Changing Epidemiology of Tardive Dyskinesia: An Overview

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Dyskinesia is found significantly more often among neuroleptic-treated psychiatric patients than among non-neuroleptic-treated patients. The epidemiology of tardive dyskinesia is changing; its reported prevalence among neuroleptic-treated psychiatric inpatients has been progressively rising and has reached 25% during the past five years. The prevalence of persistent *tardive dyskinesia that may be attributable to neuroleptics is about 13%. Tardive dyskinesia is not restricted to old, brain-damaged inpatients but also occurs with a noticeable frequency among younger patients, including outpatients, treated with neuroleptics. Yet neuroleptics are the most effective available treatment for schizophrenia; hence, any drastic curtailment of their use in the treatment of chronic schizophrenic patients may not be justified. Cautious use of these drugs, along with intensified research on tardive dyskinesia, is warranted.*

Tardive dyskinesia is the most important complication of long-term neuroleptic use. What was initially thought to be a rare clinical curiosity has become a significant public health hazard. The task of the physician, who usually needs to maintain the majority of his or her chronic schizophrenic patients on neuroleptics (1), is made difficult by the fear of producing tardive dyskinesia with all its physical, psychological, social, and medicolegal implications (2). Yet answers to a number of basic questions about this syndrome remain controversial: Does tardive dyskinesia occur significantly more frequently than spontaneous dyskinesia? Is the prevalence of tardive dyskinesia really increasing? What is the prevalence of this disorder today? How often are the symptoms reversible? In this article we have sought answers to these questions by reviewing the literature on the epidemiology of tardive dyskinesia. Also, in the light of our review, we have made some suggestions for the treatment of adult psychiatric patients with neuroleptics.

THE SYNDROME OF TARDIVE DYSKINESIA

Typically, tardive dyskinesia occurs after years of neuroleptic administration, although occasionally it may be seen after much shorter treatment. The syndrome consists of abnormal involuntary movements of the orofacial region, extremities, and trunk. We have described elsewhere (3) the diagnostic criteria for tardive dyskinesia. The pathophysiology of dyskinesia is not precisely understood. Although many investigators believe that a supersensitivity of postsynaptic dopaminergic receptors in the nigrostriatal area is responsible for the symptoms of dyskinesia, this hypothesis is far from being an established fact. There is no satisfactory treatment for persistent tardive dyskinesia. A number of excellent reviews (4–8) of the syndrome are available for interested readers.

PROBLEMS IN EPIDEMIOLOGIC STUDIES OF TARDIVE DYSKINESIA

There are many problems in conducting and interpreting findings of epidemiologic surveys of drug-induced disorders such as tardive dyskinesia. Jick (9) has outlined some of the major problems and research needs for studying drug-induced illnesses. He considered the magnitude of two risks—the added risk of illness (e.g., dyskinesia) experienced by the users of a drug and the baseline risk if the drug is not used. Jick added that identification of a drug-induced syndrome might be considerably delayed if the time necessary to induce the illness were long. It is apparent that epidemiologic studies of drug-induced tardive dyskinesias should be complemented by similar work on spontaneously occurring dyskinesias to show that the risk of drug-induced illness is significantly greater than the baseline risk of developing dyskinesia. Such epidemiologic studies should satisfy three other basic require-

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ments: development of an acceptable and clinically useful definition of the syndrome to be studied, specification of objective criteria for diagnosis, and a measure of quantitative assessment of the severity of the condition. Since it is difficult to totally exclude subjective bias in psychiatric evaluation, at least for research purposes, two or more examiners should assess the subject on several different occasions. Unfortunately, only a small number of studies on the epidemiology of tardive dyskinesia satisfy these criteria.

IS TARDIVE DYSKINESIA MORE COMMON THAN SPONTANEOUS DYSKINESIA?

One criticism of the concept of tardive dyskinesia is that dyskinesia frequently occurs spontaneously among chronic psychiatric patients, especially the elderly—the group that is also most prone to develop tardive dyskinesia. It has also been stated that similar movement disorders were described in mental hospital patients long before neuroleptics were introduced into psychiatry (10). We should, therefore, look at studies on the prevalence of dyskinesia before and after the introduction of neuroleptics into psychiatry.

Preneuroleptic Studies

There are few formal studies on abnormal involuntary movements of a dyskinetic or choreoathetoid type before 1955. In his classic book, *Dementia Praecox and Paraphrenia*, Kraepelin (11) referred to a number of bodily symptoms of schizophrenia. In the subcategory of "spasmodic phenomena," Kraepelin (p. 83) described movements of the musculature of the face and other parts of the body.

It is instructive to note differences between Kraepelin's description of abnormal movements and the characteristics of tardive dyskinesia. Kraepelin labeled the disorders "spasmodic phenomena," a term that is closer to dystonias (disturbances of muscle tone) than to dyskinesias (disturbances of movement), although such a distinction is not always made. Some of the movements Kraepelin described resemble those of tardive dyskinesia, e.g., smacking of the lips and choreoathetoid movements of the extremities, while others, such as nystagmus, laughing, and tremors of outstretched hands, are not a part of the tardive dyskinesia syndrome. Had the characteristic symptom complex of tardive dyskinesia been as prevalent among mental hospital patients in Kraepelin's days as it is today, an astute clinician like Kraepelin would have given more specific descriptions of it. (Kraepelin gave longer descriptions of "seizures" than of "spasmodic phenomena," as symptoms of schizophrenia.) Furthermore, the abnormal involuntary movements Kraepelin described occurred in his patients with poor-prognosis, late-stage schizophrenia. There is no evidence that tardive dyskinesia patients have a poorer prognosis schizophrenia than nondyskinetic patients chronically treated with neuroleptics. Indeed, tardive dyskinesia is also seen frequently among outpatients, as well as among patients who have neurotic and affective disorders and have received neuroleptics.

Mettler and Crandell (12) conducted a study of neurologic disorders at a state hospital in 1955—before neuroleptics had been introduced into general use there. They found that only about .5% of the total hospital population had chorea or athetosis.

