Gender Differences in Tardive Dyskinesia: A Critical Review of the Literature

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Abstract

We analyzed data from 76 selected studies on prevalence of tardive dyskinesia (TD), published through 1989. The primary focus was on gender differences. The overall prevalence of TD in the 39,187 patients included in these reports was 24.2 percent, and prevalence was significantly higher in women (26.6%) than in men (21.6%). The gender difference in TD prevalence appeared to narrow intriguingly in more recent studies. Overall, the TD prevalence seemed to reach its peak in the 50–70-year-old age group in men and continued to rise after age 70 in women. Also, women tended to have more severe TD than men. Spontaneous dyskinesia too was found to be more common in women. The material was also analyzed for cultural differences by comparing studies in four continents: North America, Europe, Africa, and Asia. Although grouping together studies from different countries in a continent into a single group is somewhat problematic, we found that Asian patients had lower prevalence of TD than North American, European, and African patients. Limitations of our review (including differences among studies in diagnostic criteria, observer bias, etc.) as well as possible explanations for the reported differences in the risk for TD are discussed.

Tardive dyskinesia (TD) is characterized by late onset of involuntary, purposeless movements in neuroleptic-treated patients (Casey and Keepers 1988). Although buccooral movements dominate the picture, other parts of the body may also be involved.

Since the syndrome was introduced into the literature more than 30 years ago, older age has been the only consistent risk factor confirmed by most of the authors (Smith and Baldessarini 1980). Several other factors have been considered as predisposing to the development of TD, including mood disorder (Yassa et al. 1984), "organicity" (Wolf et al. 1982), type of neuroleptic prescribed (Cole et al. 1986), age at first neuroleptic treatment (Jeste et al. 1982*a*), amount of neuroleptic used (Casey and Keepers 1988), number of lengthy drug-free periods (Jeste et al. 1979; Yassa et al. 1986), and development of early extrapyramidal side effects (Casey and Keepers 1988), but the status of these variables as risk factors for TD is still not fully established (Lam et al. 1988).

Gender has also been advocated by some authors as an important factor in the development of TD. Some authors concluded that women had a higher prevalence of TD than men, whereas others found no gender difference in TD prevalence (Jeste and Wyatt 1981). Seeman (1983) related the increased frequency of TD among postmenopausal women to hormonal changes and suggested an interaction among gender, age, and neuroleptic effects.

The aim of our literature review was to critically examine the association between gender and TD in terms of prevalence, severity, and manifestations, with special attention to confounding variables such as age, ethnicity, spontaneous dyskinesia, and neuroleptic treatment.

Material and Method

We reviewed all the available prevalence studies on TD published through 1989. The studies were retrieved

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through a Medline search as well as through references cited in major review articles (Smith and Baldessarini 1980; Jeste and Wyatt 1981; Kane and Smith 1982; Simpson et al. 1986; Barnes 1987; Waddington 1987; Casey and Keepers 1988; Driesens 1988; Villeneuve and Lajeunesse 1988; Yassa 1988; Lajeunesse and Villeneuve 1989) and books (Baldessarini 1979; Jeste and Wyatt 1982; Shah and Donald 1986; Tanner 1986; Lohr and Wisniewski 1987). Only articles published in English and French (or in other languages, if there was a detailed summary of the study given in English or French) were reviewed.

We found a total of 94 prevalence studies published in the two languages through August 1989. To be included in this survey, a study had to do the following:

1. Report on 50 patients or more. This criterion excluded one study in which the total number of patients assessed was 39 (Crane and Smeets 1974).
2. Include both genders in its sample. This criterion excluded five studies that examined only women (Uhrbrand and Faurbye 1960; Pryce and Edwards 1966; Edwards 1970) or men (Dynes 1970; Goldberg et al. 1982).
3. Indicate the number of men and women affected by TD or at least allow the number to be computed from figures or tables. This criterion excluded 12 studies (Hunter et al. 1964; Paulson 1968; Yagi et al. 1976; Bell and Smith 1978; Alexopoulos 1979; Gardos et al. 1980; Cunningham-Owens et al. 1982; McCreadie et al. 1982; Holden et al. 1984; Lieberman et al. 1984; Kane et al. 1985; Waddington and Youssef 1986).

For the final analysis, a total of 76 prevalence studies comprising 39,187 patients were reviewed (table 1). The sample sizes ranged from 50 (Famujiwa et al. 1979) to 3,319 patients (Simpson et al. 1978) with a mean of 530 patients per study.

Study Characteristics. The survey covered studies from many continents, including Canada, China, Eastern European countries, France, Germany, India, Italy, Japan, Morocco, Scandinavian countries, South Africa, United Kingdom, and the United States.

