The Impact of Neuroleptic Medication on Tardive Dyskinesia: A Meta-Analysis of Published Studies

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Abstract: To quantify the impact of chronic exposure to neuroleptic medication on the occurrence of tardive dyskinesia (TD), we conducted a meta-analysis of data collected from 21 studies published between 1966 and 1985. The observed prevalence of dyskinesia was greater among exposed subjects in all 21 studies; we estimate that, on the average, the occurrence rate was 2.9 times greater in exposed persons than would be expected if they had been unexposed. We estimate that 65 per cent of exposed cases and 51 per cent of all cases in these investigations were caused by long-term neuroleptic exposure. Among adult United States residents in 1980, we estimate that there were approximately 193,000 neuroleptic-induced TD cases of which about 60 per cent occurred in outpatients. We also observed substantial heterogeneity of effect (rate ratio) across studies, however, partially explained, by changes and differences in the rate of dyskinesia, by differences in the frequency of certain effect modifiers, and by differences in diagnostic methods. Methodologic limitations of the studies and their possible effects on our results are discussed. (*Am J Public Health* 1987; 77:717–724.)

Introduction

Tardive dyskinesia (TD) is an abnormal involuntary movement disorder characterized primarily by choreoathetoid (i.e., nonrepetitive and purposeless) movements of the orofacial region, trunk, and extremities. Although the pathophysiology of TD is not well understood, it is believed to occur as a relatively late side effect of long-term treatment with neuroleptic (anti-psychotic) medication.[1–4] TD is rapidly becoming an important public health problem because of the medical and psychosocial complications experienced by cases, the purported iatrogenic origin of the disorder, and the resulting likelihood of malpractice litigation.[5–7] While the disorder is now relatively common among chronic neuroleptic users, there does not appear to be any alternative treatment that both relieves psychotic symptoms and is free of dyskinetic side effects.[8]

Although a standard diagnostic criterion for TD is evidence of exposure to neuroleptics for at least three months before symptoms,[9–11] it is also commonly recognized that "spontaneous dyskinesias," which are clinically similar to TD, occur in the absence of exposure.[12,13] Consequently, the practice of defining TD in terms of its presumed cause limits further attempts to understand the role of neuroleptics in the development and course of this disorder. Most investigators of movement disorders acknowledge that neuroleptic exposure is neither a necessary nor sufficient cause of TD;[1–4,12–14] some maintain that neuroleptics only precipitate or promote the occurrence of TD in persons already at high risk[15,16] or that neuroleptics may not contribute at all to its occurrence.[17,18]

The purpose of this paper is to estimate from published data the *effect* of neuroleptic exposure on dyskinesia—i.e., the magnitude of the statistical association between exposure and the occurrence of the clinically defined disorder. From these estimates, we will derive estimates of the *impact* of neuroleptic exposure on the frequency of TD—i.e., quantitative measures that reflect the number of neuroleptic-induced cases of dyskinesia in the population.[19] While effect measures, such as the relative risk, are most useful for making inferences about cause-and-effect relationships, impact measures are more appropriate for applications involving decisionmaking, such as priority setting, program or policy planning, clinical practice, and personal injury litigation.

Although other researchers have concluded that neuroleptics increase the risk of dyskinesia,[1,2,12] they have not estimated the effect and impact of exposure, controlling for the potentially confounding effects of age, sex, and other differences among studies.

Methods

The selection of previous studies for our meta-analysis was limited to published reports comparing neuroleptic users and nonusers from the same source population. In addition, reports had to include data on the joint distribution of exposure status and dyskinesia as well as descriptions of diagnostic and selection criteria. Using computer searches for the years 1966 to 1984, a systematic review of psychiatric journals since 1975, and references cited[1–18] in many recent publications, we found 21 studies[20–38] that met these criteria, all of which were cross-sectional involving (point) prevalence data. The studies were conducted in six countries and were published between 1966 and 1985, although 14 of the 21 were published before 1975. Reports of nine studies provided the exposure-disease data stratified by sex, and two studies provided age-, sex-specific data.

Descriptions of all 21 studies are summarized in Table 1. It is important to note the differences among studies with respect to the composition of the study population and the criteria for diagnosing abnormal movements. For example, some studies were restricted to elderly patients while others included primarily young adult or middle-aged populations. Fourteen studies involved hospitalized patients, six involved nursing home residents, and one study was conducted among psychiatric outpatients. Diagnostic criteria also varied considerably; 12 studies relied on global assessments of dyskinesia by clinicians and nine used standardized instruments for quantifying symptom severity. In all studies, information on current and past neuroleptic exposure was abstracted

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Acronyms: AF, attributable fraction in the total population; AFE, attributable fraction in the exposed population; CI, confidence intervals; COR, crude odds ratio; SOR, [internally] standardized odds ratio; TD, tardive dyskinesia.

