# Neuroleptic-induced tardive dyskinesia among Arab psychotic patients

*A. Osman,[1] M. Marghalani,[2] I.Y.A. Turkistani,[3] M. Al-Swaf[4] and B. Bin Sadiq[5]*

## خلل الحركة الآجل المحدث بفعل الأدوية المضادة للذهان لدى المرضى المصابين به

عبد الكريم عثمان، منال مرغلاني، إبراهيم يعقوب تركستاني، منى الصواف، بكر بن صديق

**الخلاصة:** أجرى الباحثون دراسة وصفية استعادية لتحديد مدى انتشار خلل الحركة الآجل، وعوامل اختطاره، بين مرضى الذُّهَان الذين يعالجون بأدوية تقليدية مضادة للذهان، في أربعة مراكز بالمملكة العربية السعودية. وقد فُحصت ملفات المرضى الذين تعاطوا دواءً تقليدياً واحداً مضاداً للذهان أو أكثر لمدة ستة أشهر أو أكثر خلال الفترة الواقعة بين كانون الثاني/يناير 1997 وكانون الأول/ديسمبر 2000. وأُدرج 151 من هؤلاء المرضى في التحليل النهائي. وأوضحت الدراسات أن 51 مريضاً فقط أصيبوا بخلل الحركة الآجل، و59 مريضاً آخرين (6.8%) أصيبوا بداء باركنسون المحدث بفعل الأدوية المضادة للذهان. وتبيَّن أن العوامل المتمثِّلة في مدة العلاج (P<0.001)، والجرعات الأعلى من الأدوية المضادة للذهان (P< 0.01)، وكون المريض فوق سن الأربعين (P< 0.01) قد ترابطت مع الإصابة بخلل الحركة الآجل. وتبيَّن أن هناك فرقاً يُعتدُّ به إحصائياً في انتشار هذا الخلل، حيث بلغ المعدل بين المرضى العرب (23.5%)، والعرب الأفارقة (45.5%) (P< 0.01)، في حين بلغ معدل الانتشار العام للإصابة بخلل الحركة الآجل بين مرضى الذهان 5.9%.

ABSTRACT We carried out a retrospective descriptive study to determine prevalence and risk factors for tardive dyskinesia (TD) among psychotic patients treated with conventional neuroleptics in 4 centres in Saudi Arabia. Records of patients who had been taking ≥ 1 conventional neuroleptic for ≥ 6 months from January 1997 to December 2000 were examined; 151 patients were included in the final analysis. Only 51 had TD; another 59 (6.8%) patients had drug-induced Parkinson disease. Duration of treatment ($P < 0.001$), higher doses of neuroleptics ($P < 0.01$) and age over 40 years ($P < 0.01$) were associated with TD. A statistically significant difference in prevalence was found between Arabs (23.5%) and Afro-Arabs (45.5%) ($P < 0.01$). Overall prevalence of TD among psychotic patients was 5.9%.

**La dyskinésie tardive post-neuroleptique chez des patients arabes psychotiques**

RÉSUMÉ Nous avons mené une étude descriptive rétrospective ayant pour objectif de déterminer la prévalence et les facteurs de risque de la dyskinésie tardive (DT) iatrogène chez des patients psychotiques traités avec des neuroleptiques classiques dans 4 centres d'Arabie saoudite. Les dossiers des patients ayant pris ≥ 1 neuroleptique conventionnel sur une période ≥ 6 mois entre janvier 1997 et décembre 2000 ont été examinés. Ont été inclus dans l'analyse finale 151 patients. Seuls 51 d'entre eux présentaient une DT, 59 autres (6,8 %) étant atteints d'un parkinsonisme iatrogène. La durée du traitement ($p < 0,001$), des doses de neuroleptiques plus élevées ($p < 0,01$) et un âge supérieur à 40 ans ($p < 0,01$) ont été associés à la DT. La prévalence a laissé apparaître une différence statistiquement significative entre les populations arabes (23,5 %) et afro-arabes (45,5 %) ($p < 0,01$). La prévalence globale de la DT chez les patients psychotiques était de 5,9 %.

