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Tardive dyskinesia in non-western countries: a review

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Abstract Tardive dyskinesia (TD) is a well-described adverse effect of treatment with neuroleptics. Studies from non-western countries are sparse and those that exist are not well publicized. We analyzed prevalence data on TD, published in English or French, and carried out in countries in Africa and Asia through December 1993. The estimated prevalence of TD among African subjects was 24% and among Asian subjects 17.20%. Both rates are in the middle range when compared with the western prevalence rates of 10–50%. Long-term hospitalization and older age were risk factors associated with TD. Female gender did not emerge as a risk factor. Also, several Asian studies showed that subjects with TD were taking lower doses of neuroleptics than subjects without TD. Prospective and controlled cross-cultural studies of TD are recommended for better understanding of associated risk factors and primary prevention.

Introduction

Tardive dyskinesia (TD) is a persistent and involuntary movement disorder afflicting various body parts particularly the bucco-lingual-masticatory muscles and the distal limbs. Since the first report in the English-language literature by Uhrbrand and Faurbye (1960), a large body of data has been gathered on its phenomenology, epidemiology, etiology, and treatment (Crane 1968; Murkherjee et al. 1982; Baldessarani et al. 1980; Waddington et al. 1986; Yassa and Jeste 1992). Some risk factors for the development of TD have been identified, the most consistent of these is advanced age; subjects over 40 years are three times more likely to develop TD than those under 40 years (Jeste and Wyatt 1981; Kane et al. 1986). Whether the condition is homogenous or heterogenous remains uncertain. There is no specific treatment for this disorder. There is limited literature on the influence of racial factors on the development of TD (Baldessarani et al. 1980; Yassa and Jeste 1992). In particular, studies from non-western countries are sparse and those that exist are not well publicized.

The objective of this review is to review and integrate TD studies from Asia and Africa. Our aims are to (a) determine universal or differential prevalence rates of TD on regional/continental basis, (b) determine racial trends, (c) compare the description of this syndrome between western and non-western regions, and (d) provide a comprehensive reference source for non-western studies.

Methods

A Medline search and previous review papers were used to locate relevant prevalence studies published up to December 1993. Items reviewed included (a) design of the study, (b) methods of assessment and diagnosis of TD, and (c) gender-specific prevalence rates of TD and associated factors, which were considered in as much detail as each study provided.

Setting and characteristics of studies reviewed

Only articles published in English or French with part translation, and studies carried out in countries in Africa and Asia, were reviewed. One study on Asian-Americans carried out in the United States was included. Personal communication with some of the authors was made. There were six prevalence studies published through December 1993 in Africa; three TD studies were reported from Nigeria, two from South Africa and one from Morocco. These studies reflect on the Northwest, West and Southern regions of the continent. Thirteen TD prevalence studies were reviewed for Asia. A study by Pi et al. (1990) consisted of a multicenter survey involving several Asian countries.

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The studies reviewed were conducted on chronic psychiatric inpatients. One study (Pi et al. 1992) used outpatient subjects. They all used standardized rating scales, namely, the Abnormal Involuntary Movement Scale (AIMS; NIMH 1976) and the Simpson Dyskinesia Scale (Simpson et al. 1979). Smith et al. (1979) and Chien et al. (1977) have shown that AIMS is a reliable instrument for assessing TD. One of the studies reviewed, Gureje (1989), gave the inter-rater reliability of AIMS as kappa = 0.925, whereas another study by Holden et al. (1984) established that the inter-rater reliability for the Simpson Dyskinesia Scale was a kappa of 0.85. Both the presence and severity of TD were rated.

Diagnosis of TD was made according to the research diagnosis-tardive dyskinesia (RD-TD) criteria by Schooler and Kane (1982); where dyskinesia was rated (3) "moderate" in at least one or (2) "mild" in at least two of seven individual areas assessed by the AIMS.