TABLE 1—Descriptions of 21 Published Studies Comparing the Prevalence of Dyskinesia in Neuroleptic Users versus Nonusers, 1966–85

Author Year (Ref.) Country	Study Population	Diagnosis of Dyskinesia
Demars 1966 (20)* England	488 chronic mental inpatients hospitalized for at least 3 months. Mean age = 61.	Global assessment of abnormal orofacial movements, done blind to neuroleptic exposure, by hospital staff.
Degkwitz, *et al.* 1967 (21)* Germany	1291 hospitalized mental patients. Ages 10–89; median = 50–54.	Global assessment of hyperkinesias of orofacial area and body (ordinal scale), by the authors.
Degkwitz, *et al.* 1967 (21) Germany	187 nondemented nursing home residents.	(Same as above)
Degkwitz, *et al.* 1967 (22)* Germany	830 hospitalized mental patients. Ages 10–89.	(Same as above)
Degkwitz, *et al.* 1967 (22)* Germany	661 hospitalized mental patients (different hospital). Ages 10–89.	(Same as above)
Siede, *et al.* 1967 (23) Canada	235 residents of an old-age home. Ages ≥ 55.	Global assessment of choreiform movements (mostly orofacial).
Crane 1968 (24)* Turkey	137 hospitalized mental patients (all male). Mean age = 36.	Global assessment of involuntary movements of the fingers and ankles, by the author.
Greenblatt, *et al.* 1968 (25) United States	153 residents of a nursing home. Ages 36–101; mean = 73.	Global assessment of abnormal orofacial and body movements, done blind by a nurse and college student, using Crane's method.
Heinrich, *et al.* 1968 (26)* Germany	755 hospitalized mental patients.	Assessment of orofacial choreiform movements, using a severity scale developed and applied by the authors.
Jones, *et al.* 1969 (27)* England	127 chronic mental inpatients hospitalized since before 1946. Ages 41–87; mean = 64.	Global assessment of choreoathetosis of orofacial area and limbs, by the authors.
Hippius, *et al.* 1970 (28)** Germany	668 psychiatric inpatients. Ages 14–89.	Assessment of abnormal finger and toe movements, by the authors, using Heinrich's scale.
Brandon, *et al.* 1971 (29)** England	910 mental inpatients hospitalized for at least 3 months. Ages 30–80+; median = 61–64.	Global assessment of persistent orofacial choreiform movements, based on 3 exams under different conditions, by the authors.
Crane 1973 (30) United States	84 hospitalized patients. Ages >65; mean = 71.	Global assessment of moderate and severe dyskinesias, by the author.
Crane, *et al.* 1974 (31) United States	39 hospitalized patients admitted to geriatric wards after 1969 and having no previous exposure to neuroleptic drugs. Ages 63–89; median = 74.	Assessment of orofacial dyskinesia, by the first author, using a 7-point severity scale.
Kane, *et al.* 1980 (32) United States	120 inpatients and 151 outpatients of one hospital. Mean age = 32.	Assessment of possible or definite dyskinesia by at least one of two independent raters, done blind, using the Simpson Dyskinesia Scale and the Abnormal Involuntary Movement Scale.
Bourgeois, *et al.* 1980 (33) France	270 nursing home residents. Mean age = 78.	Assessment of abnormal movements of orofacial area and extremities, done blind by the author, using Villeneuve's Severity Scale.
Blowers, *et al.* 1981 (34) England	500 nursing home residents. Ages 59–102; mean = 83.	Assessment of at least mild dyskinetic movements, using a modification of the Abnormal Involuntary Movement Scale.
Jeste, *et al.* 1982 (35) United States	286 psychiatric inpatients. Ages ≥ 50.	Global assessment of abnormal movements by 2 independent psychiatrists (with exclusion criteria for differential diagnoses).
Owens, *et al.* 1982 (36) England	411 hospitalized patients with chronic schizophrenia. Ages 21–91; mean = 58.	Assessment of abnormal movements in 7 anatomical areas, using the Abnormal Involuntary Movement Scale; total score ≥ 3.
Lieberman, *et al.* 1984 (37) United States	370 geriatric residents of a chronic-care facility. Ages 59–99; mean = 84.	Assessment of at least mild dyskinesia, done blind by 2 independent raters, using the Simpson Dyskinesia Scale and the Abnormal Involuntary Movement Scale.
Chacko, *et al.* 1985 (38) United States	87 outpatients from one psychiatric clinic. Ages 55–91; mean = 67.	Assessment of mild abnormal movements in at least one of 7 anatomical areas, by one rater, using the Abnormal Involuntary Movement Scale.