Forty-six of the studies were conducted in an inpatient setting of a psychiatric hospital, 12 studies took place in an outpatient setting of a psychiatric hospital, and 11 studies were conducted in a psychiatric department of a general hospital. One study was done in a private hospital, and one multicenter investigation involved various countries. In five reports, it was difficult to determine the nature of the center where the work had been done.

Most of the earlier studies used no rating scales to measure TD (Hunter et al. 1964; Demars 1966; Dincmen 1966; Crane and Paulson 1967; Degkwitz and Wenzel 1967; Siede and Muller 1967; Turunen and Achté 1967; Heinrich et al. 1968). Later studies employed a scale, mainly the Abnormal Involuntary Movement Scale (AIMS; Guy 1976), or the Rockland TD Scale (Simpson et al. 1979).

Of the total number of studies reviewed, only 20 indicated the mean ages of both men and women (Demars 1966; Jones and Hunter 1969; Lehmann et al. 1970; Kennedy et al. 1971; Jus et al. 1976; Asnis et al. 1977; Simpson et al. 1978; Smith et al. 1978; Chouinard et al. 1979, 1986; Smith et al. 1979; Perenyi and Arato 1980; Rey et al. 1981; Ananth and Yassa 1982; Mukherjee et al. 1982; Yesavage et al. 1982; Yassa et al. 1983, 1988; Rittmannsberger and Schony 1986; Holden 1987). In nine studies (Crane 1970; Lehmann et al. 1970; Ogita 1972; Famujiwa et al. 1979; Ezrin-Waters et al. 1981; Brainin et al. 1983; Branchey and Branchey 1984; Richardson et al. 1984; Kok and Christopher 1985) there were no patients older than 65 years, while in two studies (Siede and Muller 1967; Ramsay and Millard 1986) only geriatric patients were included. Although most studies dealt with patients diagnosed as suffering from schizophrenia, three studies dealt only with mentally retarded patients (Richardson et al. 1986; Youssef and Waddington 1988; Stone et al. 1989).

Wherever there was sufficient documentation, we included only those cases in which the diagnosis of TD appeared to be reliable. An odds ratio (OR) of the relative risk of TD in men to that in women along with a 95 percent confidence interval (CI_{95}) was calculated for each study.

Results

The prevalence of TD was estimated at 24.2 percent (range 3.3% to 62%). In men, the prevalence of TD was estimated at 21.6 percent (range 0% to 53.5%) and in women, 26.6 percent (range 3.2% to 73.8%).

Table 1 summarizes the results of individual studies in terms of proportion of men to women (M:W) with TD as well as the ORs. Combining results from all studies, the mean OR was found to be 1.34 (CI_{95} = 1.3–1.4). Eighteen of the 76 studies found significantly higher W:M relative risk for TD ($p < 0.05$; lower boundary of 95% CI > 1.0). Only two studies (Perenyi and Arato 1980; Moussaoui et al. 1988) found significantly higher M:W relative risk ($p < 0.05$; upper boundary of 95% CI < 1.0). Note that the ORs for two studies (Hunter et al. 1964; Fanget et al.

