 | 1.3% |
| Crane and Paulson[32] | 48 | 10 | 20.8% |
| Siede and Muller[13]* | 160 | 2 | 1.2% |
| Crane[30] | 91 | 0 | 0% |
| Greenblatt *et al.*[15]* | 101 | 2 | 2.0% |
| Eckmann[7] | 588 | 25 | 4.2% |
| Heinrich *et al.*[16]* | 100 | 2 | 2.0% |
| Degkwitz[11] | 2000 | 18 | 0.9% |
| Jones and Hunter[17] | 45 | 1 | 2.2% |
| Hippius and Lange[8]† | 137 | 19 | 13.9% |
| Brandon *et al.*[23]** | 285 | 55 | 19.3% |
| Crane[48] | 46 | 1 | 2.0% |
| Crane[27]* | 8 | 3 | 37.5% |
| Delwaide and Desseilles[31]* | 240 | 88 | 36.7% |

* Geriatric Population
† May include extrapyramidal disorders other than dyskinesias.
** Only 2 female patients who developed dyskinesia were under 40 years old.

### Other Drug Therapy

Use of anticholinergic agents has been said to lower the threshold for developing tardive dyskinesia.[48] Since many patients may be receiving other drugs, some of which have anticholinergic properties (antiparkinsonian and antidepressant drugs), ancillary drug therapy must be considered and explicitly documented. A +/+ on Table 1 means that data were provided on drug therapy other than neuroleptic agents for both tardive dyskinesia cases and the total population.

**Antiparkinsonian Agents.** Three studies found that use of antiparkinsonian drugs was not associated with either increased prevalence of tardive dyskinesia[22,43] or patient dyskinesia scores.[30] Crane[27] observed that the use of antiparkinsonian drugs ceased to be positively correlated with development of tardive dyskinesia once account was taken of the high doses and long duration of neuroleptic treatment usually associated with anticholinergic use. Thus, in the few studies directly addressing this relationship, no association between administration of antiparkinsonian medication and severity or frequency of tardive dyskinesia has been documented.

**Other Agents.** Neither alcohol nor drug addiction was found to be related to tardive dyskinesia in a study of psychiatric inpatients by Faurbye et al.[23] Insulin therapy was not associated with increased risk of tardive dyskinesia, according to Heinrich et al.[16] Brandon et al[23] observed an unexpectedly low incidence of tardive dyskinesia in patients who had insulin shock therapy. Only 8% of the patients, however, were over the age of 30. In a study by Jus et al,[3] there was no increased prevalence of tardive dyskinesia among neuroleptic-treated patients either with a history of alcoholism or insulin shock therapy. Thus, increased frequency of tardive dyskinesia has not been associated with use of nonneuroleptic drugs.

### Electroconvulsive Shock Therapy (ECT)

Five studies addressing the question of whether prior ECT predisposes to neuroleptic-induced tardive dyskinesia had negative conclusions.[3,10,16,23,33] However, Faurbye et al[20] found that among female schizophrenic patients who had previously been treated with ECT, tardive dyskinesia was twice as prevalent as in those who had not undergone such treatment.

### Presence of Structural Brain Lesions

Many studies have examined the possibility that a structural brain disease might significantly alter a patient's chance of developing tardive dyskinesia. If a study gave diagnostic information for all patients and for those with tardive dyskinesia, this was recorded as +/+ in Table 1.

**Organic Brain Syndrome.** Crane and Paulson[32] noted an increased prevalence of tardive dyskinesia in neuroleptic-treated patients with organic brain syndrome. Two studies[15,16] found no relationship between dyskinesia and the presence of organic brain syndrome. However, in a study of a group of female tardive dyskinesia patients matched by age, sex, and total neuroleptic intake with patients from the same hospital who showed no signs of tardive dyskinesia, more frequent and more severe organic brain disease was present in the tardive dyskinesia group.[19] A study of spontaneous dyskinesias in the geriatric age group noted that the prevalence of dyskinesias was not significantly higher in demented patients than in other elderly patients.[31]

Thus, 2 studies found a positive association, and 2 found no association between tardive dyskinesia and organic brain syndrome. One study suggested increased spontaneous dyskinesia in older patients. Therefore, no conclusions can be drawn.

**Leucotomy.** In two groups of female schizophrenic patients with and without pre-frontal leucotomy but with similar age distribution there was no difference in prevalence of tardive dyskinesia.[20] In 3 other studies,[3,23,33] no relationship was found between leucotomy and tardive dyskinesia. Four studies, then, failed to detect any positive relationship.