*Studies in which the exposure-disease data are presented by sex.
**Studies in which the exposure-disease data are presented by sex and age.

from medical records. In only one study[36] did the investigators attempt to confirm the medical record information with patient recall and nurse reports.

To measure the effect of neuroleptic exposure on dyskinesia, we used the prevalence odds ratio which, in cross-sectional or case-control studies, is an estimate of the incidence rate ratio, comparing exposed with unexposed subjects.[19] To control analytically for potential confounders, we standardized the odds ratio for age, sex, and/or "study" by using the exposed group as the standard population.[19] The standardized odds ratio is the ratio of the number of cases observed in the exposed group to the number expected if there had been no independent effect of the exposure. Each study was treated as a separate stratum since diagnostic and other differences among studies may confound the observed effect. That is, if studies with a higher frequency of neuroleptic use in noncases also have a higher or lower prevalence of spontaneous dyskinesia, the crude or unstandardized odds ratio will be a biased estimate of the true neuroleptic effect. Tests of significance for stratified data were based on Mantel-Haenszel statistics for several 2×2 contingency tables.[19,39] The methods of Woolf and Schlesselman[39] were used to test for heterogeneity of effect across studies and to test for a difference in standardized effects between two groups.

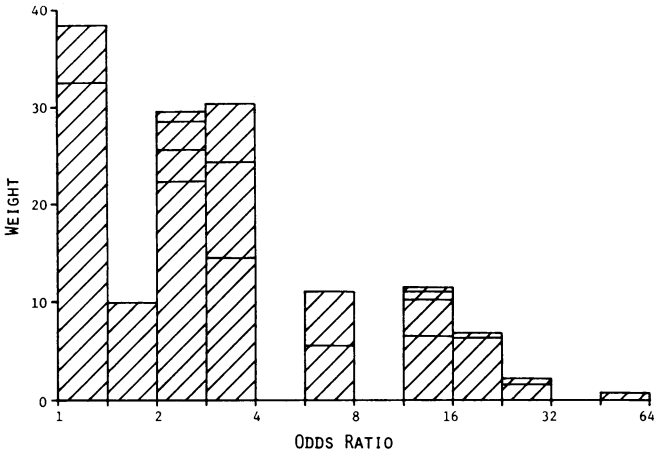

FIGURE 1—Distribution of Estimated Neuroleptic Effects for All 21 Studies: Weighted Histogram* of the Crude Prevalence Odds Ratios
***Each bar in the histogram represents one or more studies (separated by horizontal lines) for which the estimated odds ratio falls in the range indicated on the horizontal axis (log scale). The weight for each study is a measure of the precision with which the neuroleptic effect is estimated; it is the inverse of the estimated variance of the natural log of the odds ratio.[45] Although all estimated odds ratios are greater than one, the histogram clearly reflects substantial heterogeneity of effect among studies ($p < 0.001$).**

The proportion of exposed cases attributable to the exposure—the *attributable* (or etiologic) *fraction* in the exposed (AFE) population—is estimated in cross-sectional studies (without the rare-disease assumption) by the quantity $(\hat{OR}-1)/\hat{OR}$, where $\hat{OR}$ is the estimated odds ratio.[19,40] To control for potential confounders, we substituted the standardized odds ratio ($\hat{SOR}$) described above for $\hat{OR}$ in the expression for $\hat{AFE}$.[40] Confidence intervals (CI) for AFE estimates were derived from the estimated variance of the natural log of $\hat{SOR}$.[41] To handle analyses involving zero cells, estimates of effect and impact were based on 2×2 tables in which .5 has been added to each cell.

The attributable fraction in the total population (AF) is equal to the AFE times the proportion of all cases that are exposed.[19,40] Thus, the AF represents the proportion of cases potentially preventable by eliminating the exposure in the source population.[42,43] To calculate 95 per cent CI for AF estimates, we used the method described by Whittemore[44] involving a logit transformation. If the total numbers of exposed (A) and unexposed (B) cases in the source population are known, we can estimate the number of exposure-induced cases ($A^* \leq A$) by multiplying $\hat{AFE}$ times A or by multiplying $\hat{AF}$ times (A + B).

Results

Estimation of Effect and Impact

The estimated prevalence of dyskinesia is greater in the exposed group than in the unexposed group in all 21 studies. Despite this consistent evidence for the etiologic importance of neuroleptics, the magnitude of the association varies considerably among studies ($p < 0.001$), ranging from an odds ratio of 1.0, indicating no effect, to a value of more than 50. The complete distribution of estimated effects is presented graphically in Figure 1. This weighted histogram[45] shows not only the number of studies having an estimated effect in each category but also the relative precision with which effects are estimated.