Table 1. Prevalence studies and gender differences

Study	Total *n*	Overall prevalence of TD (%)	Men total *n*	Men with TD (%)	Women total *n*	Women with TD (%)	*p*[1]	Odds ratio	95% CI
Hunter et al. (1964)	450	3.3	200	0	250	5.2	<0.005	10.92[2]	1.4–84.2
Demars (1966)	371	7.0	166	4.8	205	8.8	NS	1.90	0.8–4.5
Dincmen (1966)	1,700	3.4	850	1.6	850	5.2	<0.001	3.26	1.8–6.0
Crane & Paulson (1967)	182	14.8	66	15.2	116	14.7	NS	0.96	0.4–2.2
Degkwitz &	766	17.0	303	10.9	463	21.0	<0.001	2.17	1.4–3.3
Wenzel (1967)	499	22.8	193	20.7	306	24.2	NS	1.22	0.8–1.9
Siede & Muller (1967)	404	11.4	109	7.0	295	13.0	NS	1.87	0.8–4.1
Turunen & Achté (1967)	480	5.4	207	3.4	273	7.3	NS	2.14	0.9–5.2
Crane (1968)	379	27.4	207	31.0	172	23.3	NS	0.68	0.4–1.1
Heinrich et al. (1968)	554	17.0	228	12.3	326	20.2	<0.025	1.81	1.1–2.9
Jones & Hunter (1969)	82	30.5	13	7.7	69	34.8	<0.05	6.40	0.8–52.2
Villeneuve et al. (1969)	3,280	2.1	1,929	1.3	1,351	3.2	<0.001	2.50	1.5–4.1
Crane (1970)	127	26.8	62	27.4	65	26.1	NS	0.94	0.4–2.1
Hipplus & Lange (1970)	531	34.4	244	34.4	287	34.1	NS	0.99	0.7–1.4
Lehmann et al. (1970)	350	6.6	168	4.2	182	8.8	NS	2.22	0.9–5.5
Brandon et al. (1971)	625	25.1	264	17.0	361	31.0	<0.001	2.19	1.5–3.2
Kennedy et al. (1971)	63	62.0	32	53.0	31	71.0	NS	2.16	0.8–6.1
Fann et al. (1972)	193	34.7	138	31.1	55	43.6	NS	1.71	0.9–3.3
Ogita (1972)	454	17.9	70	17.1	53	18.9	NS	1.12	0.4–2.8
Lehmann & Ban (1974)	123	6.8	199	5.5	255	7.8	NS	1.45	0.7–3.1
Bourgeois et al. (1976)	1,660	7.2	737	4.9	923	9.1	<0.001	1.95	1.3–2.9
Jus et al. (1976)	332	56.0	142	53.5	190	58.0	NS	1.19	0.8–1.9
Asnis et al. (1977)	69	43.4	16	31.0	53	47.0	NS	1.96	0.6–6.4
Simpson et al. (1978)	3,319	11.0	1,577	7.5	1,742	13.8	<0.001	1.97	1.6–2.5
Smith et al. (1978)	293	45.7	150	39.0	143	52.4	<0.025	1.70	1.1–2.7
Chouinard et al. (1979)	261	31.0	138	29.0	123	32.5	NS	1.18	0.7–2.0
Famujiwa et al. (1979)	50	34.0	26	26.9	24	41.7	NS	1.94	0.6–6.4
Jeste et al. (1979)	88	23.9	27	22.2	61	24.6	NS	1.14	0.4–3.4
Perris et al. (1979)	347	17.0	213	9.4	134	29.8	<0.001	4.11	2.3–7.4
Perenyi & Arato (1980)	200	23.5	100	31.0	100	16.0	<0.02	0.42[2]	0.2–0.8
Wojcik et al. (1980)	208	18.0	92	16.0	116	19.0	NS	1.20	0.6–2.5
Ezrin-Waters et al. (1981)	94	43.6	58	39.6	36	50.0	NS	1.52	0.7–3.5

Table 1. Prevalence studies and gender differences—*Continued*

Study	Total *n*	Overall prevalence of TD (%)	Men total *n*	Men with TD (%)	Women total *n*	Women with TD (%)	p^1	Odds ratio	95% CI
Jeste & Wyatt (1981)	95	31.6	25	24.0	70	34.3	NS	1.65	0.6–4.7
Rey et al. (1981)	66	43.9	39	39.0	27	52.0	NS	1.72	0.6–4.7
Ananth & Yassa (1982)	223	20.6	116	16.3	107	25.2	NS	1.72	0.9–3.3
Doongaji et al. (1982)	1,801	9.6	1,141	9.5	660	9.8	NS	1.04	0.8–1.4
Kane et al. (1982*b*)	328	15.8	193	13.5	135	19.2	NS	1.53	0.8–2.8
Mukherjee et al. (1982)	153	30.7	41	34.1	112	29.1	NS	0.81	0.4–1.7
Yesavage et al. (1982)	3,140	8.2	1,568	5.8	1,572	10.6	<0.001	1.93	1.5–2.5
Brainin et al. (1983)	335	14.6	132	15.0	203	14.3	NS	0.93	0.5–1.7
Yassa et al. (1983)	180	27.0	83	22.0	97	32.0	NS	1.70	0.9–3.3
Branchey & Branchey (1984)	57	24.6	43	25.6	14	21.4	NS	0.79	0.2–3.4
Itoh et al. (1984)	2,274	19.0	969	19.6	1,305	18.8	NS	0.95	0.8–1.2
Kane et al. (1984)	554	12.4	288	12.8	266	12.0	NS	0.93	0.6–1.5
Kulhanek et al. (1984)	861	15.0	398	14.8	463	15.3	NS	1.04	0.7–1.5
Richardson et al. (1984)	167	61.7	87	50.6	80	73.8	<0.005	2.75	1.4–5.3
Yassa et al. (1984)	108	7.4	55	5.5	53	9.4	NS	1.81	0.4–8.0
Fleischhauer et al. (1985)	608	31.6	255	29.8	353	32.9	NS	1.15	0.8–1.6
Guy et al. (1985)	768	11.0	430	11.0	338	11.0	NS	1.00	0.6–1.6
Kok & Christopher (1985)	211	9.9	100	7.0	111	12.6	NS	1.92	0.7–5.0
Waddington & Youssef (1985)	68	41.0	22	36.4	46	43.4	NS	1.35	0.5–3.8
Chouinard et al. (1986)	224	45.0	113	45.0	111	44.0	NS	0.96	0.6–1.6
Fanget et al. (1986)	52	4.0	22	0	30	6.7	NS	1.50[2]	0.1–17.7
Kolakowska et al. (1986)	91	25.0	59	27.0	32	22.0	NS	0.75	0.3–2.1
Ramsay & Millard (1986)	426	11.5	92	7.6	334	12.6	NS	1.75	0.8–4.0
Richardson et al. (1986)	211	30.0	139	23.0	72	43.0	<0.005	2.53	1.4–4.7
Rittmannsberger & Schony (1986)	76	25.0	46	19.6	30	33.3	NS	2.06	0.7–5.9
Williams & Dalby (1986)	196	34.2	106	34.0	90	34.4	NS	1.02	0.6–1.8
Yassa et al. (1986)	76	25.0	32	22.0	44	40.9	NS	2.47	0.9–6.9
Binder et al. (1987)	126	35.0	66	41.0	60	28.3	NS	0.57	0.3–1.2
Gurge (1987)	70	37.0	54	39.0	16	31.0	NS	0.94	0.3–3.0
Holden (1987)	100	39.0	50	26.0	50	52.0	<0.01	3.08	1.3–7.1