## DEMOGRAPHIC FACTORS

Finally, age and sex of patients must be considered as possible predictors for neuroleptic toxicity. In Table 1, a +/+ was given only for studies where the age distribution of patients with and without tardive dyskinesia was given, and likewise for the number of male and female patients, with and without tardive dyskinesia.

**Age.** Fifteen studies addressed the effect of age on risk of developing tardive dyskinesia. Six studies[9,11,23,30,32,34] noted a higher prevalence on tardive dyskinesia in patients over 50 years of age. Crane[14] found a trend towards a higher risk of tardive dyskinesia in patients over 40, but the trend did not reach a statistically significant level. Four other studies found older age to be associated with increased risk of tardive dyskinesia.[3,8,27,33] Crane [27] noted a positive correlation between age and tardive dyskinesia not explained by dose and duration. Jus et al[3] observed a prevalence of tardive dyskinesia in patients under 49 years of 40%. In patients 50 to 70, prevalence was 60%, and in those over 70, 75%. Age played no role as a predisposing factor for tardive dyskinesia in 4 other studies.[16,18,22,47]

In summary, out of 15 studies examining age as a risk factor for neuroleptic-induced tardive dyskinesia, 9 identified a significantly increased risk in older age groups (generally over 50 years of age). Of the 6 studies which failed to document this relationship, 1 showed a trend in this direction.

**Sex.** Seventeen studies considered the relative frequency of tardive dyskinesia in males and females. Twelve of these found a higher proportion of tardive dyskinesia cases among females treated with neuroleptic agents than males.[3,8,11–13,16,17,22,23,30,35,38] Five studies did not find a significant association between risk of neuroleptic related tardive dyskinesia and patient's sex.[9,14,27,34,36] Spontaneous dyskinesias were three-fold more common in females in the geriatric population studied by Delwaide and Desseilles.[31]

Although in aggregate these studies suggest females are more at risk for tardive dyskinesia than are males, it should be noted that in several of the populations studied, females were somewhat older than males. Brandon et al,[23] however, noted a two-fold excess of tardive dyskinesia in females within each age strata from 18 to over 80 years old. A role for age in explaining, at least in part, some of the differences in tardive dyskinesia prevalence cannot be fully discounted, but is unlikely to completely explain sex differences of the magnitude observed.

## PREVALENCE OF TARDIVE DYSKINESIA IN NEUROLEPTIC TREATED PATIENTS

Numerical estimates of tardive dyskinesia prevalence from those studies providing data on the number of patients treated with neuroleptics and on the number of these who developed tardive dyskinesia are summarized in Table 3. Five of these studies used both a scale for rating severity of tardive dyskinesia and some measure of interobserver reliability.[3,15,22,23,28] Prevalence of tardive dyskinesia in these 5 studies is fairly high, ranging from 24%[23] to 56%.[3] This no doubt reflects the sensitivity of approach in recording subtle dyskinesias afforded by the use of a scale of severity. The validity of these estimates is supported by interobserver confirmation. Greenblatt et al[15] observed a geriatric population, and their data probably reflect the increased tardive dyskinesia prevalence associated with aging. Paulson et al[28] observed a pediatric population, where the entity of tardive dyskinesia is not as clearly established. The remaining 3 studies estimated a prevalence at between 24% and 56%. That is, one-quarter to one-half of patients treated chronically with neuroleptics will develop tardive dyskinesia.

The number of patients chronically using neuroleptics is not known, but can be estimated from several studies, of which the 2 selected have surveyed the greatest number of patients.[51,52] Parry et al[52] estimated that 1% of prescriptions in 2,552 patients in 1971 were for neuroleptics. Twenty-seven percent of the neuroleptic prescriptions were for schizophrenia and these patients, at least, are likely to be chronic users. Using these numbers, if 1% of the current 220 million Americans[53] had neuroleptics prescribed in 1978 (2.2 million), 27% of these (or 594,000) had chronic schizophrenia and thus constitute patients at risk for tardive dyskinesia. If one-third of these develop tardive dyskinesia, then 198,000 patients chronically treated with neuroleptics in 1978 will have tardive dyskinesia. Although compliance problems may have in the past lowered the true number of chronic neuroleptic users and thus the number developing tardive dyskinesia, increasing use of intramuscular depot neuroleptic therapy (fluphenazine) may increase the incidence of tardive dyskinesia in ambulatory patients.