Results of the stratified analysis combining data from all 21 studies are presented in Table 2. Controlling for "study", we estimate that the rate of dyskinesia was 2.9 times greater in persons exposed to neuroleptics than would be expected if they had not been exposed. The difference between this standardized estimate and the crude estimate (3.5) indicates the positive confounding effect of differences among studies. We also estimate that 65 per cent of exposed cases or 51 per cent of all cases in these populations were attributable to neuroleptic exposure. Thus, about 786 cases ($A^* = 0.652 \times 1207$) in these 21 studies developed dyskinesia as a result of neuroleptic exposure.

Since age and possibly sex are risk factors for both tardive dyskinesia[1–4] and spontaneous dyskinesia,[14] these factors may have confounded or modified the effect of neuroleptic exposure. Therefore, if the age-sex distribution differed among studies, the effect modification by age or sex might explain part of the observed heterogeneity of effect across studies. Table 3 presents the results of the stratified analysis of the nine studies with published sex-specific data. As shown in the bottom row of the Table, the estimated effect ($\hat{SOR}$ = 2.9) and impact ($\hat{AFE}$ = 0.65) of neuroleptic exposure, controlling for both sex and study, are nearly identical to estimates controlling only for study.‡ Thus, it appears that sex is not a confounder. Sex does appear to be an effect modifier, however, since the standardized effect and impact of neuroleptic exposure is somewhat greater for men ($\hat{SOR}$ = 3.7; AFE = 0.73) than for women ($\hat{SOR}$ = 2.6; $\hat{AFE}$ = 0.61) ($p = 0.16$). It should be noted that there is substantial heterogeneity of effect even within gender groups.

In a similar analysis of the two studies[28,29] with published age-, sex-specific data, there was little confounding due to age or sex and additional evidence for the role of sex as an effect modifier for the odds ratio (results not shown).

Closer inspection of the sex-specific results from the nine studies reveals that the exposure-sex interaction effect is observed only on a multiplicative scale. As shown in Figure 2, the standardized prevalence difference, unlike the standardized odds ratio, is a little smaller for men (11.8 per cent) than for women (14.5 per cent). That is, the finding in Table 3 of a stronger effect in men may be due to the greater frequency of dyskinesia in women. Although an excess rate in women has not been observed in a few exposed populations,[3,46–50] our finding, which is consistent with the results of most other studies,[1–4,13] may reflect a higher frequency of affective disorders[51,52] and degenerative nonvascular dementias[53–55] in women, both of which may be risk factors for dyskinesia.[3,14,16,56–60]

Heterogeneity of Effect

The observed heterogeneity of effect across studies may be due to actual differences, methodologic artifacts, or chance. To help explain the variability, we have further stratified the 21 studies separately by five dichotomous variables: year of publication (before 1970 vs 1970+); country (US vs other); type of study population (hospital inpatients vs other); diagnostic instrument (quantitative severity scale vs global assessment); and diagnostic method (blind vs not blind to exposure status). The results, presented in Table 4, suggest some difference in effect and/or impact between groups of studies classified by each of these variables. The largest difference is observed for year of publication. While the estimated SOR was 6.9 (95% CI = 4.8, 9.9) for studies published before 1970, the corresponding estimate was 2.1

‡This finding holds when comparing the above estimates to both the results shown in Table 2 (all 21 studies) and the results standardizing only for study in Table 3 (nine studies).

TABLE 2—Estimated Prevalence of Dyskinesia, by Status of Exposure to Neuroleptic Medications, and Estimated Neuroleptic Effect: Meta-Analysis of 21 Studies, 1966–85

Neuroleptic Exposure Status	No. Subjects	No. Cases	Prevalence	Crude Odds Ratio (95% CI)	Standardized Odds Ratio* (95% CI)	Attributable Fraction* (95% CI)
Exposed	4952	1207	0.244	3.49 (3.06, 3.98)	2.87 (2.34, 3.52)	0.652 (0.573, 0.716)
Unexposed	3808	322	0.085	1.00	1.00	—
Total	8760	1529	0.175	—	—	0.512 (0.445, 0.578)

*Standardized for "study," using the exposed group as the standard population. The odds ratio varies substantially across studies ($p < 0.001$).

TABLE 3—Estimated Effect and Impact of Neuroleptic Exposure on Dyskinesia,‡ by Sex: Meta-analysis of Nine Prevalence Studies with Published Sex-specific Data

Sex	Sample Size	Effect		Impact			
		CÔR	SÔR*	AF̂E*	95% CI (AF̂E)	AF̂*	95% CI (AF̂)
Male	2783	5.4	3.7†	0.73	0.61, 0.82	0.62	0.51, 0.72
Female	3084	4.0	2.6†	0.61	0.45, 0.73	0.54	0.42, 0.65
Total	5867	4.9	2.9†	0.65	0.54, 0.73	0.57	0.48, 0.65

*Estimates for each sex are standardized for "study", and estimates for the total population are standardized for both "study" and sex. All estimates are different from their null values ($p < 0.001$).