Table 1. Prevalence studies and gender differences—*Continued*

Study	Total *n*	Overall prevalence of TD (%)	Men total *n*	Men with TD (%)	Women total *n*	Women with TD (%)	p^1	Odds ratio	95% CI
Morgenstern et al. (1987)	180	33.0	89	37.0	91	30.0	NS	0.72	0.4–1.3
Ahrens et al. (1988)	385	19.7	256	17.0	129	26.0	<0.05	1.66	1.0–2.8
Delance (1988)	262	39.0	126	37.3	136	40.7	NS	1.14	0.7–1.9
Moussaoui et al. (1988)[2]	400	12.5	130	16.3	270	10.8	NS	0.62[2]	0.3–1.1
Moussaoui et al. (1988)	1,070	12.1	272	16.7	798	10.7	<0.05	0.60	0.4–0.9
Yassa & Nair (1988)	315	32.4	150	26.0	165	38.1	<0.025	1.76	1.1–2.8
Yassa et al. (1988)	135	45.0	58	45.5	77	44.8	NS	0.97	0.5–1.9
Youssef & Waddington (1988)	77	19.5	51	19.6	26	19.2	NS	0.98	0.3–3.2
Arisco & Holden (1989)	90	5.5	50	2.0	40	10.0	NS	5.44	0.6–50.8
Gurge (1989)	137	27.0	101	27.7	36	25.0	NS	0.87	0.4–2.1
Ko et al. (1989)	866	8.4	641	10.0	225	6.6	NS	0.65	0.4–1.2
Muscettola et al. (1989)	1,651	19.0	991	15.7	660	24.2	<0.001	1.73	1.3–2.2
Stone et al. (1989)	1,227	48.0	638	45.0	589	52.0	<0.05	1.33	1.1–1.7
Total	39,187	24.2	19,337	21.6	19,850	26.6		1.34	1.3–1.4

Note.—TD = tardive dyskinesia; CI = confidence interval; NS = not significant.

[1]χ^2 test. For four studies with relatively small sample sizes (Jones and Hunter 1969, Yassa et al. 1984, Fanget et al. 1988, and Arisco and Holden 1989), Fisher's exact test was used.

[2]Significantly lower odds ratio.

1986) are somewhat arbitrary because 1 replaced 0 for calculation purposes.

On analyzing the prevalence of TD during the past three decades (1960–69, 1970–79, and 1980–89), we found that the mean TD prevalence during the 1960s was 13.5 percent, during the 1970s 28.6 percent, and during the 1980s 25.1 percent. Analyzing the difference between men and women in TD prevalence, we found that during the 1960s it was estimated at 9.6 percent in men and 15.6 percent in women (M:W = 1:1.6) versus 25.0 percent in men and 33.1 percent in women (M:W = 1:1.3) during the 1970s. During the 1980s, the figures were 23.5 percent for men and 27.1 percent for women (M:W = 1:1.2). Of the 12 studies during the 1960s, 6 (50%) reported that TD was significantly more common in women than in men, versus 5 of the 18 studies (27.7%) during the 1970s and 9 of the 46 studies (19.6%) during the 1980s.