*[1]Psychiatric Department; [5]Department of Family Medicine and Medical Statistics, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia (Correspondence to A. Osman: akarimosman@yahoo.co.uk).*
*[2]Jeddah Psychiatric Hospital, Jeddah, Saudi Arabia.*
*[3]Department of Psychiatry, Al-Noor Hospital, Mecca, Saudi Arabia.*
*[4]Department of Psychiatry, King Fahad General Hospital, Jeddah, Saudi Arabia.*
*Received: 04/10/04; accepted: 30/11/04*

## Introduction

Neuroleptic-induced movement disorders consistent with the term tardive dyskinesia (TD), which was coined in 1964 [*1*], were reported in the literature as early as the 1950s. It was described as a movement disorder caused by the prolonged use of neuroleptic drugs. The condition is defined as a disorder characterized by involuntary movements, which may involve oro-facial dyskinesia, coarse tics or choreoathetosis, with abnormal oro-facial movements being the commonest [*2*]. It usually appears while the patient is still on the offending agent or appears for the first time when the drug is discontinued or its dose is reduced.

Reported prevalence rates of TD from across the world have varied widely. Rates from as low as 0.5% to as high as 65% have been reported [*3–11*]. Some of the confounders that have been proposed as contributing to such wide variability include heterogeneity of the populations under investigation, lack of agreement upon definition of what constituted TD and, more importantly, the confounding effect of the type, dosage and duration of the offending agents, and the duration of the illness itself, both prior to and after the commencement of the drug [*4,5,7,9,11–13*].

Tardive dyskinesia remains an enigma without a convincing explanation to its underlying pathophysiology. Two of the most persuasive current hypotheses are the dopamine hypersensitivity hypothesis and the serotonin–dopamine antagonist hypothesis. The dopamine hypersensitivity hypothesis states that neuroleptics may induce a compensatory dopamine hyperfunction owing to the prolonged blocking effect they have on the receptors. The serotonin–dopamine antagonist hypothesis maintains that drugs which have a high affinity for blocking serotonin receptors in the striatum, such as the new atypicals, may lead to increased release of dopamine, which attenuates the blocking effect of neuroleptics to dopamine receptors in the nigrostriatal system due to the inhibitory effect serotonin has on dopamine release in these areas [*14–16*]. Although there are no concrete biological or pathological findings which support these 2 hypotheses, the clinical empirical evidence lend them some good support. Despite the lack of concrete evidence for the underlying pathophysiology of TD, there have been a few consistently reported risk factors which were found to make some patients more vulnerable to developing TD if treated with neuroleptics. These include the prolonged continued use of neuroleptics, especially in large doses; polypharmacy; advancing age of the patient, particularly > 40 years; brain damage; strong negative symptoms or a strong affective component in schizophrenic patients; and the indiscriminate use of anticholinergic agents [*7,8,12,17–22*].

To the best of our knowledge, prevalence rate of TD has not been recorded for patients from Arab countries diagnosed with psychosis and being treated with conventional neuroleptics.

The aim of the study was to determine the prevalence rates of TD among Arab patients with psychosis who had been treated with conventional neuroleptics for a prolonged period. We also looked for any risk factors or protective factors among these patients.

## Methods

We carried out a retrospective cross-sectional study to compare patients with neuroleptic-induced TD with those who did not develop it under comparatively similar conditions.