†There is heterogeneity of effect across studies ($p < 0.05$). The estimated SORs for men and women are somewhat different ($p = 0.16$).

‡COR = crude odds ratio; SOR = internally standardized odds ratio; AFE = attributable fraction in the exposed population; AF = attributable fraction in the total population; CI = confidence intervals.

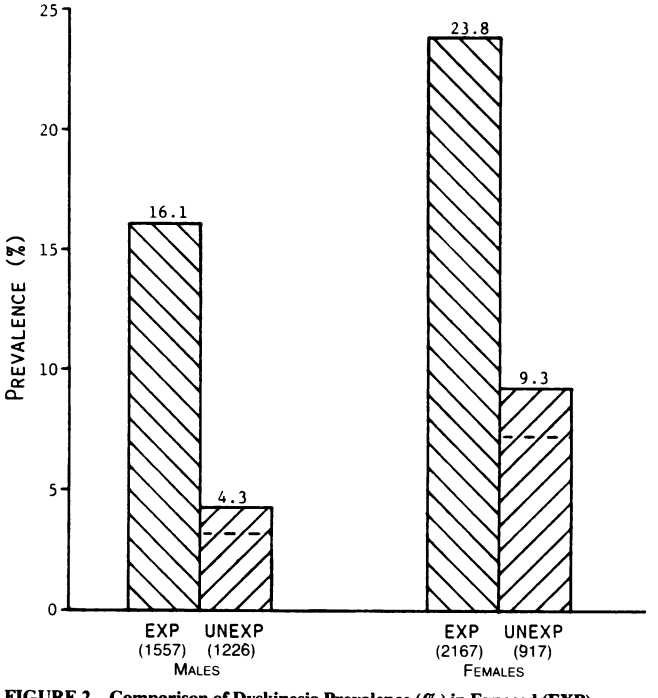

FIGURE 2—Comparison of Dyskinesia Prevalence (%) in Exposed (EXP) versus Unexposed (UNEXP) Subjects* in Nine Studies, by Sex (number of subjects)
***Sex-specific prevalences for unexposed subjects are standardized to the study-specific distributions of the corresponding exposed groups. Dotted lines indicate crude prevalences in the unexposed groups.**

(95% CI = 1.7, 2.7) for studies published later. This difference is reflected in the estimates of AFE (86 per cent vs 53 per cent) and AF (78 per cent vs 38 per cent). It appears, therefore, that the effect and impact of neuroleptic exposure has decreased during the past 20 years.

One possible explanation for this time trend is that it reflects our choice of the odds ratio as a measure of effect (i.e., the multiplicative scale) and results from the increasing rate of dyskinesia over time (analogous to the exposure-sex interaction effect). To address this hypothesis, we estimated the time trends in prevalence separately for subjects exposed and not exposed to neuroleptics, using weighted least-squares regression.[61] As shown in Figure 3, there were modest linear increases for both groups ($p < 0.01$). The average rate of increase in prevalence was 62 per cent larger for exposed subjects (1.5 per cent per year) than for unexposed subjects (0.9 per cent per year), although this difference may be due to chance ($p = 0.22$). Thus, the prevalence difference may have increased a little over time even though the odds ratio decreased during the same period. Since the rate of TD is likely to be related to the duration of neuroleptic exposure,[1–4,50] the difference in slopes in Figure 3 might be due to the likely increase in the average duration of neuroleptic exposure over the past two decades. Alternatively, the difference in slopes might be due to the increasing use of neuroleptics in high-risk groups (e.g., those with affective disorders or degenerative dementias).

The finding that both exposed and unexposed subjects show positive trends might indicate an increase in the prevalence of other risk factors for dyskinesia, such as the psychiatric disorders mentioned above. Alternatively, since the frequency estimates are based on prevalence (not incidence) data, the positive trends in both groups might indicate an increasing proportion of persistent or irreversible cases whose symptoms last relatively longer. This change in

TABLE 4—Estimated Effect and Impact of Neuroleptic Exposure on Dyskinesia,‡ by Year of Publication, Country, Type of Study Population (hospital inpatients vs other), Diagnostic Instrument (quantitative severity scale vs global assessment), and Diagnostic Method (blind vs not blind to neuroleptic exposure): Meta-analysis of 21 Prevalence Studies, 1966–85