TD and Cultural Differences. We divided the studies reviewed into those performed in North America (Canada and the United States: 36 studies with a total of 15,150 patients); Europe (Austria, England, Finland, France, Germany, Hungary, Ireland, Italy, and Sweden: 27 studies comprising 16,025 patients); Asia (China, India, Japan, and Singapore: 6 studies with a total of 5,401 patients); and Africa and the Middle East (South Africa, Morocco, and Nigeria: 5 studies including 1,777 patients) (table 2). Two studies, one international (Guy et al. 1985) and one from Australia (Rey et al. 1981), were not included because they did not belong to any of the four continent groupings described above.

The overall mean prevalence of TD in the North American studies was 27.6 percent (men 24.9%, women 30.6%, M:W = 1:1.3); for the European studies, the mean prevalence was 21.5 percent (men 17.9%, women 24.2%, M:W = 1:1.35); for the Asian studies, it was 16.6 percent (men 17.3%, women 15.8%, M:W = 1.1:1); and for the African and Middle Eastern studies, the overall mean prevalence of TD was 25.5 percent (men 15.1%, women 25.9%, M:W = 1:1). When we divided the studies of

Table 2. Prevalence of tardive dyskinesia in different continents

	North American n = 15,150 (36 studies)	Europe n = 16,025 (27 studies)	Asia n = 5,401 (6 studies)	Africa n = 1,777 (5 studies)
Prevalence (%)	27.6	21.5	16.6	25.5
Men (%)	24.9	17.9	17.3	25.1
Women (%)	30.6	24.2	15.8	25.9
M:W[1]	1:1.3	1:1.35	1.1:1	1:1

[1]Proportion of men to women.

TD into 10-year spans, we found published reports spanning the three decades only for the North American and European Continents. Comparing the studies from these two continents, we found that the mean prevalence of TD in the North American studies during the 1960s was 11.8 percent (men 11.2%, women 11.9%, M:W = 1:1.1) versus 14.7 percent (men 8.5%, women 17.3%, M:W = 1:2.0) in the European studies. During the 1970–79 period, the North American studies had a mean TD prevalence of 29.7 percent (men 26.1%, women 32.7%, M:W = 1:1.25) versus 29.9 percent (men 24.3%, women 36.1%, M:W = 1:1.48) in the European studies. On the other hand, during the 1980–89 period, the North American studies had a higher mean prevalence of 29.1 percent (26.5% for men, 32.8% for women, M:W = 1:1.2) versus the European prevalence of 21.3 percent (men 20%, women 22.4%, M:W = 1:1.1).

Age and Gender Interaction. As indicated previously, only 20 studies presented mean ages for both men and women. In general, the mean ages of women were greater than those of men in all the studies, usually by 5 to 10 years. In these studies, severe TD was not significantly different between the two genders (Jones and Hunter 1969; Kennedy et al. 1971; Simpson et al. 1978; Smith et al. 1978; Perenyi and Arato 1980; Yesavage et al. 1982; Holden 1987; Yassa and Nair 1988).

In an incidence study, Kane and colleagues (1986) found that the hazard rate for TD was slightly (but not significantly) higher for women than for men ($\chi^2 = 2.20$, $p = 0.14$) and that the interaction of gender by age was not significant.

We found six studies (Degkwitz and Wenzel 1967; Villeneuve et al. 1969; Brandon et al. 1971; Smith et al. 1978, 1979; Yassa et al. 1988) that presented the prevalence of TD according to age groups and gender. TD increased with age (see table 3) in women, but not in men. TD was significantly more prevalent in women than in men in the age groups 51–70 and over 70, but it was equally distributed between the genders in lower age groups. This increase in prevalence was particularly apparent in the over-70 age group.

Gender and TD Severity. TD severity and its assessment are controversial issues that have not been adequately addressed. At present, severe TD is classified arbitrarily according to the authors' experience (Degkwitz and Wenzel 1967; Villeneuve et al. 1969; Brandon et al. 1971; Bourgeois et al. 1976), or according to an item in a scale, such as an AIMS rating of 4 (severe) (Smith et al. 1978, 1979; Perenyi and Arato 1980; Richardson et al. 1984; Yassa et al. 1990), or according to the patient's incapacitation from TD (Gardos et al. 1987). Of the nine studies we found (covering 7,964 patients) that discussed severe TD (Degkwitz and Wenzel 1967; Villeneuve et al. 1969; Brandon et al. 1971; Simpson et al. 1978; Smith et al. 1978; Chouinard et al. 1979; Perenyi and Arato 1980; Yesavage et al. 1982; Richardson et al. 1984), two did not differentiate between moderate and severe forms (Perenyi and Arato 1980; Richardson et al. 1984).