## CONCLUSIONS

Forty-four studies were examined for rigor of methodology in identifying predictors for tardive dyskinesia. Few of these studies provided adequate data for analysis of any particular association. The preponderance of available evidence showed increased prevalence of neuroleptic-induced tardive dyskinesia with increasing age and in female patients. A higher prevalence of spontaneous dyskinesias in the elderly was also noted. Dose and duration of neuroleptic medication were not clearly related to prevalence of tardive dyskinesia, although prevalence of tardive dyskinesia may

Table 3
Prevalence of Tardive Dyskinesia in Patients Treated with Neuroleptics

| Study | No. of patients on neuroleptics | No. of patients on neuroleptics developing tardive dyskinesia | Percent |
|---|---|---|---|
| Hall *et al.*[6] | 90 | 6 | 6.7% |
| Hunter *et al.*[38] | 450 | 13 | 2.9% |
| Demars[33] | 371 | 34 | 9.2% |
| Degkwitz and Wenzel[11] | 1,265 | 244 | 19.3% |
| Hoff and Hoffman[2] | 10,019 | 46 | 0.46% |
| Crane and Paulson[32] | 134 | 17 | 12.5% |
| Siede and Muller[13] | 75 | 2 | 2.7% |
| Crane[14] | 368 | 105 | 27.7% |
| Crane[40] | 127 | 19 | 12.8% |
| Greenblatt *et al.*[15] | 52 | 20 | 38.5% |
| Eckmann[7] | 804 | 24 | 2.9% |
| Heinrich *et al.*[16] | 554 | 94 | 17.0% |
| Jones and Hunter[17] | 82 | 17 | 20.7% |
| Degkwitz[36] | 87 | 25 | 28.7% |
| Degkwitz *et al.*[34] | 53 | 19 | 34.7% |
| Crane[18] | 127 | 34 | 26.2% |
| Lehmann *et al.*[35] | 350 | 23 | 6.5% |
| Dynes[19] | 1,200 | 103 | 8.6% |
| Hippius and Lange[8] | 531 | 182 | 34.3% |
| Kennedy *et al.*[22] | 63 | 26 | 41.3% |
| Brandon *et al.*[23] | 625 | 150 | 24.0% |
| Fann *et al.*[9] | 204 | 73 | 35.8% |
| Polizios *et al.*[44] | 28 | 15 | 44.1% |
| Crane[48] | 926 | 157 | 17.0% |
| Crane and Smeets[26] | 31 | 16 | 51.6% |
| Englehardt *et al.*[42] | 141 | 68 | 48.2% |
| Paulson *et al.*[28] | 103 | 21 | 20.4% |
| Yagi *et al.*[37] | 259 | 19 | 7.3% |
| Jus *et al.*[3] | 330 | 186 | 56.0% |
| Asnis *et al.*[50] | 69 | 28 | 41.0% |

be decreased with longer drug-free interruptions of neuroleptic treatment.

No specific neuroleptic class or subclass was free of risk or associated with increased prevalence of tardive dyskinesia. Use of neuroleptics as antiemetics, antipruritics and tranquilizers for even periods as short as 2 months carries the danger of long-term permanent toxicity.

Neither acute extrapyramidal toxicity nor structural brain disease were clearly associated with increased tardive dyskinesia prevalence. Contrary to a widely held clinical belief, no evidence could be found that use of anticholinergic medication increases prevalence of tardive dyskinesia.

Use of neuroleptics in elderly patients and female patients for transient, self-limited disorders should be discouraged. Periods of treatment of neuroleptics should probably be interspersed with drug free intervals.

Prevalence of tardive dyskinesia ranges from 24-56% in chronic neuroleptic users. Using data generated on neuroleptic prescriptions, we estimate close to 200,000 patients may develop tardive dyskinesia as a result of neuroleptics prescribed in 1978.

Future cross-sectional prevalence surveys and incidence studies of tardive dyskinesia and its association with use of neuroleptic drugs should identify the entire population at risk. The population under study should be clearly defined in terms of the institutions and time periods from which it is drawn. The same data collection methods must be applied to the entire group of patients, including those not on neuroleptics and those who do not develop tardive dyskinesia.

A valid, reproducible mechanism of identifying cases should be developed employing clear diagnostic criteria and supplemented by interobserver reliability determinations, scales of severity and objective measurements. Data should be collected at the outset on potentially important factors such as patterns of neuroleptic drug use, other treatment modalities, acute extrapyramidal toxicity, and patient factors like age, sex, underlying diagnoses, and duration of illness. These factors should be taken into account in analysis through the use of statistical methods able to identify and distinguish interactions involving multiple-related variables. Because of the iatrogenic nature of tardive dyskinesia, we have a special responsibility to carry out these studies expeditiously.