Group	Sample Size	Effect		Impact			
		CÔR	SÔR*	AF̂E*	95% CI (AF̂E)	AF̂*	95% CI (AF̂)
Before 1970	4864	10.9	6.9†§	0.86	0.79, 0.90	0.78	0.70, 0.84
1970+	3896	2.4	2.1†§	0.53	0.40, 0.63	0.38	0.30, 0.48
United States	1290	6.7	3.6	0.72	0.52, 0.84	0.59	0.41, 0.74
Not US	7470	3.1	2.8†	0.64	0.55, 0.71	0.50	0.43, 0.57
Hospital	6687	5.3	2.9†	0.66	0.57, 0.73	0.58	0.49, 0.66
Other	2073	2.6	2.7†	0.64	0.45, 0.76	0.33	0.24, 0.43
Severity Scale	3371	2.4	2.6	0.62	0.49, 0.71	0.46	0.37, 0.56
Global Assessment	5389	5.6	3.2†	0.69	0.59, 0.77	0.58	0.50, 0.66
Blind Assessment	1552	2.1	2.4†	0.58	0.27, 0.76	0.39	0.23, 0.58
Not Blind	7208	3.8	3.0†	0.66	0.58, 0.73	0.53	0.46, 0.60
Total	8760	3.5	2.9†	0.65	0.57, 0.72	0.51	0.45, 0.58

*Estimates are standardized for "study", using the exposed group as the standard population. All estimates differ from their null values ($p < 0.001$).

†There is substantial heterogeneity of effect across studies ($p < 0.01$); for the two remaining groups, there is little heterogeneity ($p > 0.10$).

§The two estimated SORs differ substantially from each other ($p < 0.001$); for the other 4 group comparisons, the SORs are more similar ($p \geq 0.30$).

‡COR = crude odds ratio; SOR = internally standardized odds ratio; AFE = attributable fraction in the exposed population; AF = attributable fraction in the total population; CI = confidence intervals.

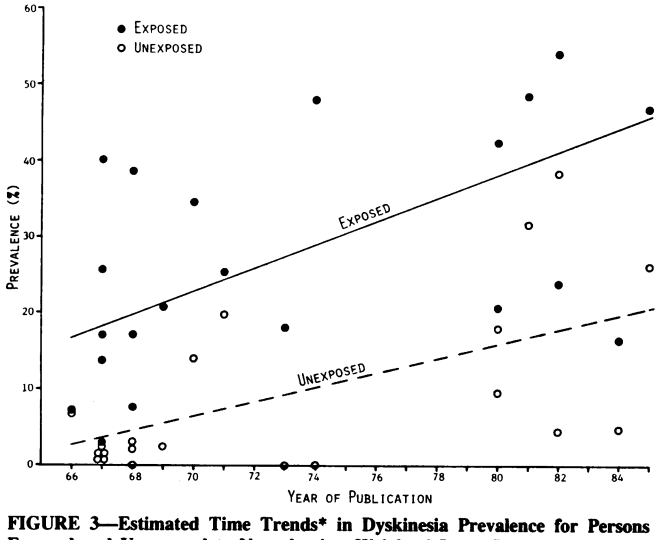

FIGURE 3—Estimated Time Trends* in Dyskinesia Prevalence for Persons Exposed and Unexposed to Neuroleptics: Weighted Least Squares Regression Analyses of 21 Prevalence Studies, 1966–85
***The estimated slopes (and standard errors) are 0.0153 (0.00317; $p < 0.001$; $R^2 = 0.462$) for exposed persons and 0.0094 (0.00293; $p = 0.005$; $R^2 = 0.352$) for unexposed persons. Thus the slope is 62% steeper in the exposed group than in the unexposed group ($p = 0.22$).**

chronicity might be due to the increasing frequency of certain prognostic factors, such as exposure to anticholinergic drugs.[62] It is unlikely, however, that the observed trends were due to an increasing sensitivity (or decreasing specificity) of diagnostic methods since our estimate of the slope for exposed subjects was nearly identical to the finding of Kane, *et al*,[2] who limited their trend analysis to studies employing similar and reliable diagnostic procedures and criteria.

Despite the marked decrease in the odds ratio between 1966 and 1985, this trend probably does not completely explain the heterogeneity of effect over our 21 studies. One reason for this inference is that there is substantial heterogeneity of effect within each period, 1966–69 and 1970–85 (Table 4). In addition, stratification on the other variables in Table 4 also affects the results. For example, the estimated effect and impact are less in studies involving quantitative severity scales for identifying cases and in studies involving diagnostic procedures that are blind to exposure status than in studies involving global assessment and nonblinded procedures. Since the former methods are probably more reliable and valid than the latter, our estimates of effect and impact summarized in Tables 2 and 3 may be exaggerated. Specifically, the "true" rate ratio, reflecting the effect of neuroleptic exposure, may be between 2.4 and 2.6, rather than 2.9. It is also likely that the resulting disease misclassification contributed to the inconsistency of results across all 21 studies. This possibility is supported by the observation of relatively less heterogeneity of effect in those studies involving severity scales (Table 4).