It seems to us that the main question here is not whether dyskinesia existed in the preneuroleptic period (it did), but whether a tardive-dyskinesia-like syndrome was as prevalent then as it is today (in all probability, it was not). There are probably few clinical entities that only the man-made drugs can produce. Usually the drugs produce syndromes similar to the naturally occurring ones, although the frequency may be different.

Postneuroleptic Studies

We found 12 major studies (8, 13–23) comparing the prevalence of dyskinesia among neuroleptic-treated and non-neuroleptic-treated patients. Ten (8, 14–20, 22, 23) of these 12 studies found a significantly higher prevalence of dyskinesia among neuroleptic-treated patients. (It is possible that the dyskinesia-suppressing effect of the neuroleptics might have been at least partly responsible for the relatively lower prevalence of tardive dyskinesia in the other two studies.) Although all of the investigators might not have used identical criteria for the diagnosis of dyskinesia, they all looked for abnormal involuntary movements in the orofacial region with or without choreiform movements of extremities. All of the studies were done with chronic patients in psychiatric hospitals or nursing homes. Some investigators (15, 18, 22, 23) included only elderly patients, while others studied patients from different age groups. In individual studies the neuroleptic-treated and non-neuroleptic-treated groups were usually comparable on variables such as age, sex, and institutionalization. In most studies the neuroleptic-treated group consisted of patients who had received neuroleptics for at least several months. Jones and Hunter (19) found a significantly higher prevalence of abnormal oral movements in the neuroleptic-treated group, although other types of movement disorders, such as tics and tremors, were also present in the non-drug-treated patients.

When all 12 studies are taken together, the overall weighted mean prevalence of dyskinesia for chronically institutionalized individuals is 3¼ times greater in the neuroleptic-treated group than in the non-neuroleptic-treated patients. It is necessary to add that dyskinesia among patients who had never received neuroleptics may be due to various causes such as ill-fitting dentures, senile chorea, and encephalitis. Ac-

cording to neurologists such as Baker (24) and Altrocchi (25), spontaneous orofacial dyskinesia not secondary to a known neurological disease is rare. Kline, who initially (26) questioned the existence of neuroleptic-induced persistent tardive dyskinesia, later (7) concluded that the disorder is common enough to make it "a matter of extreme importance."

There are two other reports of low prevalence of spontaneous dyskinesia among residents of homes for the elderly. Heinrich and associates (16) found dyskinesia in only 2 of 110 such persons. Degkwitz and Wenzel (14) found the disorder in 6 of 750 men and 6 of 750 women (.8% each) who were not demented.

Two other studies of abnormal involuntary movements in psychiatric patients have a serious drawback. Dincmen (27) observed choreoathetoid movements in 3.4% of 1,700 chronic patients from back wards of two state hospitals. He proposed the identification of a new syndrome called "chronic psychotic choreo-athetosis." However, Dincmen did not mention whether his patients were receiving neuroleptics. It is possible that at least some of the patients showing those movements had tardive dyskinesia. Similarly, Delwaide and Desseilles (28) reported a rather high prevalence of spontaneous dyskinesia among the elderly, but gave no information about past neuroleptic treatment of their subjects, 76% of whom were inpatients of a psychogeriatric unit.

The evidence considered thus far permits us to conclude that the symptom complex that constitutes tardive dyskinesia is significantly more common in neuroleptic-treated patients than in comparable populations not treated with neuroleptics. It is, of course, possible to argue that the two groups were not exactly comparable; otherwise, they would not have received different treatments. This argument may be valid, but can be countered by the fact that the tardive-dyskinesia-like syndrome was uncommon in preneuroleptic years. Hence, the higher prevalence of dyskinesia in neuroleptic-treated patients is unlikely to be due to their primary psychiatric illness.

REVIEW OF EPIDEMIOLOGIC STUDIES ON TARDIVE DYSKINESIA

Although acute dyskinesia has been known as a side effect of neuroleptics since the early years of the use of these drugs in psychiatry, to our knowledge tardive dyskinesia was not described during the 1950s except for two brief reports from Europe (29, 30). Until 1965 only three epidemiologic surveys (31–33) appeared in the literature. Since 1966 the number of such studies has increased considerably. Most of them have been cross-sectional studies of point prevalence, i.e., the number of cases that existed at a specific point in time. A few investigators (23, 34) have studied period prevalence, i.e., the number of cases that existed during a period of time such as a year. To our knowledge there have been no large-scale longitudinal prospective studies of the incidence or the lifetime prevalence of tardive dyskinesia. Also, there have been only a few major studies (35, 36) on the prevalence of tardive dyskinesia among children.

Some investigators have used indirect methods of collecting epidemiologic data on tardive dyskinesia. For example, Crane (8, 37) computed the total number of articles on tardive dyskinesia published and cases of the syndrome reported. He found that the number of articles on this subject jumped from 21 published before 1966 to 60 between 1966 and 1971; the latter number was double that in the previous 10 years. Crane therefore suggested that tardive dyskinesia was becoming an increasingly common iatrogenic disorder among psychiatric patients.

PREVALENCE OF TARDIVE DYSKINESIA AMONG CHRONIC PSYCHIATRIC INPATIENTS

There have been many reports on prevalence of tardive dyskinesia among hospitalized, chronically ill adult psychiatric patients. These studies differ considerably in their methodology. In order to obtain a reasonably reliable estimate of the prevalence of tardive dyskinesia, we selected those studies which met certain minimum requirements: 1) publication in scientific journals or books in the English or German language, 2) some description of the original patient population that was screened for tardive dyskinesia, 3) the involvement of at least 50 patients in the total study group, and 4) an apparently valid diagnosis of tardive dyskinesia based on clinical examination by the investigators.

We found 36 studies that met these requirements (see table 1).