We selected the 4 hospitals which had psychiatric services situated in the western region of Saudi Arabia for this study. The Jeddah Psychiatric Hospital, which is the only general psychiatric hospital in the region and serves the city of Jeddah and the towns around, is a state hospital. It has 150 beds and 3 clinics a day, with 100 to 125 patients attending daily. There are 4 consultants, 8 psychiatric specialists and 3 senior registrars working in the hospital. King Fahad General Hospital is the largest state general teaching hospital in Jeddah, with about 900 beds. It is the main general hospital serving the inner city of Jeddah and the surrounding areas. Two psychiatrists provide the services, which are mainly outpatient clinics and consultation–liaison duties. Al-Noor General Teaching Hospital in Mecca, the second largest city in the area, is a state general hospital. There are 2 consultant psychiatrists and 2 associate specialists, whose main duties include outpatient clinics and liaison services in the hospital. They see about 60–75 patients in their clinics per day. King Faisal Specialist Hospital and Research Centre is in Jeddah; it has 1 full time consultant, 1 part time consultant and 1 specialist psychiatrist. Their main duties are outpatient clinics, liaison–consultation services and a limited number of inpatient cases as the hospital is mostly a tertiary care service hospital.

All patients suffering from a chronic psychosis who were seen between January 1997 and December 2000 in 1 of the 4 participating centres and who had been prescribed neuroleptic drugs for longer than 6 months were selected. Their medical records were examined to identify those patients who were eligible to be included in the study. Taking into consideration all the major drawbacks and pitfalls of a retrospective, multi-centre study, the following inclusion criteria were used:

- age 18–65 years;
- diagnosed as suffering from 1 of the following: schizophrenia, schizoaffective disorder or bipolar affective disorder that had been present for $\geq 3$ years;
- well-defined diagnostic criteria, including persistent delusions and/or auditory hallucinations, which must have been documented at least 3 times during follow-up;
- patient had been taking $\geq 1$ of the conventional (typical) neuroleptics continuously for $\geq 6$ months;
- patient had been taking only conventional (typical) neuroleptics and none of the new atypical antipsychotics had been used at any time prior to the time of inclusion in the study;
- patient had been followed up in the same clinic for at least 3 years.

## Results

A total of 866 patients were diagnosed with $\geq 1$ of the 3 conditions and had been taking $\geq 1$ of the conventional neuroleptics; 783 of them were concurrently taking > 1 anticholinergic drugs. Only 151 patients met all the inclusion criteria and only 51 of these (5.9%) were found to have some movement disorder that was consistent with TD. A further 59 patients (6.8%) were described as having symptoms of drug-induced Parkinson disease.

When only those with complete medical records, including the more frequently and consistently reported risk factors, were identified, the records of only 151 patients [116 (67.8%) males and 35 (23.2%) females] were suitable for inclusion in the final analysis. Among these, 115 were Arabs (27 of whom developed TD) and 22 were Afro-Arabs (10 of whom developed TD) (Table 1). It was not possible to reli-

Table 1 **Association of tardive dyskinesia with diagnosis, duration of illness, and sociodemographic characteristics**

| Variable | Total | Tardive dyskinesia[a] | | $\chi^2$ | df | *P*-value |
|---|---|---|---|---|---|---|
| | No. | No. | % | | | |
| *Diagnosis* | | | | | | |
| Schizophrenia | 90 | 30 | 33.3 | 0.385 | 2 | 0.8 |
| Schizoaffective disorder | 23 | 9 | 39.1 | | | |
| Bipolar affective disorder | 38 | 12 | 31.6 | | | |
| *Duration of illness (years)* | | | | | | |
| < 5 | 47 | 7 | 14.9 | 33.48 | 3 | < 0.001 |
| 5–9 | 40 | 7 | 17.5 | | | |
| 10–19 | 43 | 21 | 48.8 | | | |
| > 19 | 21 | 16 | 76.2 | | | |
| *Sex* | | | | | | |
| Male | 118 | 38 | 32.2 | 0.596 | 1 | 0.44 |
| Female | 33 | 13 | 39.4 | | | |
| *Ethnicity* | | | | | | |
| Arab | 115 | 27 | 23.5 | 6.11 | 1 | < 0.01 |
| Afro-Arab | 22 | 10 | 45.5 | | | |

[a]*Mean age (SD) 46.4 (11.4) years for those who had tardive dyskinesia and 36.7 (12.2) years for those who did not ($\chi^2$ = 4.72;* P = *0.01).*

ably determine the ethnicity of the other 14 patients.