Results

Tardive dyskinesia studies in Africa

Prevalence rates of TD

The prevalence of TD was estimated as 24% (range 9.30–39%). If the study of Holden et al. (1984) is excluded because of the impossibility of computing separately the total number of male and female subjects that participated in their study, the gender prevalence rates of TD were 18.80 and 14.00% for males and females, respectively. Table 1 summarizes the results of the individual studies regarding TD and gender differences in rates. Three of the studies (Gureje 1987, 1989; Moussaoui et al. 1988) showed higher TD prevalence rates for males; however, only the study by Moussaoui et al. (1988) showed significant difference between the genders at $P < 0.05$. A higher TD prevalence rate for females was reported by Holden (1987; $P < 0.01$).

Factor associated with TD

The association between demographic and pharmacological characteristics such as mean age, duration of treatment with neuroleptics, and daily mean neuroleptic dose in chlorpromazine equivalents (Davis 1976), between subjects with TD and those without TD, was considered by treating each study as a single observation. Equal weighting was given to each study. Table 2 shows the three studies compared. Generally, TD was found not to be significantly associated with either mean age or daily mean neuroleptic dose. However, when gender was taken into consideration, significant differences were observed between the group with dyskinesia and that without dyskinesia. For instance, Gureje (1987) established that the mean age of men with TD was 45.7 years (SD 12.7 years); whereas the mean age for men without TD was 35.8 (SD 9.8 years; $t = 2.87$; $P < 0.01$). The mean age for women with TD was 43 years (SD 13.9 years) whereas that for women free of TD was 36.6 years (SD 10 years; $t = 0.84$; NS). Holden (1987) observed that women with TD were receiving more dosages of neuroleptics than men with TD ($P < 0.01$) and that this group of women had been hospitalized for duration less than in men with TD (15.3 vs 23.6 years;

Table 1 Prevalence of tardive dyskinesia (TD) and gender differences in Africa

Authors	Prevalence of TD (%)	Study population		Total with TD		Percentage with TD		*P*
		Male	Female	Male	Female	Male	Female	
Gureje (1987)	39	54	16	21	6	39	31	
Gureje (1989)	27	101	36	28	9	27	25	
Holden et al. (1984; $n = 278$)	17	*	*	25	24	*		
Holden (1987)	39	50	50	13	26	26	52	< 0.01
Moussaoui et al. (1988)	12	272	798	46	85	16	10	< 0.05
Odejide (1980)	9	157	69	11	10	7	14	

* Total for gender could not be computed

Table 2 Comparison of TD and non-TD groups among African subjects (SD in parentheses)

Authors	Characteristics	Patients with TD		Patients without TD	
		Male	Female	Male	Female
Gureje (1987)	Mean age	45.70 (12.70)	43.00 (13.90)	35.80 (9.80)	36.60 (10.00)
Holden (1987)	Mean age	Both genders 49.30		Both genders 44.70	
Odejide (1980)	Mean age	41.00 (9.10)	44.50 (13.30)	41.09 (8.90)	44.70 (12.44)
Gureje (1987)	Mean neuroleptic dose[a]	Both genders 251.00 (188)		Both genders 392 (743)	
Holden (1987)	Mean neuroleptic dose[a]	Both genders		Both genders 92.00	
Odejide (1980)	Mean neuroleptic dose[a]	554.00 (375.97)	635 (280.10)	495.45 (241.30)	630.00 (292.60)

[a] Neuroleptic dose is in chlorpromazine equivalent units (mg)

Table 3 Tardive dyskinesia prevalence studies and gender differences among Asian subjects