## REFERENCES

1. Tarsy D and Baldessarini R: The Tardive Dyskinesia Syndrome. In: Clinical Neuropharmacology, Volume 1. Edited by Klawans HL. New York, Raven Press, 1976

2. Hoff H and Hoffman G: Das persistierende extrapyramidale Syndrom bei neuroleptika Therapie. Wien med Wschr 117:14-17, 1967

3. Jus A, Pineau P, Lachance R, et al: Epidemiology of tardive dyskinesia. Part I. Dis Nerv Sys 37:210-214, 1976
4. Gifford RH and Feinstein AR: A critique of methodology in studies of anticoagulant therapy for acute myocardial infarction. N Engl J Med 280:351-357, 1969
5. Fahn S: Tardive dyskinesia may be only akathisia. (Letter) N Engl J Med 299:202-203, 1978
6. Hall RA, Jackson RB and Swain JM: Neurotoxic reactions resulting from chlorpromazine administration. JAMA 161:214-218, 1956
7. Eckmann F: Zur Problematik von Dauerschaden nach neuroleptischer Langzeitbehandlung. Ther Ggw 107:316-323, 1968
8. Hippius H and Lange G: Zur Problematik der spaten extrapyramidalen Hyperkinesen nach langfrostiger neuroleptischer. Therapie Arzneim Forschung 20:888-889, 1970
9. Fann WE, Davis JM and Janowsky DS: The prevalence of tardive dyskinesias in mental hospital patients. Dis Nerv Sys 33:182-186, 1972
10. Pryce IG and Edwards H: Persistent oral dyskinesia in female mental hospital patients. Br J Psychiatry 112:983-987, 1966
11. Degkwitz R and Wenzel W: Persistent extrapyramidal side effects after long-term application of neuroleptics. Excerpta Med. Foundation, International Congress. Neuropsychopharmacology Ser. No. 129:608-615, 1967
12. Turunen S and Achté KA: The bucco-linguo-masticatory syndrome as a side effect of neuroleptics therapy. Psychiatr Q 11:268-279, 1967
13. Siede H and Muller HF: Choreiform movements as side effects of phenothiazine medication in geriatric patients. J Am Geriatr Soc 15:517-522, 1967
14. Crane GE: Tardive dyskinesia in schizophrenic patients treated with psychotropic drugs. Agressologie 9:209-217, 1968a
15. Greenblatt DL, Dominick JR, Stotsky BA, et al: Phenothiazine-induced dyskinesia in nursing home patients. J Am Geriatr Soc 16:27-33, 1968
16. Heinrich K, Wegener I, Bender HJ et al: Spât extrapyramidale Hyperkinesen bei neuroleptischer Langzeitterapie. Neuro-Psychopharmakologie I:169-195, 1968
17. Villeneuve A, Lavallée JC and Lemieur LH: Dyskinesie tardive post-neuroleptique. Laval Med 40:832-837, 1969
18. Crane GE: High doses of trifluoperazine and tardive dyskinesia. Arch Neurol 22:176-180, 1970
19. Edwards H: The significance of brain damage in persistent oral dyskinesia. Br J Psychiatry 116:271-275, 1970
20. Faurbye A, Rasch PJ, Petersen PB, et al: Neurological symptoms in pharmacotherapy of psychoses. Acta Psychiatr Scand 40:10-27, 1964
21. Ettinger M and Curran J; Liver disease and phenothiazines. Minn Med 53:731-736, 1970
22. Kennedy PF, Hershon HI and McGuide RJ: Extrapyramidal disorders after prolonged phenothiazine therapy. Br J Psychiatry 118-509-518, 1971
23. Brandon S, McClelland HA and Protheroe C: A study of facial dyskinesia in a mental hospital population. Br J Psychiatry 118:171-184, 1971
24. Crane GE: Pseudoparkinsonism and tardive dyskinesia. Arch Neurol 27:426-430, 1972
25. Elie R, Gagnon MA, La Montagne Y, et al: The extrapyramidal neuroleptic syndrome: Description and measurement. Current Therapeutic Res 15:427-440, 1973
26. Crane GE and Smeets RA: Tardive dyskinesia and drug therapy in geriatric patients. Arch Gen Psychiatry 30:341-343, 1974
27. Crane GE: Factors predisposing to drug-induced neurologic effects. In: Advances in Biochemical Psychopharmacology, Volume 9. Edited by Forrest IS, Carr CJ and Usdin E. New York, Raven Press, 1974, pp. 269-279
28. Paulson GW and Crane GE: Tardive dyskinesia as a possible sequel of long-term therapy with phenothiazines. Clin Pediatr (Phila) 14:953-955, 1975