We excluded 7 studies for specified reasons. Hoff and Hofmann (61) and Ettinger and Curran (62) obtained figures for the prevalence of tardive dyskinesia in the respective hospitals from data provided by staff members in charge of various wards. This method is similar to, and therefore has all the disadvantages of, the questionnaire technique of collecting epidemiologic data, particularly in the absence of objective criteria for the assessment of tardive dyskinesia. Eckman's method of diagnosing tardive dyskinesia (63) is questionable. He mentioned the following symptoms in three of his patients with tardive dyskinesia whose clinical descriptions are provided. One patient had tremors, akathisia, convulsions, and weakness of the arm, while the second one had tremors and akathisia. Only the third patient had oral dyskinesia. The first two patients' symptoms do not conform to those typical of tardive dyskinesia. Roxburgh (64) restricted his diagnosis of tardive dyskinesia to severely debilitated patients and obtained a low prevalence figure of 1.7%.

TABLE 1
Prevalence of Tardive Dyskinesia Among Chronically Ill Neuroleptic-Treated Psychiatric Inpatients, 1960–1980

Study	Population	Patients		Comments
		Number	Percent with Tardive Dyskinesia	
Uhrbrand and Faurbye, 1960 (31)	Women treated with perphenazine	155	9.7	
Faurbye and associates, 1964 (32)	Schizophrenic women	216	7.9	Patients with buccolingual masticatory triad
Hunter and associates, 1964 (33)		450	2.9	Patients with severe persistent dyskinesia
Demars, 1966 (13)		371	7	
Turunen and Achte, 1967 (38)		480	5.6	
Degkwitz and Wenzel, 1967 (14)		767	10.3	Patients with moderate to severe tardive dyskinesia; another 6.6% had mild tardive dyskinesia
		499	22.8	Severity of tardive dyskinesia not mentioned
Crane and Paulson, 1967 (39)		182	13.2	
Siede and Muller, 1967 (15)	Elderly	404	11.4	
Paulson, 1968 (40)		500	7	Patients with "conspicuous" persistent tardive dyskinesia
Heinrich and associates, 1968 (16)		554	17	
Crane, 1968 (17)	Men in U.S.A., "heavily" treated with neuroleptics	98	16.3	
	Men in Turkey, "moderately" treated for a mean of 13 months	40	7.5	
Crane, 1968 (41)	"Chlorpromazine study"	379	27.7	
Greenblatt and associates, 1968 (18)	Nursing home residents	52	38.5	
Jones and Hunter, 1969 (19)	Over 40 years of age	82	30.5	Patients with oral dyskinesia
Edwards, 1970 (42); Pryce and Edwards, 1966 (43)	Women	184	18.5	Patients with moderate to severe tardive dyskinesia; another 20.1% had mild or doubtful tardive dyskinesia
Dynes, 1970 (44)		1,200	8.6	Patients with oral dyskinesia
Lehmann and associates, 1970 (45)		350	6.6	
Crane, 1970 (34)	"Trifluoperazine study"	127	26.8	
Hippius and Lange, 1970 (20)		531	34.3	
Brandon and associates, 1971 (21)		625	25.4	
Kennedy and associates, 1971 (46) and 1972 (47)		63	41.3	Patients with moderate to severe tardive dyskinesia; another 20.6% had mild or doubtful tardive dyskinesia
Kinoshita and associates, 1972 (48)	Japanese hospital	396	14.1	
Fann and associates, 1972 (49)		204	35.8	
Crane, 1973 (8)		669	13	Patients with moderate to severe tardive dyskinesia; another 31.8% had mild tardive dyskinesia
Ogita and associates, 1975 (50)	Japanese hospital	123	17.9	
	French hospital	131	18.3	
Jus and associates, 1976 (51)		332	22.9	Patients with moderate to severe tardive dyskinesia; another 33.1% had mild tardive dyskinesia
Gardos and associates, 1977 (52)		50	46	
Mehta and associates, 1977 (53) and 1978 (54)	Follow-up study	178	22.5	
Pandurangi and associates, 1978 (55)	Indian patients hospitalized for 2 or more years	77	23.3	
Bell and Smith, 1978 (56)		1,329	26	Patients with definite tardive dyskinesia; another 14% had mild tardive dyskinesia
Smith and associates, 1978 (57) and 1979 (58)		293	30	Patients with moderate to severe dyskinesia
Jeste and associates, 1979 (23)	Elderly patients in a university hospital	88	23.9	Diagnosis of tardive dyskinesia based on specifically defined criteria; borderline and mild dyskinesia excluded

TABLE 1, continued

Study	Population	Patients: Number	Patients: Percent with Tardive Dyskinesia	Comments
Famuyiwa and associates, 1979 (59)	Schizophrenic patients below 60 years of age	50	34	
Perris and associates, 1979 (60)		347	17.3	
Bourgeois and associates, 1980 (22)	Residents of a retirement home of a hospital	59	42.4	
Jeste and Wyatt, 1980 (unpublished data)[a]	State hospital	95	31.6	Patients with moderate to severe dyskinesia
Total		12,730	17.5	

[a]In this study, specific diagnostic criteria (22) were used. Patients who scored less than 2 on the 0-4 Abnormal Involuntary Movements Scale were excluded.

Yagi and associates (65) differentiated "acute dyskinesia" from persistent dyskinesia. They subdivided the latter into reversible and irreversible forms. However, they did not specify the features distinguishing between acute and persistent dyskinesia; further, the subtype of "reversible persistent dyskinesia" sounds self-contradictory. Frangos and Christodoulides (66) computed the overall prevalence of tardive dyskinesia among their inpatients and outpatients, but did not separate the two populations. Simpson and associates (67) briefly screened the entire population of a state hospital to identify patients with obvious dyskinesia. The investigators were careful to add that the prevalence of tardive dyskinesia would have been higher if they had examined all of the patients more intensively. (This study, however, contains useful analyses of data on psychotropic drug history.)