Forty-seven patients were > 40 years old, mean 46.4 [standard deviation (SD) 11.4] years and 114 were ≤ 40 years of age, mean 36.7 (SD 12.2) years. From the records, we found 51 patients [38 (74.5%) males and 13 (25.5%) females] had TD; all were described as having oro-facial movement disorder (Table 1). A statistically significant positive association with TD was found only with advancing age of the patients [mean age of those with TD was 46.4 (SD 11.4) years compared with mean age 36.7 (SD 12.2) years for those without TD ($\chi^2$ = 4.72; $P < 0.01$)], longer duration of illness ($P < 0.001$) (Table 1) and longer duration of treatment ($P < 0.001$) (Table 2).

As almost all our patients had been prescribed > 1 drug, we calculated the daily intake in terms of approximate equivalents to chlorpromazine in accordance with the British National Formulary [21]. Only 2 of the drugs used, chlorpromazine ($\chi^2 = 13.70$, $P = 0.001$) and haloperidol ($\chi^2 = 8.70$; $P = 0.012$), had a statistically significant positive association with TD. No association was established between trifluoperazine and TD.

## Discussion

We considered very carefully the confounding effects that a retrospective, multi-centre study such as this may have had on our findings and conclusions. We were also cognizant of the drawbacks of this study which included:

- the lack of any inter-rater reliability or validity tests for the diagnostic skills

Table 2 **Association of tardive dyskinesia with type of neuroleptic and duration of treatment**

| Variable | Total | Tardive dyskinesia | | $\chi^2$ | df | *P*-value |
|---|---|---|---|---|---|---|
| | No. | No. | % | | | |
| *Haloperidol (mg/day)* | | | | | | |
| 5–9 | 14 | 1 | 7.1 | 8.70 | 2 | 0.012 |
| 10–19 | 51 | 7 | 13.7 | | | |
| ≥ 20 | 19 | 8 | 42.1 | | | |
| Total | 84 | 16 | 19.0 | | | |
| *Trifluoperazine (mg/day)* | | | | | | |
| 5–9 | 14 | 3 | 21.4 | 0.50 | 2 | 0.877 |
| 10–19 | 33 | 6 | 18.2 | | | |
| ≥ 20 | 23 | 6 | 26.1 | | | |
| Total | 70 | 15 | 21.4 | | | |
| *Chlorpromazine (mg/day)* | | | | | | |
| 50–< 200 | 75 | 6 | 8.0 | 13.70 | 2 | < 0.001 |
| 200–< 400 | 31 | 9 | 29.0 | | | |
| ≥ 400 | 11 | 5 | 45.5 | | | |
| Total | 117 | 20 | 17.1 | | | |
| *Duration of treatment (years)* | | | | | | |
| < 5 | 59 | 3 | 5.1 | 19.28 | 3 | < 0.001 |
| 5–9 | 44 | 5 | 11.4 | | | |
| 10–19 | 34 | 10 | 29.4 | | | |
| ≥ 20 | 13 | 26 | 46.2 | | | |
| Total | 150[a] | 24 | 16.0 | | | |

[a]*Data missing for 1 case.*
*df = degrees of freedom.*

of the psychiatrists who made the diagnoses;

- the diagnostic criteria which were used by the different psychiatrists at the time of diagnosis and the value of their diagnostic significance in reaching that diagnoses;
- what exactly was meant by TD by each of the psychiatrists and how accurate their descriptions and documentations were.

Some of our findings were also related to a relatively small sample size which may, therefore, have made any generalizations or conclusions more difficult to draw up.