The mean reported prevalence of severe TD in the nine investigations was 2.2 percent (1.3% in men, 3.1% in women, $\chi^2 = 31$; $df = 1$; $p < 0.001$). In six studies, women had more severe TD than men (Degkwitz and Wenzel 1967; Brandon et al. 1971; Simpson et al. 1978; Smith et al. 1978; Yesavage et al. 1982; Richardson et al. 1984), whereas in three studies the genders were equally affected (Villeneuve et al. 1969; Chouinard et al. 1979; Perenyi and Arato 1980).

TD Manifestations in Men Versus Women. Only a few studies compared TD manifestations in men and women. Two studies found that men had more faciobuccooral manifestations (Perris et al. 1979; Binder et al. 1987), while women had more generalized movements (Perris et al. 1979). Fleischhauer and colleagues (1985) found that women had more perioral, head, abdominal, trunk, hand, and knee movements than men, but move-

Table 3. Studies comparing age and gender prevalence

	Patients ≤ 50 years old				Patients 51-70 years old				Patients > 70 years old			
Study	Men *n*	% Men with TD	Women *n*	% Women with TD	Men *n*	% Men with TD	Women *n*	% Women with TD	Men *n*	% Men with TD	Women *n*	% Women with TD
Degkwitz and Wenzel (1967)	216	6.9	187	7.0	79	20.2	231	29.9	8	25.0	45	33.3
Villeneuve et al. (1969)	137	8.8	65	1.5	136	8.1	133	17.3	85	2.0	68	27.9
Brandon et al. (1971)	124	4.0	86	15.1	158	27.2	120	50.0	79	22.8	130	57.7
Smith et al. (1978, 1979)	90	26.7	61	19.7	90	48.9	131	54.2	66	39.4	68	66.2
Yassa et al. (1988)	60	6.7	37	10.8	62	41.9	60	30.0	28	32.1	68	60.3
Total	627	10.6	436	10.8	525	29.3[1]	675	36.3[1]	266	24.3[2]	379	49.1[2]

Note.—TD = tardive dyskinesia.

[1]$\chi^2 = 10.7, p < 0.001$.
[2]$\chi^2 = 58.8, p < 0.001$.

ments of the eye, neck, shoulder, and elbow did not differ. Also, Smith and colleagues (1979), using multiple regression, found that women had more lip movement than men. However, Ezrin-Waters and colleagues (1981) found that men had more affliction of the total body in the over-40 population than women did. Thus, there is no consensus regarding gender differences in TD manifestations.

The Prevalence of Spontaneous Dyskinesia (SD). Only five studies (Brandon et al. 1971; Delwaide and Desseilles 1977; Klawans and Barr 1982; Kane et al. 1982*a*; Yassa 1988) dealt with gender difference in SD (table 4). The mean prevalence of SD in these five studies was 14.5 percent (range 4%-36%). Of the men, 30 of 427 (7%) had SD versus 125 of 639 (19%) in women (M:W = 1:2.7). There were no significant age differences between the genders in these studies.

Followup Studies. A number of followup studies have now been published (Seeman 1981; Smith et al. 1981; Barnes et al. 1983; Casey and Toeniessen 1983; Gardos et al. 1983, 1985, 1988; Kane et al. 1984; Yassa et al. 1984; Casey et al. 1986; Robinson and McCreadie 1986; Bergen et al. 1989; Fornazzari et al. 1989). Of these, only three indicated any gender differences in the outcome of TD. Seeman (1981) discontinued medication and evaluated her patients over a 2-year period. Fornazzari and colleagues (1989) followed the same patients over a 5-year period without changing the treatment. Yassa and colleagues (1984) followed their patients over a 2-year period. Of the 65 men who were reported in these three studies, 32 (49.2%) showed no change versus 43 of 73 women (58.9%). On the other hand, 20 of 65 men were reported improved (30.8%) versus 21 of 73 women (28.8%). Of the patients whose TD got worse, 13 (20%) were men and 9 were women (12.3%). There was no difference in mean age between men and women in these three studies.