Whenever possible, we sought to reanalyze the data on prevalence of tardive dyskinesia in the 36 studies to exclude patients whose diagnosis of tardive dyskinesia seemed questionable (19, 32) and to include only those patients whose dyskinetic symptoms were moderate to severe in intensity (8, 14, 42, 46, 51, 56, 57). Furthermore, we tried to separate neuroleptic-treated patients from those who had received either no neuroleptics or neuroleptics in very small total amounts, in order to obtain a proper estimate of the prevalence of tardive dyskinesia among neuroleptic-treated patients. Table 1 summarizes the 36 studies in chronological order. It is apparent that there are differences in the prevalence rates reported; there are several possible reasons for such differences.

Methodological Differences

1. *Diagnostic criteria.* Many studies do not define the criteria for diagnosis of tardive dyskinesia. Overinclusive data are likely to inflate the figures of prevalence. Faurbye and associates (32) reported a prevalence of 26%, but a careful look at their data shows that they included a number of patients with tremors, rigidity, and akathisia in their group of tardive dyskinesia patients. We preferred the conservative estimate of 17 patients (out of 216 schizophrenic patients) with the typical buccolingual masticatory triad and arrived at the prevalence figure of 7.9% of their patients. It is likely, however, that diagnostic differences may have contributed to some of the variance in the prevalence rates reported by different investigators.

2. *Severity of dyskinesia.* The inclusion of cases of borderline or mild dyskinesia may result in an unrealistically high prevalence rate, while selection of only severe cases may artificially lower the percentage of patients with dyskinesia. Bell and Smith (56) noted that the prevalence of tardive dyskinesia in their 1,329 patients would be 12% if only the severe cases were included, 26% if moderately severe cases were added, and 40% if patients with mild symptoms of dyskinesia were included. Smith and associates (57, 58) also concluded that the prevalence figure varied according to the criterion of severity of dyskinesia as measured by the Abnormal Involuntary Movements Scale. With all of the studies in which severity of dyskinesia was mentioned (8, 14, 42, 46, 51, 56, 57), we have chosen the proportion of patients with moderate to severe dyskinesia and excluded those with borderline or mild symptoms.

3. *Type of dyskinesia.* Not all dyskinesia seen in psychiatric patients is tardive dyskinesia, and tardive dyskinesia is not necessarily an irreversible or incapacitating syndrome. Surveys done soon after withdrawal of neuroleptics may uncover a high proportion of withdrawal dyskinesias. In some patients withdrawal dyskinesia may herald the onset of tardive dyskinesia, while in others it may be a readily reversible syndrome different from tardive dyskinesia. A follow-up may help differentiate between the two. A one-time survey of dyskinesia may make it difficult for the investigators to decide on the inclusion or exclusion of such cases. On the other hand, restricting the diagnosis of tardive dyskinesia to irreversible or incapacitating cases may result in an underestimation of the prevalence of the disorder.

Population Differences

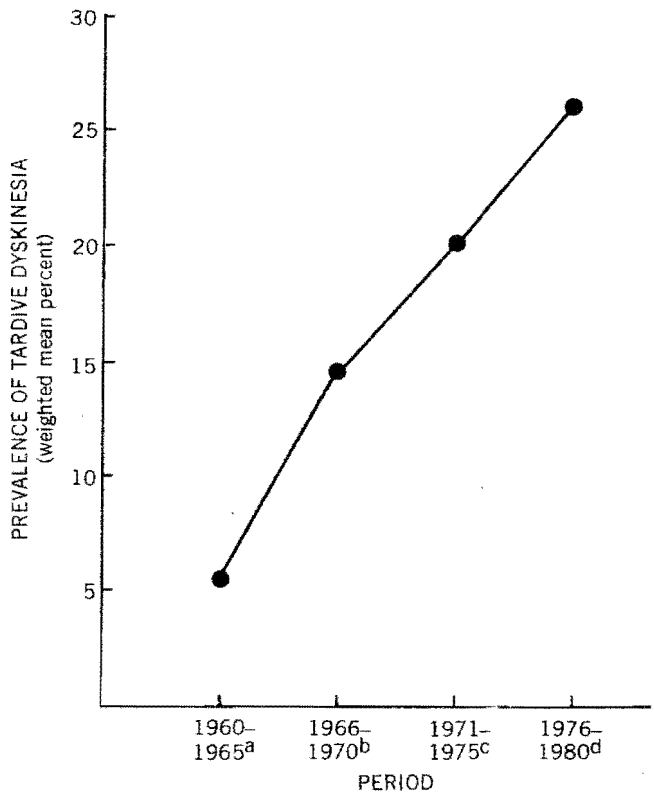
There is usually a higher prevalence of tardive dyskinesia among geriatric patients than among younger subjects. Table 1 specifies those studies which were done exclusively on elderly populations. Some reports have noted a higher prevalence of dyskinesia among women. Studies done with one gender only are identified as such in table 1. Other variables such as race and primary psychiatric diagnosis are not known to affect the prevalence of dyskinesia. Different investigators have used different criteria for defining brain damage, and the contribution of such brain damage to the development of tardive dyskinesia has been uncertain. It is necessary to separate neuroleptic-treated patients from those who had received either no neuroleptics or neuroleptics in small amounts for a brief period. As we saw earlier, the prevalence of spontaneous dyskinesia in the non-neuroleptic-treated population is low. Defining neuroleptic-treated patients as those who had received neuroleptics for at least three months in total amounts in excess of 100 g chlorpromazine equivalents, we found (23) dyskinesia in 23.9% of such patients and in only 4.5% of those who had been treated with smaller amounts of neuroleptics or no neuroleptics. Even among neuroleptic-treated patients, the prevalence of tardive dyskinesia may be higher among those who received greater total amounts of the drugs (16, 17, 43, 45).

Because of the possible effects of methodological and population differences on the prevalence of tardive dyskinesia, we have included only those studies which met certain minimum requirements. We have specified relevant aspects of those studies (e.g., severity of dyskinesia, age of population) in table 1 to facilitate proper evaluation of the findings.