29. Bourgeois M, Graux C and Arrethche-Berthelot N: Les dyskinesies tardives des neuroleptiques: enquete sur 1660 malades d-hopital psychiatrique, Ann Med Psychol (Paris) 134:737-746, 1976
30. Bell RCH and Smith RC: Tardive dyskinesia: Characterization and prevalence in a statewide system. J Clin Psychiatry 39:39-47, 1978
31. Delwaide PJ and Desseilles M: Spontaneous buccolingual-facial dyskinesia in the elderly. Acta Neurol Scand 56:256-262, 1977
32. Crane GE and Paulson G: Involuntary movements in a sample of chronic mental patients and their relation to the treatment with neuroleptics. Int J Neuro Psychiatry 3:286-291, 1967
33. Demars JPCA: Neuromuscular effects of long-term phenothiazine medication, electroconvulsive therapy and leucotomy. J Nerv Mental Dis 143:73-79, 1966
34. Degkwitz R, Baver MP, Griber M, et al: Der Zeitliche Zusammenhand Zwischen dem Aufretan persistierende extrapyramidale Hyperkinesen and Psychoserecidiver nach abrupter Unterbrachung langfristiger Neuroleptischer Behandlung Chronische Schizophrener Kranken. Arzneim Forsch 20:890-893, 1970
35. Lehmann HE, Ban TA and Saxena BM: A survey of extrapyramidal manifestations in the in-patient population of a psychiatric hospital. Laval Med 41:909-916, 1970
36. Egkwitz R: Extrapyramidal motor disorders following long-term treatment with neuroleptic drugs. In: Psychotropic Drugs and Dysfunction of the Basal Ganglia. Edited by Crane GE and Gardner R, Jr. Wash., D.C.: Public Health Service Publ. # 1938, 1969, pp. 22-23
37. Yagi G, Ogita K, Ohtsjkan N, et al: Persistent dyskinesia after long-term treatment with neuroleptics in Japan. Keio J Med 25:27-35, 1976
38. Hunter R, Earl CJ and Thornicroft S: An apparently irreversible syndrome of abnormal movements following phenothiazine medication. Proc Soc Med 57:758-762, 1964
39. Uhrbrand L and Faurbye A: Reversible and irreversible dyskinesia after treatment with perpherazine, chlorpromazine, reserpine and ECT. Psychopharmacology 408-418, 1960
40. Crane, GE: Dyskinesia and neuroleptics. Arch Gen Psychiatry 19:700-703, 1968b
41. Paulson GW: "Permanent" or complex dyskinesias in the aged. Geriatrics 23:105-116, 1968
42. Ayd, FJ (describing Engelhardt DM, Polizios P and Waizer J) Neurologic effects of abrupt withdrawal of neuroleptic medicines in schizophrenic children. Int Drug Therapy Newsletter 9:25-28, Sept. 1974
43. Jus A, Pineau R, LaChance R, et al: Epidemiology of tardive dyskinesia. Part 2. Dis Nerv Sys 37:257-261
44. Polizos P, Engelhardt DM and Hoffman SP: Central nervous system consequences of psychotropic drug withdrawal of schizophrenic children. Psychopharm Bull 9:34-35, 1973
45. Roxburgh PA: Treatment of persistent phenothiazine-induced oral dyskinesia. Br J Psychiatry 116:277-280, 1970
46. Crane GE: Persistent dyskinesia. Br J Psychiatry 122:395-405, 1973

47. Jones M and Hunter R: Abnormal movements in patients with chronic psychiatric illness. In: Psychotropic Drugs and Dysfunction of the Basal Ganglia. Edited by Crane GE and Gardner R. Jr. Wash., D.C.: Public Health Service Publ. #1938, 1969, pp. 53-65

48. Klawans HL: The pharmacology of tardive dyskinesia. Am J Psychiatry 130:82-86, 1973

49. Dynes JB: Oral dyskinesias—occurrence and treatment. Dis Nerv Sys 31:854-859, 1970

50. Asnis G, Leopold MA, Duvoisin RC, et al: A survey of tardive dyskinesia in psychiatric outpatients. Am J Psychiatry 134:1367-1370, 1977

51. Balter MB and Levine J: The nature and extent of psychotropic drug usage in the U.S. Psychopharm Bull 5:3-13, Oct. 1969

52. Parry HJ, Balter MB, Mellinger GD, et al: National patterns of psychotherapeutic drug use. Arch Gen Psychiatry 28:769-783, 1973

53. U.S. Bureau of the Census. Statistical Abstract of the U.S.: 1975. (96th edition). Washington, D.C.: 1975