Discussion

An obvious limitation of a literature review is that the studies reviewed vary in what detailed information they give. Also, there are likely to be differences among studies in terms of diagnostic criteria, use of rating scales, observer bias, and so on. Use of very strict criteria for including studies in this meta-analysis would have resulted in excluding many of the studies. On the other hand, including all the published studies in this field would have led to mixing findings from some unsatisfactory investigations. We chose a middle path and relied on certain minimum criteria for including studies in this overview. We also selected only appropriate studies for subanalyses, such as those on age

Table 4. Prevalence of spontaneous dyskinesia (SD)

	Total population		Men		Women	
Study	*n*	% SD	*n*	% SD	*n*	% SD
Brandon et al. (1971)	152	19.1	81	11.1	71	28.2
Delwaide & Desseilles (1977)	240	35.8	64	15.6	176	43.8
Klawans & Barr (1982)	423	6.8	176	4.5	247	8.5
Kane (1982*a*)	127	3.9	53	0	74	6.8
Yassa et al. (1988)	124	4.0	53	5.7	71	2.8
Total	1,066	13.9	427	7.4	639	18.0

or severity of TD. It is conceivable that dropping some studies may have skewed the overall data set; this alternative is better, however, than including methodologically faulty studies.

Our review of the prevalence of TD indicates that TD was reportedly present in an estimated 24.2 percent of the neuroleptic-treated population studied, covering nearly 40,000 patients. The prevalence of TD apparently increased from 13.5 percent during the 1960s to 28.6 percent during the 1970s and stabilized at 25.0 percent during the 1980s. One possible explanation for this phenomenon may be that a number of studies carried out during the 1960s did not use scales to measure TD, and some included only patients with buccooral movements, thus missing some cases that may today be diagnosed as exhibiting TD. Other changes that have occurred in the past three decades, such as improvements in study designs, narrowing of the concept of schizophrenia, and increased awareness of TD, may also have contributed to the observed differences in TD prevalence. Nonetheless, we believe it is notable that the reported mean prevalence of TD did not change appreciably from the 1970s to the 1980s. The limitation in combining data from investigations done at different times must, of course, be taken into account.

We found that the mean W:M OR of TD was 1.34 (CI_{95} = 1.3–1.4). The W:M OR was significantly higher in 15 of the studies reviewed, while only two studies (Perenyi and Arato 1980; Moussaoui et al. 1988) found a significantly higher M:W OR. When studies are divided by decade (1960–69, 1970–79, 1980–89), the M:W ratio seemed to narrow in the latter decades (from 1:1.6 during the 1960s to 1:1.2 during the 1980s), although many studies found that the women assessed were older than the men. Although there is no clear explanation for this finding, it is conceivable that the narrowing of the concept of schizophrenia in the *DSM-III* (American Psychiatric Association 1980) might have had differential effects on men and women. Thus, perhaps more women (than men) with an affective disorder (which is a risk factor for TD) who would have been diagnosed as suffering from schizophrenia in the previous decades are no longer receiving a diagnosis of schizophrenia and are not being treated with neuroleptics.

We also found that TD was not as prevalent among Asians (17%) as among patients in North America (28%), Europe (22%), or the Middle East (26%). Several possible reasons for this discrepancy between Asian and North American studies may be considered. Of the six Asian studies reviewed (Ogita 1972; Doongaji et al. 1982; Itoh et al. 1984; Kok and Christopher 1985; Binder et al. 1987; Ko et al. 1989), only one was based on outpatient populations (Kok and Christopher 1985). The same study used more stringent diagnostic criteria for minimum TD severity. Outpatient populations have been reported to have less TD than inpatients, at least in Singapore, from which the Kok and Christopher population was drawn (Tan and Tay 1991). Tan and Tay found that psychogeriatric inpatients in Singapore had a TD prevalence of 31.5 percent versus 10.5 percent in psychogeriatric outpatients. Hence, the lower prevalence of TD in the Asian studies cannot be attributed to including only outpatients. Also, in four of the five studies younger patients (aged 40 or younger) formed a large majority of the patient population. It is well known that aging increases the prevalence of TD (Jeste et al. 1990). This may also explain the nearly equal M:W ratio found in these studies.

It is also conceivable that physicians in Asia treat their patients with smaller doses than their counterparts in the Western countries do. Indeed, the only Asian study (Binder et al. 1987) that used high daily doses of neuroleptic (mean daily dose of 1,633 mg chlorpromazine equivalent) found a higher prevalence of TD (35%) than

the other studies, which used lower doses (in the range of 300 mg/day chlorpromazine equivalent).

Although the above explanations may be plausible, the constitutional factors have not been fully explored. An intriguing finding by Tan and Tay (1991) was that the TD prevalence differed with ethnicity. Malaysian, Indian, and Chinese patients in their study all had a similar prevalence of TD (21% to 27%) while 54 percent of the Eurasian patients had TD. Thus, at present, the influence of ethnicity on the prevalence of TD remains to be studied.

A limitation of these comparisons is that the racial genetic makeup of the patients included in these studies was usually not described; a single study might have included patients from different racial and ethnic backgrounds. Also, there are likely to be differences among patients as well as treatment practices in countries from the same continent. Hence, the cross-cultural comparisons should be interpreted with caution. We recommend that ethnic background be fully described and compared in future prevalence studies.