CHANGING EPIDEMIOLOGY

Combining data from the 36 studies published from 1960 through 1980 (table 1), we found that the overall weighted mean prevalence of tardive dyskinesia among chronically ill psychiatric inpatients treated with neuroleptics appears to be 17.5%. A careful look at the reports, arranged in chronological order, shows that the reported prevalence of dyskinesia has been on the rise during the past two decades (see figure 1). The overall weighted mean prevalence of tardive dyskinesia among inpatients was 13.6% until 1970 (based on 19 studies) and has jumped to 23.3% since 1971 (based on 17 studies). Moreover, 13 of the last 17 studies individually found a prevalence exceeding 22%. The weighted mean prevalence in the 11 studies published during the past five years (1976 through 1980) is 25.7%. We must first consider the possibility that this increase in reported prevalence may not be a real one, but may be merely an artifact of methodological and population differences. In the following material we will discuss various arguments for and evidence against such a possibility.

FIGURE 1
Prevalence of Tardive Dyskinesia Among Chronically Ill Neuroleptic-Treated Psychiatric Inpatients



[a]Three studies (821 patients).
[b]Sixteen studies (6,800 patients).
[c]Six studies (2,211 patients).
[d]Eleven studies (2,898 patients).

Argument 1

It may be argued that the apparent increase in prevalence is due to a heightened awareness of the condition. Whereas tardive dyskinesia could have been underdiagnosed in the earlier years, it may now be overdiagnosed as a result of the increased publicity that this syndrome has received in recent years.

Probably the only direct way of testing this hypothesis would be for the same investigators, using the same diagnostic criteria to conduct prospective long-term studies of the incidence (i.e., the occurrence of new cases) of tardive dyskinesia in the same patient population. We are not aware of any published studies that were done on inpatients in this manner. Hence, we have to rely on the following indirect evidence to answer argument 1.

There have been seven reports since 1971 (references 8, 23, 47, 51, 56, 58, and Jeste and Wyatt, 1980 unpublished data) in which the diagnosis of tardive dyskinesia was restricted to patients with dyskinesia

of moderate to severe intensity (table 1). Borderline and mild cases were specifically excluded. The overall weighted mean prevalence of tardive dyskinesia in these seven studies is 23.5%. It is likely that a number of these patients had persistent dyskinesia. These findings can be contrasted with a communication (cited by Schmidt and Jarcho, reference 68) from the National Institutes of Health—National Clearinghouse for Mental Health Information (NCMHI). This communication, which was published in the early 1960s, stated that there was nothing in the NCMHI document collection which referred to permanent movement disorders caused by phenothiazines.

Crane (34, 41) examined the same patients at six-month and one-year follow-ups and reported an apparent increase in the prevalence of tardive dyskinesia between the first and second examinations. This finding could be attributed to a heightened sensitiveness for detecting dyskinesia. There was no further increase in prevalence between the second and third examinations. There is a limit to which awareness of a condition can be increased. It seems unlikely that the increased prevalence seen in figure 1 could be fully explained by a progressive and stepwise accentuation of researchers' diagnostic acumen for detecting tardive dyskinesia throughout the world during the past two decades.

Crane (69) found that oral discussion of tardive dyskinesia, as well as the publication of numerous articles on this subject, had little impact on the prescribing practices of physicians, which suggests that there probably was no marked increase in the general awareness about this condition.

It may be argued that the cases of tardive dyskinesia diagnosed during the 1960s were those of persistent dyskinesia, whereas many of the cases being diagnosed now are those of early and reversible dyskinesia. We therefore compared treatment response over the last 20 years. Elsewhere (70) we have reviewed the literature on the treatment of tardive dyskinesia. The only major treatment for tardive dyskinesia that has been reported throughout the past two decades has been withdrawal of neuroleptics. Of the 422 patients in the studies published through 1970, 37.2% had symptom remission after withdrawal of neuroleptics for at least three months. The improvement rate among the 123 patients from the studies published since 1971 was 42.3%. This difference between pre- and post-1970 reports is not significant. Other treatments (e.g., cholinergic drugs) have been tried mostly during the 1970s. We contrasted the treatment response through 1975 and since 1976. Of the 615 patients reportedly treated through 1975, 50.7% improved. This rate dropped to 41.7% for the 583 patients in the studies published since 1976. Thus, there is no indication that the cases of tardive dyskinesia that have been diagnosed in recent years are more reversible than those in the earlier periods.

If an increased awareness were responsible for the rising prevalence of tardive dyskinesia, then one might expect a similar increase in the prevalence of other long-term side effects of neuroleptics. Skin pigmentation and eye changes are thought to result from prolonged used of neuroleptics. In 1964 Greiner and Berry (71) reported 70 cases of ocular and dermatologic complications of chronic treatment with chlorpromazine. Their article stirred considerable interest and was followed by a number of papers, editorials, and letters to the editor on that subject; yet the reported prevalence of eye and skin changes caused by neuroleptics has not increased dramatically. Appleton (72) reviewed studies published during the 1960s and found that the overall weighted mean prevalence of ocular changes in patients receiving drug therapy was 29.1% (usually varying between 26% and 36% in different reports). In 1978 Ban (73) reported the prevalence of these changes to be 20% to 35%. Similarly, the prevalence of changes in skin pigmentation has remained around 1%.

Argument 2

It may be contended that the increased prevalence of tardive dyskinesia is due to the aging of patients during the last 20 years. This is not a valid objection, since only 2 of the 17 studies published since 1971 have been done in selectively elderly populations.

Argument 3

The number of chronic inpatients has been progressively decreasing since the mid-1950s. It may be argued that the patients who are currently in hospitals are generally sicker than the inpatients of earlier decades. This might be true; however, in recent studies (74–76) the prevalence of tardive dyskinesia among outpatients receiving long-term neuroleptic treatment has usually been comparable to that among the inpatients.