Another finding in Table 4 is the larger effect and impact of neuroleptic exposure in the United States than in other countries. This difference cannot be explained by previous results since all but one US study were done after 1970 and they tended to employ more accurate diagnostic procedures. Furthermore, this difference in effects is not due simply to our choice of the multiplicative scale, since both the standardized odds ratio and standardized prevalence difference are larger in the United States. It is possible, therefore, that the US study populations had a higher frequency of one or more factors that enhanced (modified) the effect of neuroleptic exposure on TD. For example, because US psychiatrists are said to diagnose many patients with affective disorders as schizophrenics, at least before 1978,[63] exposed groups in US studies may have included a higher proportion of patients with affective disorders than did exposed groups in other countries.

Finally, the estimated SOR and AFE are approximately the same for hospitalized inpatients and nonhospitalized individuals (Table 4). It should be noted, however, that the attributable fraction in the total population (AF) is substantially higher in hospitalized populations (58 per cent) than in nonhospitalized populations (33 per cent) because the frequency of neuroleptic exposure is much greater in the former.

TABLE 5—Estimated Impact of Neuroleptic Exposure on TD Prevalence among US Adult Residents (Ages > 17) in 1980, by Residence Status

	Mental Inpatients	Nursing Home	Not in an Institution	Total Population
No. Adults (Ages > 17) Living in US†	245,029	1,426,371	161,119,445	162,790,845
No. (%) Persons Exposed to Neuroleptics within the Past Year§	—	—	2,033,414 (1.26)	—
No. (%) Persons Chronically Exposed to Neuroleptics*	153,632 (62.7)	326,028 (22.9)	677,805 (0.42)	1,157,465 (0.71)
No. TD Cases (A) among Persons Chronically Exposed to Neuroleptics¶	38,408	81,507	169,451	289,366
No. TD Cases (A*) Attributable to Neuroleptic Exposure‡	25,580	54,284	112,854	192,718

†According to the 1980 US Census (references 63 and 64).

§According to a 1979 national survey of US adults (reference 65).

*Chronic exposure is daily exposure for at least 3 or 4 continuous months. The proportion of exposed (noninstitutionalized) outpatients who were chronically exposed was assumed to be 33% (reference 65).

¶The prevalence of TD is assumed to be 25% among chronic neuroleptic users in each residence population (references 1, 2, and 4).

‡The attributable fraction in the exposed population (AFE) is assumed to be 66.6% in each residence population, based on the results of the 4 US studies published after 1975 (references 32, 35, 37, and 38).

Estimation of Attributable Number and Attributable Risk

To estimate the number (A*) of adult TD cases attributable to the effect of neuroleptic treatment in the United States in 1980, we have combined results from four sources: our meta-analysis of 21 prevalence studies; other reviews of the TD literature;[1,2,4] the 1980 US Census;[64,65] and a 1979 national survey of psychotropic drug use.[66] Our calculations are summarized in Table 5 by type of residence: psychiatric hospitals, nursing homes, and other living quarters (noninstitutions).

According to the 1979 survey,[66] 1.0 per cent of noninstitutionalized adult men between the ages of 18 and 79 and 1.5 per cent of noninstitutionalized adult women used neuroleptic medications within the past year. Among neuroleptic users, about one-third received their medications on a daily basis for at least four months. We have assumed that this group of "chronic" users represents the exposed population at risk of TD.[9–11] The comparable rates of chronic exposure in institutionalized populations were estimated from our data to be 63 per cent in mental patients and 23 per cent in nursing home residents; both estimates are consistent with the results of other restricted surveys of similar populations.[67–70] The prevalence of TD in 1980 among exposed adults in each residence population was assumed to be 25 per cent, according to consistent estimates from three composite analyses[1,2,4] (see also Table 2). To derive the attributable number, we multiplied the number of TD cases in each group by our estimate of the AFE (66.6 per cent), which is based on the four US studies published after 1975.[32,35,37,38] From these calculations, we estimate that there were about 193,000 neuroleptic-induced cases of TD among US adults in 1980, of which about 60 per cent occurred in noninstitutionalized patients. These estimates are probably a little conservative since they ignore persistent cases, especially among inpatients, in whom neuroleptic drugs had previously been discontinued.