Study	Total *n*	Males		Females		Overall prevalence of TD (%)
		Total *n*	With TD (%)	Total *n*	With TD (%)	
Ogita (1972)	454	–	17	–	18	17
Doongaji et al. (1982)	1801	1141	9	660	9	9
Itoh et al. (1984)	2274	969	19	1305	18	19
Kok and Christopher (1985)	211	–	7	–	12	9
Binder et al. (1987)	126	66	25	60	15	20
Ko et al. (1989)	886	582	10	211	6	8
Pi et al. (1990)	982	570	–	412	–	17
Pi et al. (1992)	115	56	–	59	–	15
Tan and Tay (1991)	514	207	16	107	34	27
Chiu et al. (1992)	917	503	–	414	–	9
Koshino et al. (1992)	647	361	23	286	21	22
Chiu et al. (1993)	274	–	–	–	–	25
Schwartz et al. (1993)	338	183	15	155	27	20

$P < 0.05$). Gureje (1989) reported that the length of hospitalization correlated significantly with orofacial dyskinesia, whereas the cumulative duration of exposure to high-potency neuroleptics and the number of electroconvulsive therapy (ECTs) received were significantly associated with appendicular TD.

Subtypes of TD

The studies reviewed varied in the descriptions and classifications of types of TD; thus, direct comparison could not be made. Gureje (1987, 1989) found that male subjects had more orofacial dyskinesias than female subjects, but this difference was not statistically significant. Female subjects had more limb dyskinesias in the lower extremities than males ($P < 0.025$). Of the group studied by Holden et al. (1979), 31% had orolingual dyskinesias, the subjects had a mean of 17.2 years (SD 12.8 years) of hospitalization and a daily dosage mean of 323.30 (SD 316) mg of chlorpromazine equivalent units. Of this group, 34 (69%) had limb dyskinesia with a mean of 27.70 years (SD 17.60 years) of hospitalization and a daily neuroleptic dosage mean of 534.90 (SD 870) in chlorpromazine equivalent units.

Tardive dyskinesia studies in Asia

Prevalence rates of TD

The overall mean prevalence of TD in Asia was 17.20%. The individual prevalence of TD in these studies was in the range of 8.40–28%. In five of the 13 studies reviewed, it was impossible to compute separately the total number of male and female subjects that had TD; thus, the gender prevalence rates for TD was computed on the remaining 8 studies. The mean prevalence of TD in Asians were 14.60 and 18.00% for males and females, respectively. Table 3 summarizes the results of the studies on TD on Asian subjects and gender differences in rates.

Factors associated with TD

All TD studies in Asia that were reviewed showed that TD appears to be more frequent in older patients. Generally, mean ages of subjects with TD were greater than those without TD. The mean age of the subjects with TD ranged from 38 to 62 years. Pi et al. (1992) found that subjects aged 40–49 years were three times more likely to have TD than those under 40 years, and subjects over 50 years were eight times more likely to have TD than those under 40 years. Only one study (Chiu et al. 1992) found that TD prevalence was significantly greater among women than men ($\chi^2 = 8.34$; $df = 1$; $P = 0.004$).

The specific contribution of drug variables such as the length of neuroleptic exposure and the resultant cumulative drug dose to the development of TD were examined by four studies (Doongaji et al. 1982; Itoh et al. 1984; Binder et al. 1987; Ko et al. 1989). The consensus findings of these studies were that there was a significant association between greater length of exposure to neuroleptic and TD. Binder et al. (1987) found that patient's with moderate or severe TD were hospitalized significantly longer than those without TD ($t = 2.08$; $df = 124$; $P < 0.5$).

An inverse relationship between the presence of TD and current neuroleptic dosages was found in three studies (Pi et al. 1990; Pi et al. 1992; Chiu et al. 1992), and patients with TD received lower current doses of neuroleptics than patients without TD. The mean current neuroleptic dosages reported by these authors ranged from 300 to 879 mg of chlorpromazine equivalent.