It therefore appears that the increase in the reported prevalence of tardive dyskinesia is not entirely an artifact. It is generally accepted that the length of neuroleptic therapy is one of the important factors in the etiology of tardive dyskinesia. Since the number of patients receiving long-term neuroleptic treatment has increased over the past two decades, so has the prevalence of tardive dyskinesia.

Here we wish to stress two aspects of tardive dyskinesia. First, tardive dyskinesia is not synonymous with irreversible dyskinesia. There are at least two clinical subtypes of tardive dyskinesia—persistent and reversible (23). Remission of dyskinetic symptoms within three months of withdrawal of neuroleptics may be considered a hallmark of reversible dyskinesia. Our review of the literature on treatment of tardive dyskinesia (70) suggests that the dyskinesia is reversible in slightly more than one-third of all patients. The rate of reversibility is likely to be higher among young patients than among elderly subjects. In addition, tardive

dyskinesia is not necessarily a severe and disabling syndrome.

The second fact to be stressed is the role of predisposing constitutional factors in the development of tardive dyskinesia. Thus, some predisposed patients may develop dyskinesia with relatively short-term use of neuroleptics, whereas others may not become dyskinetic in spite of prolonged intake of these drugs. Even in predisposed individuals a "threshold" may have to be reached before the dyskinetic symptoms appear. It is possible that with increasingly long-term use of neuroleptics, a higher proportion of patients are reaching that threshold today than ever before. This may also mean that in the future the prevalence of tardive dyskinesia may not increase progressively but may at some point reach a plateau. It is conceivable that such a plateau may have already been reached in the case of ocular and dermatologic complications of prolonged neuroleptic administration.

It is also useful to consider various changes that have occurred in psychopharmacologic practice during the last 20 years. The popularity of depot preparations, preference for once-a-day medication, concomitant use of the so-called high-potency neuroleptics along with antiparkinsonian agents, and the use of higher doses of certain neuroleptics—these are believed to be some of the major changes in the drug treatment of schizophrenia. It is, of course, rash even to suggest that any of these changes is directly responsible for the increasing prevalence of tardive dyskinesia. Indeed, the data on neuroleptic prescriptions collected by IMS America, Ltd. (Ambler, Pa.), challenge the notion that the increasing prevalence of tardive dyskinesia can be directly correlated with increasing use of high-potency neuroleptics. These data, which are a measure of the outflow of neuroleptic prescriptions from a representative panel of 800 retail pharmacies across the continental United States from 1964 through 1978, show that the five most commonly prescribed neuroleptics have been two phenothiazines with predominantly sedative side effects (chlorpromazine and thioridazine) and three neuroleptics with predominantly acute extrapyramidal side effects (trifluoperazine, fluphenazine, and haloperidol). Whereas the combined mean annual number of prescriptions for chlorpromazine and thioridazine rose from 6,700,000 during 1964 and 1965 to 14,500,000 10 years later (1974 and 1975), that for trifluoperazine, fluphenazine, and haloperidol was almost unchanged (5,500,000 during 1964 and 1965 and 6,220,000 during 1974 and 1975). It is possible, however, that hospital pharmacies might show a different trend, particularly with regard to the use of long-acting intramuscular fluphenazine. Much more epidemiologic and experimental work is required before we can state that there is an association between certain treatment practices and the occurrence of tardive dyskinesia.

There are other aspects of the changing epidemiology of tardive dyskinesia. The earlier stereotype of an old, brain-damaged woman, who has been hospitalized and treated for a number of years, as a typical candidate for tardive dyskinesia is no longer exclusively valid. Tardive dyskinesia is now known to occur with a noticeable frequency in younger patients, non-brain-damaged subjects, and nonpsychotic patients (77) who have received neuroleptics.

In summary, during the past 5 years the overall weighted mean prevalence of tardive dyskinesia among hospitalized, chronically ill, neuroleptic-treated adult psychiatric patients has been 25.7%. About two-thirds of these patients (17% of the total) have persistent dyskinesia. Assuming that nearly one-fourth of them may have non-drug-related dyskinesia, the prevalence of persistent dyskinesia that may be attributable to neuroleptics is about 13%. It is not known how many of these patients have symptoms that are disabling.

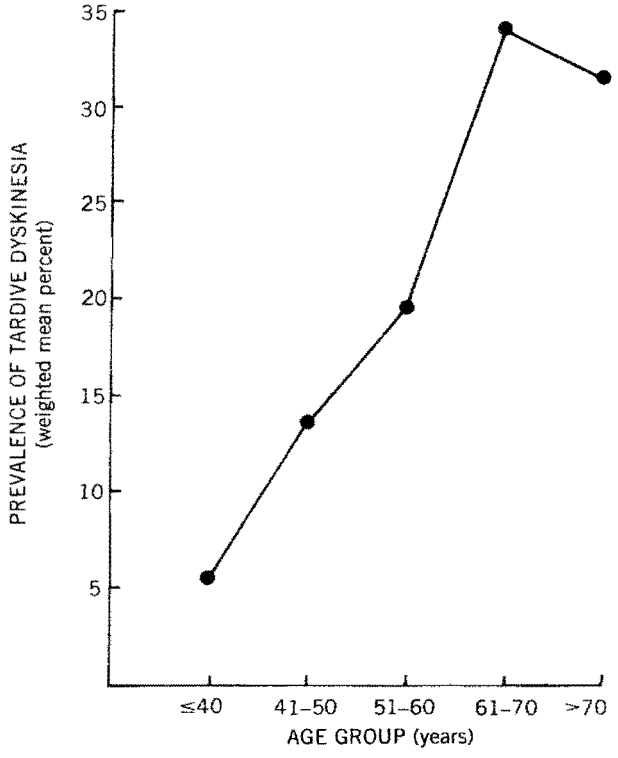
PATIENT-RELATED AND TREATMENT-RELATED VARIABLES

Differences among patient populations and treatment practices are at least partly responsible for the differences in prevalence of tardive dyskinesia reported in various studies. Age, gender, and length and nature of neuroleptic treatment are among the variables influencing the prevalence of tardive dyskinesia.