The *attributable risk* (or risk difference) is equal to the attributable number (A*) divided by the total number of exposed persons at risk in the source population.[71] Using the results in Table 5 for US adults in 1980, we estimate the attributable risk to be 192,178/1,157,465, which is equal to about 17 per cent. That is, for every 100 persons initially exposed to neuroleptics and maintained on the drug for at least three months, we would expect to observe 17 cases of TD which would not have occurred in the absence of the exposure. We must emphasize, however, that since this finding is based on prevalence data, it may reflect the course of the disorder as well as its development. Furthermore, the attributable risk probably varies with the duration of exposure because the cumulative incidence of TD increases with increasing duration of exposure.[3] Yet we do not have valid and consistent estimates of this dependency since it is not clear how the incidence rate (incidence density) of TD varies with duration of exposure, especially after several years,[72–76] and since the effect of exposure duration is probably confounded with the effect of age at first exposure.[76] If we were able to estimate the attributable risk by age and duration of exposure (and other relevant factors), physicians and clinical administrators could use these estimates to make informed decisions about weighing the risks, benefits, and costs of: 1) maintenance neuroleptic therapy; 2) various tests (e.g., CT scans) for making differential diagnoses; and 3) alternative institutional policies for TD screening.

Discussion

Perhaps the greatest limitation of the studies included in this analysis is that they are all cross-sectional.[19,77] Thus, we cannot determine from the data alone to what extent neuroleptic exposure increased the risk of TD or affected the course of the disease among cases. Since all studies involved clinical populations, it is also possible that certain results were biased by different utilization rates for cases and noncases (i.e., Berkson's bias). In addition, observed cases of dyskinesia were selected from studies conducted in six countries and, therefore, may not be representative of all

cases in any target population, making generalizations somewhat difficult. Although there do seem to have been differences in effect among countries, such differences are difficult to separate from the temporal trend described above. Furthermore, it is possible that the likelihood of negative results being published changed over time as dyskinesia and its possible relationship with neuroleptic exposure became more recognized and controversial.

Another potential source of bias is the possible misclassification of case status. Although we have controlled analytically for diagnostic differences among studies (by standardizing for "study"), misclassification bias might still have occurred within studies. There are two reasons to support this contention. First, there is clinical evidence suggesting that high doses of neuroleptic medication can mask the symptoms of TD, which later appear when the dose is reduced or the medication is discontinued.[5,9,10] The influence of this masking phenomenon would be to reduce the estimated effect in a prevalence study. Of course, it is quite possible that the degree of masking varied among the 21 studies. The second basis for misclassification bias is that methods of rating dyskinetic symptoms may not have been very accurate in certain studies. This possibility is very difficult to rule out, since most of the authors did not demonstrate the reliability or validity of their diagnostic methods. As we have already pointed out, those studies involving better diagnostic methods (i.e., quantitative severity scales and blind assessment) provided somewhat smaller estimates of neuroleptic effect and impact, partially accounting for the heterogeneity observed among studies (Table 4).

Misclassification bias might also have resulted from the collection of exposure data. Although determination of current neuroleptic exposure is quite straightforward in clinical settings where patients receive their medications, use of medical records to determine previous exposure is certainly prone to error. Most likely, there would be a tendency to misclassify some previous users as never exposed, especially among noncases, which would result in an overestimate of the true effect. If, on the other hand, exposure misclassification was the same for cases and noncases, the effect would have been underestimated.[19] Another source of exposure misclassification, especially with outpatients, is noncompliance with prescribed medications. Yet we do not think that noncompliance was a major source of bias in our analyses because the estimated exposure effect was about the same in hospitalized and nonhospitalized populations (Table 4).

Finally, in any observational study, there is always the possibility of confounding by unmeasured and, perhaps, unknown risk factors for the disease. Although we found no evidence for confounding by age and sex, neither the original investigators nor we were able to control for differences in psychopathology and the use of other drugs, both of which may affect the risk of dyskinesia.[1-4,13] Given the relative lack of knowledge of the etiology and course of both tardive and spontaneous dyskinesias, it is important to conduct additional follow-up studies of these disorders to identify other risk and prognostic fctors.

In summary, our meta-analysis of 21 published prevalence studies has found that long-term exposure to neuroleptics is consistently related to the presence of dyskinetic movements. Also observed, however, was substantial heterogeneity of effect and impact across studies. We believe that this heterogeneity was largely due to three phenomena: 1) changes and differences between populations in the rate of both tardive and spontaneous dyskinesias; 2) differences in the frequency of certain modifiers of the neuroleptic effect; and 3) differences in diagnostic methods.

Despite several methodologic limitations with the available studies covered in this report, we believe that our statistical approach of impact estimation may play an important role in bridging the gap between epidemiologic research and decision-making activities, such as clinical practice, health planning, policy making, and litigation. We hope that similar meta-analytic approaches will be applied in the future to better data sets collected from well-designed prospective studies of dyskinesia and other diseases.

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