The total number included for the final analysis in this study was only 151 patients. Despite this relatively small sample, however, we believe some of our findings merit careful consideration. The lower overall prevalence rate of TD among our patients (5.9%) is not in keeping with most of the reported rates from studies done in Western Europe and North America, where reported rates are 20%–39%, and in the Far East, where reported rates are 29.0%–40.6% [*6,7,10,18,20,22*].

Perhaps more important is the inter-ethnic difference in the prevalence rate of TD between Arabs from the Middle East and the Afro-Arabs, who are of African origin. While TD rate was 23.5% among

the Arabs, it was 45.5% among Afro-Arabs. Although the size of the sample was rather small, this finding, coupled with the relatively high rate of TD (39.7%) reported by Van Harten et al. among the mostly Negroid population in a state public hospital in the Netherlands indicate that some interethnic difference may indeed exist [*19*]. However, the existence of some variability in rates of TD due to ethnocultural factors has not been consistent or agreed upon by all researchers. While some researchers believe that some biological or genetic difference in susceptibility to TD may be found [*16,23*], others believe that susceptibility is most likely related to psychopharmacological factors such as duration of exposure and level of daily intake of neuroleptic drugs rather than to any ethnocultural or biological factors [*8,10,11,22*]. Our findings are more in support of differences related to either ethnocultural or genetic factors. If an interethnic difference in susceptibility between Arabs and Afro-Arabs does indeed exist, it will have important financial implications, particularly as almost all the Afro-Arabs included in this study came from poor African countries. Such a background may emphasize the importance of either early adverse neurodevelopmental factors such as poor prenatal care, infections or birth complications, or a genetic susceptibility which may be operating in these individuals.

We also found that many patients had been prescribed relatively low daily doses of neuroleptics to treat their psychosis. For example, among patients on haloperidol, 65 of them (77.4%) were taking < 20 mg/day with only 8 of those (12.3%) developing TD compared to 8 patients out of 19 patients (42.1%) who were on ≥ 20 mg/day. The same was true among patients taking chlorpromazine: 106 of 117 (90.1%) were taking < 400 mg/day and only 15 of them (14.2%) developed TD compared to 5 out of 11 (45.5%) receiving ≥ 400 mg/day. This finding, coupled with the consistently reported strong positive association of TD with higher daily doses of neuroleptics [*5,7,9,12*] suggests that the lower rates of both TD and Parkinson disease among our patients may be mostly related to the low daily doses of neuroleptics needed to effectively treat their condition. This could have important economic implications for the continuation of the conventional neuroleptics in poorer countries as first choice drugs, especially in countries where the affordability of drugs is the main determining factor in treatment.

One of the risk factors for increased susceptibility to neuroleptic-induced TD is the indiscriminate prescription of anticholinergic agents [*4,7,10,12,18,24*]. In our study, only 51 of the 783 patients taking ≥ 1 anticholinergic drugs developed TD and 59 Parkinson disease, which is not in keeping with what has previously been reported in the literature. We therefore believe that this trend in developing countries for prescribing an anticholinergic drug whenever a neuroleptic drug is given to a psychotic patient, as has been noted among our patients, may prove to have some protective or preventive role in keeping the rate of TD relatively low. This is in contrast to previous findings where anticholinergics have been identified as one of the risk factors. A longitudinal prospective study would be needed to determine if this is so.

In conclusion, in this study we found the overall prevalence rate of TD among Arab patients to be lower than the general rates reported in the literature, as well as the existence of some interethnic difference in rates between Arabs and Afro-Arabs. It is also possible that Arabs who suffer from chronic psychosis might need relatively lower daily doses of neuroleptics to be effective for their illness.

Prevalence of TD and drug-induced Parkinson disease were both relatively low among our patients, and in general, relatively low daily doses of conventional neuroleptics were prescribed. Consequently, we believe that the conventional neuroleptics could still continue to be first choice antipsychotics for the treatment of chronic psychosis rather than the relatively more expensive new atypical drugs which poorer countries may find it difficult to afford.