Age

It is generally agreed that tardive dyskinesia is more common among the elderly than among younger patients. A number of studies (13, 33, 42, 48) found that the mean age of tardive dyskinesia patients was higher than that of nondyskinetic patients. Eight studies (14, 23, 34, 39, 41, 49, 50), including our study at Saint Elizabeths Hospital (Jeste and Wyatt, 1980 unpublished data), compared the prevalence of tardive dyskinesia in patients under 40 with that in patients over 40. The overall weighted mean prevalence of tardive dyskinesia in patients over 40 was three times that in younger subjects. Except for two studies (34, 41) that included only patients up to age 56, the others found that patients over 40 had a prevalence of dyskinesia 2–22 times higher than that of patients under 40. Crane and Paulson (39), Degkwitz and Wenzel (14), Jones and Hunter (19), Brandon and associates (21), Fann and associates (49), and Jeste and Wyatt (present study) have noted that there was a progressive increase in the prevalence of tardive dyskinesia until age 70, after which there was no further significant increase. Figure 2 shows the weighted mean prevalence in various age groups, based on these six studies. It should be noted that these were not prospective longitudinal studies of the incidence of tardive dyskinesia with increasing age but were quasilongitudinal studies

FIGURE 2
Prevalence of Tardive Dyskinesia Among Various Age Groups of Chronically Ill Neuroleptic-Treated Psychiatric Inpatients[a]



[a]Based on the studies of Crane and Paulson (39), Degkwitz and Wenzel (14), Jones and Hunter (19), Brandon and associates (21), Fann and associates (49), and Jeste and Wyatt (1980, unpublished data).

comparing the prevalence in different age groups at the same time.

Gender

Table 2 summarizes data from 19 studies on the relative prevalence of tardive dyskinesia in men and women. These studies differ in their findings. Hunter and associates (33), Kennedy and associates (46, 47), and Perris and associates (60) reported a markedly higher prevalence in women, whereas Crane (17) noted a slightly higher prevalence in men. Hippius and Lange (20) and Jeste and associates (23) found almost no difference in the prevalence of dyskinesia between men and women. Based on all 19 studies, the overall weighted mean prevalence in women is about 41% higher than that in men. It is not clear whether the gender differences in the prevalence of dyskinesia are a result of certain biological characteristics (e.g., brain neurotransmitter concentrations or the role of hormones) or merely reflect differences in treatment. Several groups of researchers (14, 19, 49, 67) have noticed that women tend to receive longer or higher-dose pharmacologic treatment than men do.

There have been too few studies to allow one to determine differential effects of age on men and women in terms of the development of tardive dyskinesia. It may be mentioned, however, that Smith and associates (57) noted that while women had a linear increase with age in the prevalence of dyskinesia, the prevalence in men decreased after age 70.

Treatment Practices

The duration of neuroleptic therapy is one of the determinants of the prevalence of tardive dyskinesia. Mode and frequency of administration, drug-free periods, and concomitant use of antiparkinsonian drugs may also have a variable influence in the occurrence of tardive dyskinesia. There is no hard evidence that certain types of neuroleptics are more likely to induce dyskinesia than others. In addition, the role of factors such as daily dosage, length of hospitalization, ECT, and leucotomy in the prevalence of tardive dyskinesia is unproven.

TARDIVE DYSKINESIA AMONG PSYCHIATRIC OUTPATIENTS

Initially, tardive dyskinesia was considered to be a rarity among psychiatric outpatients. Recent studies, however, have demonstrated that this is not the case. The number of studies done with outpatients is, unfortunately, small. In addition, they are even more difficult to evaluate than the studies on inpatients because of heterogeneous populations and variations in treatment practices, not to mention methodological aspects of the studies. One common but frequently ignored problem in outpatient studies is that of noncompliance. As many as 25%–50% of outpatients may fail to take their medication (78). This makes it difficult to assess the exact proportion of patients receiving regular long-term neuroleptic treatment. Moreover, temporary noncompliance may result in withdrawal dyskinesia. As noted earlier, the relationship between withdrawal dyskinesia and tardive dyskinesia is uncertain.

Jeste and associates (79) found a low prevalence of tardive dyskinesia at the outpatient department of a hospital in Newark, N.J. Alexopoulos (80) reported corresponding findings at a nearby hospital with a similar outpatient department. The low prevalence in these two studies can be explained by the fact that the departments primarily served younger patient populations; also, the studies included relatively small proportions of chronically ill psychiatric patients receiving long-term neuroleptic treatment. In contrast, Asnis and associates (74), Chouinard and associates (75), and Smith and associates (76) found a prevalence of over 30% in their outpatients on long-term neuroleptic treatment. As the community mental health programs expand, more and more of the patients who might have been long-term inpatients in the past are now returning to the community. An increasing prevalence of tardive dyskinesia among psychiatric outpatients is therefore

TABLE 2
Gender Difference in the Prevalence of Tardive Dyskinesia Among Chronically Ill Neuroleptic-Treated Psychiatric Inpatients

Study	Men		Women	
	Number	Percent with Tardive Dyskinesia	Number	Percent with Tardive Dyskinesia
Hunter and associates, 1964 (33)	200	0	250	5.2
Demars, 1966 (13)	166	4.8	205	8.8
Turunen and Achte, 1967 (38)	207	3.4	273	7.3
Crane and Paulson, 1967 (39)	66	15.2	116	14.7
Degkwitz and Wenzel, 1967 (14)	303	4.6	464	14
	193	20.7	306	24.2
Heinrich and associates, 1968 (16)	228	12.3	326	20.2
Crane, 1968 (17)	207	31	172	23.3
Jones and Hunter, 1969 (19)	13	7.7	69	34.8
Lehmann and associates, 1970 (45)	168	4.2	182	8.8
Crane, 1970 (34)	62	27.4	65	26.1
Hippius and Lange, 1970 (20)	244	34.4	287	34.1
Brandon and associates, 1971 (21)	264	17.4	361	31.3
Kennedy and associates, 1971 (46) and 1972 (47)	32	25	31	58
Ogita and associates, 1975 (50)	70	17.1	53	18.9
Smith and associates, 1978 (57)	150	24.7	143	35.7
Jeste and associates, 1979 (23)	27	22.2	61	24.6
Famuyiwa and associates, 1979 (59)	26	26.9	24	41.7
Perris and associates, 1979 (60)	213	9.4	134	29.8
Jeste and Wyatt, 1980 (unpublished data)	25	24	70	34.3
Total	2,864	14.6	3,592	20.7