Table 3 suggests that only women had a continuing increase in the prevalence of TD with age. This increase was fivefold when women aged over 70 were compared to women younger than 50. In men, this increase in the prevalence of TD with age was only twofold when the two extremes of age groups were compared.

TD severity and its assessment are controversial issues that have not been adequately addressed (Yassa et al. 1990). At present, there is an arbitrary classification of severe TD according to the investigators' experience (Degkwitz and Wenzel 1967; Villeneuve et al. 1969; Brandon et al. 1971; Bourgeois et al. 1976), or according to an item in a scale, such as an AIMS rating of 4 (severe) (Smith et al. 1978, 1979; Perenyi and Arato 1980; Richardson et al. 1984; Yassa et al. 1990), or according to the patient's incapacitation from TD (Gardos et al. 1987). Thus, one may expect a large variation in the definition of severe TD according to the authors' criterion. Nonetheless, women seemed to have more severe TD than men, with a mean prevalence of 3.1 percent versus 1.3 percent; TD was more common in women than men, particularly in older patients (aged 50 and older), and TD in women tended to be more severe than in men.

SD is the presence of abnormal involuntary movements without prior use of neuroleptics and without other known causes of dyskinesia. As noted, only five studies dealt with the prevalence of SD in relation to gender. Men had less evidence of SD than women, following the general trend noted in TD.

Few followup studies have compared men and women. In these studies, there was no consistent evidence that the prognosis and course of TD differed between men and women. However, this point needs further investigation.

Several hypotheses have been put forward to explain the discrepancy in the TD prevalence between men and women. Some investigators reported that women tended to have more chronic illness and longer hospitalizations than men (Kennedy et al. 1971). There are reports that women tended to receive larger doses (Degkwitz and Wenzel 1967; Kane and Smith 1982) or longer duration of neuroleptic treatment (Doongaji et al. 1982) than men. Evidence has accumulated in studies conducted on schizophrenic patients, however (most of the TD prevalence studies referred to in this review dealt mainly with schizophrenic patients), that women have a better prognosis than men (Huber et al. 1980; Seeman 1983; Goldstein 1988; Yassa et al. 1990). Only in follow-up studies of more than 20 years does one find that the prognosis of schizophrenia in the genders is similar (Yassa et al. 1991). It is thus difficult to attribute the higher prevalence of TD in women to poorer prognosis schizophrenia.

Another possible explanation is the fact that in some studies, women were older than men. Women have a longer lifespan than men and therefore tend to be overrepresented in surveys of older patients (Yesavage et al. 1982). Aging is accompanied by a tendency for developing more severe TD (Smith and Baldessarini 1980; Yassa et al. 1986), and studies that failed to include older women in their samples reported an absence of severe TD (Gardos et al. 1980; Mukherjee et al. 1982). In our review, we found 20 studies in which women were older than men. Of these, seven indicated a higher prevalence of TD in women than men (Jones and Hunter 1969; Kennedy et al. 1971; Simpson et al. 1978; Smith et al. 1978; Yesavage et al. 1982; Holden 1987; Yassa 1988). Age did not seem to increase the prevalence of TD in men to the same degree as in women. Thus, older women seem to be more vulnerable to TD, especially the severe forms of TD.

A third possibility is that psychosis may develop later in life in women than in men. Some studies have indicated this finding (Harris and Jeste 1988). TD was found to develop with a shorter period of neuroleptic treatment and in a more severe form when neuroleptics were given later in life than when neuroleptics were started earlier in life (Jeste et al. 1982*a*). Another possible explanation is that women may be protected by estrogens earlier in life. Estrogens have an antidopaminergic activity (Raymond et

al. 1978), thus possibly protecting premenopausal women from developing TD. This may explain a reported finding that premenopausal women needed lower doses of neuroleptics than men of the same age (Seeman 1983). Some studies have reported improvement in TD during estrogen administration in both men and women (Villeneuve et al. 1980), although this finding has not been replicated by others (Jeste et al. 1988).

A caveat in our review of gender differences in TD is a lack of research on plasma concentrations of neuroleptics comparing the genders. To date, most of the studies on plasma concentrations of neuroleptics have been conducted on men alone (Yesavage et al. 1987), or on women alone (Jeste et al. 1982*b*), or have not compared plasma concentrations in the genders (Csernansky et al. 1983; Smith et al. 1983).

Finally, it is possible that catecholaminergic changes with aging may play a role in the development of TD in older patients (Smith and Baldessarini 1980; Jeste and Wyatt 1987). The role of these changes in the pathophysiology of TD needs further study.

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