Pi et al. (1990) in a multinational study involving five Central Asian countries compared subjects of the same ethnic background, but within different geographical regions; they obtained an overall mean prevalence of 17.0% for TD. The prevalence of TD for Koreans in Seoul, Ko-

Table 4 Tardive dyskinesia prevalence studies in Asia. CPZ chlorpromazine equivalent units (mg)

Study	Ogita (1972)	Doongaji et al. (1982)	Itoh et al. (1984)	Kok and Christopher (1985)	Binder et al. (1987)	Ko et al. (1989)	Pi et al. (1990)	Pi et al. (1992)	Tan and Tay (1991)	Chiu et al. (1992)	Koshino et al. (1992)	Chiu et al. (1993)	Schwatz et al. (1993)
Location	Japan	India	Japan	Singapore	Japan	China	China Hong Kong Japan Korea	Los Angeles, California (mixed Asians)	Singapore	Hong Kong	Japan	Hong Kong	Israel
N	454	1801	2274	211	126	866	982	115	514	917	647	274	338
% Female	–	36.6	57	52.6	48	26	42	51	60	45	44	–	49
Average age (years)	–	–	–	–	38	43	44	38	69	61.7	49.8	–	56.3
TD prevalence (%)	17.9	9.6	19	9.9	20.6	8.40	17.00	15.70	27.6	9.30	22.3	25.90	20
Average neuroleptic dose (CPZ)	–	240	–	–	1634	311	546	300	–	876	276.8	–	–
Risk factors	–	Older age Longer hospitalization	Older age Longer hospitalization Male > Female (n.s.)	–	Older age Longer	Older age High (current) neuroleptic dose Long neuroleptic use	Older age Low (current) neuroleptic dose	Older age Low (current) neuroleptic dose	–	Older age Low (current) neuroleptic dose	Older age Low (current) neuroleptic dose	Older age Low (current) neuroleptic dose	Older age female gender

rea, was 15.8%, whereas that for the Koreans in Yanji, China, was 20.30%. The prevalence of TD for Chinese in Hong Kong was 19.40%, and that for Chinese in Yanji, China, was 18.60%. They found that Koreans in Korea and China have different rates from those in Beijing: The prevalence rates were 11.20 and 10.40%, respectively. Pi et al. (1992) found an overall TD prevalence of 15.70% among 115 Asian-American psychiatric outpatients in California. The ethnic composition of the group was 25.7% Chinese, 23.5% Korean, 20.9% Japanese, 17.45% Filipino, 1.7% Vietnamese, and 0.9% Cambodian. Among this group with diverse ethnic composition, they did not find significant association between the presence or absence of TD and ethnic origins.

Discussion and Conclusion

The major aim of this study was to review and integrate available TD prevalence studies in Africa and Asia and provide cross-continental prevalence rates and patterns of TD. The estimated prevalence of TD in Africa was 24%. This rate is comparable to 27.60% and 21.50% reported by Yassa and Jeste (1992) in a review of TD studies from North America and Europe, respectively. The rate in Asia was 17.30%; this rate is comparable to the rates reported in earlier TD studies from Asia (Yassa and Jeste 1992; Pi et al. 1993). Yassa and Jeste (1992) reviewed six TD studies conducted in Asia with a total of 5401 subjects; they reported a prevalence rate of 16.60%. Pi et al. (1993) reviewed five TD studies in Asia with a combined sample size of 3006; the prevalence of TD was 17%. There were 9539 Asian subjects in our review.

This review shows that the actual prevalence rate of TD varied from one study to another and within countries. The variation in prevalence rates could be due in part to methodological factors. If cross-continental differences in prevalence rates can be shown to persist after controlling for methodological differences, age and gender, neuroleptic dosage, and pharmacogenetic factors may emerge as relevant etiological/associated risk factors of TD.