to be expected. In one of the few studies on the annual incidence of tardive dyskinesia, Gibson (81) followed 374 outpatients receiving parenteral forms of depot neuroleptics from 1974 to 1977. He observed a progressive increase in the number of patients with oral dyskinesia—from 7% in 1974 to 22% in 1977. More studies of a similar type are needed with different types of patient populations.

IMPLICATIONS

The rising prevalence of tardive dyskinesia has obvious implications for the use of neuroleptics. It must be stated at the outset, however, that development of tardive dyskinesia is only one aspect of neuroleptic treatment. Neuroleptics have had a far greater impact than any other treatment on the management of schizophrenic patients. Nearly three decades after the discovery of chlorpromazine as an antipsychotic agent, there is still no single substitute for neuroleptics for control of symptoms and prevention of relapse in the majority of chronic schizophrenic patients (1). Denying these patients the benefit of the neuroleptic action without offering any suitable alternative may be considered a clinical error. Indeed, given the unfortunate choice of selecting between two evils, relapse of schizophrenia versus development of tardive dyskinesia, some patients may accept the risk of tardive dyskinesia rather than experience another psychotic breakdown. At the same time, a physician cannot afford to ignore the clinical and medicolegal implications of the danger of tardive dyskinesia. It is necessary to develop certain guidelines, however tentative they may be, for practical use. Elsewhere (82) we have discussed certain recommendations for the prevention and management of tardive dyskinesia in clinical practice. The report of the American Psychiatric Association Task Force on Late Neurological Effects of Antipsychotic Drugs (83) is also likely to have an influence on the future treatment of patients with neuroleptics. Here we will briefly mention some suggestions for the effective use of neuroleptics.

1. The routine, long-term administration of neuroleptics to nonschizophrenic psychiatric patients (e.g., patients with anxiety neurosis) should be discouraged, particularly because of the availability of alternative treatments that are at least as effective as neuroleptics for the majority of these patients.

2. Neuroleptics should be prescribed with caution for elderly subjects.

3. The value of neuroleptics in the maintenance treatment of chronic schizophrenia is generally unquestionable (1). However, the need for prolonged treatment with neuroleptics should be ascertained and documented in individual patients.

4. The possible risk of tardive dyskinesia should be discussed with all patients and, if feasible, with their families when neuroleptics are needed for more than three months.

5. The issue of a written informed consent for neuroleptic administration is controversial (82, 84, 85). In the absence of a consensus on this issue among those concerned with the use of neuroleptics, court decisions are likely to dictate the practice of obtaining consent from patients. We feel that a written consent

may not be *routinely* necessary with nondyskinetic patients who are to be treated with neuroleptics, but that a physician should discuss the possible risk of tardive dyskinesia with the patient and/or the patient's family and then make a note of that discussion in the patient's record.

6. The issue of treating committed patients with neuroleptics is one that is being argued in the courts; it will undoubtedly be a long time before it is settled. Our own view is that patients are committed to hospitals and physicians' care for the best treatment available and that neuroleptic drugs are the single best available treatment for schizophrenia. This is not to say that they are the only treatments to be used—they are not—or that they should be used for all schizophrenic patients—they should not be. Furthermore, they only become the best treatment when they are used properly.

7. The routine prophylactic use of antiparkinsonian agents should be curtailed. These drugs exacerbate preexisting tardive dyskinesia (70). They have also been thought to increase the likelihood of the development of tardive dyskinesia (86), although there is no convincing evidence to support this assertion.

8. The value of lengthy drug interruptions in the prevention of persistent tardive dyskinesia is, at best, uncertain. Two clinical studies (14, 23) found that persistent dyskinesia was significantly associated with a past history of interrupted neuroleptic therapy. In an experiment on an animal model for tardive dyskinesia (87), intermittent administration of haloperidol did not reduce behavioral supersensitivity to amphetamine in rats. (There are, however, some questions about the validity of this animal model for human tardive dyskinesia.) We have not found any reports in the literature on the effects of short interruptions (e.g., drug-free weekends) on the prevalence of tardive dyskinesia.

9. There is an urgent necessity for studying the constitutional factors and treatment practices that may affect the incidence and prevalence of tardive dyskinesia. Wegner and associates (88) suggested that a beta-mitten pattern in the EEG may indicate a predisposition to tardive dyskinesia. While brain damage has sometimes been thought to be a predisposing factor, the available methods for detecting structural abnormalities in the brain, including computerized tomography (89, 90), have failed to show consistent differences between patients with and without tardive dyskinesia. However, we found certain biochemical differences between elderly women with tardive dyskinesia and a control group of patients matched for age, gender, primary psychiatric diagnosis, and length of neuroleptic treatment. The dyskinetic patients had significantly lower platelet and lymphocyte monoamine oxidase activities and higher plasma dopamine-beta-hydroxylase activity than the controls (91, 92). Furthermore, among patients who were still receiving neuroleptics, those with dyskinesia had significantly greater serum neuroleptic activity (measured with a radioreceptor assay) than did nondyskinetic subjects (93). We have recently confirmed this finding, using a liquid chromatographic assay (unpublished data.) There is as yet no evidence that these differences are related to constitutional susceptibility to tardive dyskinesia. However, work along similar lines may help uncover at least some of the predisposing factors. Identifying the high-risk patient and treatment variables is of great clinical and theoretical importance.

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