## *References*


1. Faurbye A et al. Neurological syndromes in pharmacotherapy of psychosis. *Acta psychiatrica scandinavica*, 1964, 40:10–27.
2. American College of Neuropsychopharmacology: Food and Drug Administration Task Force. Neurologic syndromes associated with neuroleptic drug use. *New England journal of medicine*, 1973, 289:20–3.
3. Tepper SJ, Haas JF. Prevalence of tardive dyskinesia. *Journal of clinical psychiatry*, 1979, 40(12):508–16.
4. Smith JM, Baldessarini RJ. Changes in prevalence, severity and recovery in tardive dyskinesia with age. *Archives of general psychiatry*, 1980, 37(12):1368–73.
5. Klawans HL, Goetz CG, Perlik S. Tardive dyskinesia: review and update. *American journal of psychiatry*, 1980, 137(8):900–8.
6. Yassa R, Nair V, Dimitry R. Prevalence of tardive dyskinesia. *Acta psychiatrica scandinavica*, 1986, 73(6):629–33.
7. Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. *Journal of clinical psychopharmacology*, 1988, 8(4 suppl.):52S–6S.
8. Gureje O. Topographic subtypes of tardive dyskinesia in schizophrenic patients aged less than 60 years. *Journal of neurology, neurosurgery, and psychiatry*, 1988, 51(12):1525–30.
9. Sweet RA et al. Duration of neuroleptic treatment and prevalence of tardive dyskinesia in late life. *Archives of general psychiatry*, 1995, 52(6):478–86.
10. Gracia-Barcelo MM et al. Dopamine-D3 receptor gene and tardive dyskinesia in Chinese schizophrenic patients. *Journal of neural transmission*, 2001, 108(6):671–7.
11. Chong SA et al. Awareness of tardive dyskinesia in Asian patients with schizophrenia. *Journal of clinical psychopharmacology*, 2001, 21(2):235–7.
12. Singh MM, Kay SR. Non-therapeutic interventions with trihexyphenidyl: therapeutic implications. *Psychopharmacologia*, 1975, 43:115–23.
13. Branchey MH, Branchey LB, Richardson MA. Effects of neuroleptic adjustment on clinical condition and tardive dyskinesia in schizophrenia. *American journal of psychiatry*, 1982, 138(5):608–12.
14. Meltzer HY. The mechanism of action of novel antipsychotic drugs. *Schizophrenia bulletin*, 1991, 17(2):263–87.
15. Huttunen M. The evolution of the serotonin-dopamine antagonist concept. *Journal of clinical psychopharmacology*, 1995, 15(1 suppl. 1):4S–10S.
16. Steen VM et al. Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenia. *Molecular psychiatry*, 1997, 2(2):139–45.

17. Morgenstern H et al. Predictors of tardive dyskinesia: results of a cross-sectional study in an out patient population. *Journal of chronic diseases*, 1987, 40(4):319–27.

18. Miller CH et al. Tardive dyskinesia prevalence rates during a ten-year follow-up. *Journal of nervous and mental disease*, 1995, 183(6):404–7.

19. Van Harten PN et al. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia. The Curacao Extrapyramidal Syndromes Study: 1. *Schizophrenia research*, 1996, 19(2–3):195–203.

20. Woerner MG et al. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. *American journal of psychiatry*, 1998, 155(11):1521–8.

21. *British National Formulary*, 48th ed. London, British Medical Association & Royal Pharmaceutical Society of Great Britain, 2004.

22. Chong SA et al. Tardive dyskinesia among Chinese and Malay patients with schizophrenia. *Journal of clinical psychopharmacology*, 2002, 22(1):26–30.

23. Basile VS et al. A functional polymorphism of the cytochrome P450 1A2 (CYP1A2) gene: association with tardive dyskinesia in schizophrenia. *Molecular psychiatry*, 2000, 5(4):410–7.

24. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophrenia research*, 1999, 35(suppl.):S61–6.