It is conceivable that racial-genetic variables may have etiological significance in the production of psychiatric disorders and pharmacological response. Africa and Asia are physically, culturally, and socially distinct from Europe and North America; thus, it would be interesting to find unique and heuristic characteristics of TD among Africans or Asians. The associations between TD and predictors have been inconclusive. Demographic and clinical factors, such as age, ethnicity, race, diagnosis, and chronicity of illness, among other factors, may influence the prevalence of TD. Few studies have compared the prevalence of TD among ethnic groups. Ogita et al. (1975) found a similar prevalence of TD in French and Japanese psychiatric hospitals. Binder et al. (1987) found that the prevalence of TD among Japanese inpatients was 21% and comparable to the mean prevalence of 20% reported in European and North American studies. Sramek et al. (1991) reported a total TD prevalence of 17.70% among patients of three mixed ethnicities (Blacks, Whites, and Hispanics), no significant differences in the prevalence of

TD or in neuroleptic dosage levels were found among the three groups.

Some western studies on TD suggest a significant association between TD and increasing age (Simpson et al. 1978; Yassa and Nair 1988; Smith et al. 1979; Smith and Baldessarini 1980). Other authors have reported that the discriminatory value of age as a risk factor of TD are equivocal (Chouinard et al. 1979; Murkherjee et al. 1982). One African TD study, Gureje (1987), established that the presence of TD was related to age in males, but not in females. Men with TD were significantly older than men without TD. Tardive dyskinesia studies from Asia showed that increasing age was the only significant and consensus risk factor associated with TD. Subjects above 40 years were more likely to have TD than those under 40 years. In contrast to the report in the literature on TD studies from the western hemisphere, only one study (Chiu et al. 1992) in this review showed that the risk of TD was significantly greater in women. This raises the possibility that female subjects in these regions might have different metabolisms, responses, and reactions to neuroleptics.

Different prevalence rates for TD were reported for different geographical sites with the same ethnic composition (Ko et al. 1989; Pi et al. 1990), whereas relatively comparable prevalence rates were reported for different ethnic groups within the same geographical location (Binder et al. 1987; Pi et al. 1990). The difference in TD prevalence among subjects of the same ethnic group, but in different sites, suggests a possible influence of environmental factors. Further cross-cultural prospective studies are necessary to examine the reasons for the apparent intra-ethnic difference in the prevalence of TD.

Ethnic differences in psychiatric symptomatology, psychopharmacological responses, and side effects have been reported. Regarding the required dosage of neuroleptic, Yamamoto et al. (1979) and Lin and Finder (1983) reported that Asians require lower dosages of neuroleptics, whereas Potkin et al. (1984) and Lin et al. (1989) reported that Asians have higher plasma neuroleptic levels at lower dosages when compared with Caucasians. In this review an inverse relationship was found between current neuroleptic dosages and the presence of TD. Patients with TD were taking significantly lower doses of neuroleptics than patients without TD. The inverse relationship between the lower current dose of neuroleptic and the high propensity of developing TD among the Asian may be due to the suppressing effect of a higher dose of neuroleptic drugs on TD. Pi et al. (1993) called this phenomenon "covert TD". This phenomenon may also be due to physicians' prescribing practices where the tendency is to reduce the dosage of neuroleptic medication after TD has been detected. Further investigations into the differences of metabolism of neuroleptic and receptor sensitivity between Asians and Caucasians would shed more light on this finding. This review has also established that the cumulative neuroleptic dose has a positive correlation with TD (Gureje 1989; Holden 1987).

Furthermore, four studies (Doongaji et al. 1982; Itoh et al. 1984; Binder et al. 1987 and Ko et al. 1989) found that the prevalence of TD increased with the length of exposure to neuroleptic. However, when Pi et al. (1990) controlled for age, the duration of treatment with neuroleptic was no longer a significant risk factor for TD.

The findings of any review paper would be limited by variance in diagnostic criteria, measurements, and reliability; this review is not an exception. In order to assess the contribution of genetic-racial factors and the degree of neuroleptic usage as risk factors for the development of TD, prospective cross-cultural multinational studies should be conducted.

There may be true continental differences and patterns; however, because of the current meager literature on TD studies in Africa and Asia, it is currently difficult to establish this. Future efforts should be directed at several studies with similar methodology and comparable subject populations across Africa and Asia.

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