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The natural history of tardive dystonia
A long-term follow-up study of 107 cases

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Summary
The clinical picture, risk factors and natural history of tardive dystonia resulting from dopamine-receptor antagonist (DRA) treatment in 107 patients (57 male and 50 female), seen between 1972 and 1995, are described. The mean age at onset (± SD) was 38.3 ± 13.7 years (range 13–68 years), and the age at last follow-up was 46.3 ± 15.7 years (range 15–80 years). These patients had received DRAs for schizophrenia (39%), for other psychiatric conditions (51.5%) and for non-psychiatric disorders (9.5%). All classes of neuroleptics used were implicated in producing tardive dystonia, which was found to develop at any time, ranging from 4 days to 23 years after their introduction (median 5, mean 6.2 ± 5.1 years); there was no 'safe' period. Men were significantly younger than women at onset of dystonia, which developed after shorter exposure in men. At onset, the dystonia was focal in 83% of cases, but progressed over months or years and remained focal in only 17% at the time of maximum severity. The craniocervical region was involved in 87% of cases, and was the most commonly affected site both at onset and at maximum severity. There was a correlation between the site and age of onset; the site of onset ascended from the lower limbs to the face as the mean age of onset increased. Overall, the phenomenology of tardive dystonia was indistinguishable from that of primary (idiopathic) dystonia, although retrocollis and anterocollis, as well as torticollis to the right, were significantly more common in tardive dystonia. It is a very persistent disorder; only 14% of our patients had a remission over a mean follow-up period of 8.5 years. Remission occurred after a mean of 5.2 years from onset (range 1–12 years) and 2.6 years after discontinuation of neuroleptics (range 1 month to 9 years). Discontinuation of neuroleptics increased the chances of remission fourfold. Patients with ⩽10 years on neuroleptics had a five times greater chance of remission than those with >10 years exposure, suggesting that the pathogenetic changes in tardive dystonia may become irreversible after long-term use of these drugs. None of the numerous treatments tried in these patients, including clozapine and botulinum toxin injections, seemed to relate to overall outcome, but there was a significant negative association between the occurrence of remission and the use of benzodiazepines. Although there were hints of a possible genetic predisposition, the question as to whether patients with tardive dystonia have an underlying vulnerability remains unanswered.

Keywords: tardive; dystonia; neuroleptics; dopamine antagonists; movement disorder

Abbreviations: DRA = dopamine-receptor antagonist; CI = confidence interval

Introduction
Following the introduction of neuroleptics, i.e. dopamine-receptor antagonists (DRAs), in 1952, several authors reported patients who developed chronic, persistent dystonia after treatment with these drugs, but such cases were generally included under the rubric of tardive dyskinesia. Keegan and Rajput (1973) first introduced the term 'dystonia tarda' when reporting a female patient with torticollis and scoliosis. The first detailed and comprehensive description of the disorder was provided by Burke *et al.* (1982), who described 42 patients with tardive dystonia. Subsequently, Kang *et al.* (1986) described the clinical features of 67 cases, including 16 of those previously reported by Burke *et al.* (1982).

In the present long-term follow-up study we examined the clinical picture, risk factors and natural history of tardive dystonia in 107 patients.

Material and methods
We identified 107 patients referrred to the Movement Disorders clinics at the Maudsley Hospital and the National Hospital for

Neurology and Neurosurgery, London between 1972 and 1995 who fulfilled published diagnostic criteria for tardive dystonia (Burke *et al*., 1982; Kang *et al*., 1986). All had had chronic, persistent dystonia for >1 month arising during treatment with neuroleptics, or within 3 months after discontinuing such drugs. Known causes of secondary dystonia were excluded by appropriate clinical and laboratory investigation. None of the patients had a family history of primary (idiopathic) dystonia. Seventeen of the patients had been reported previously by Burke *et al*. (1982) and then followed by us.

We reviewed our detailed movement disorder records of all patients and, using a standard protocol, obtained the following information: (i) demographic data; (ii) primary (psychiatric or other) diagnosis; (iii) drug-related data, including age at first neuroleptic treatment, interval from first exposure to DRAs to dystonia onset, the use of depot preparations and whether DRA use was continuous or intermittent (drug-free periods of >3 months); (iv) movement disorder-related data, including age at onset of tardive dystonia, and distribution of dystonia at onset and at time of maximum severity; (v) past history, including other drug-induced movement disorders, perinatal injury, mental retardation, epilepsy, essential tremor, treatment with electroconvulsive therapy and cranial or peripheral injury; (vi) family history, including that of movement disorders, epilepsy, dementia and psychiatric disorders; (vii) treatment-related data, including the use of DRA after the onset of dystonia and therapeutic intervention; and (viii) outcome related data, including the presence and distribution of dystonia at last follow-up, the presence of other movement disorders and the treatment at last follow-up.

Sixty-five of these 107 patients were traced and seen personally by one of us (V.K.) in 1996, and the follow-up data about the rest was based on their case notes.

The data were analysed using a DBASE IV program and statistical analysis was performed using the INSTAT and STATGRAPHICS programs. The following tests were used for statistical comparisons: odds ratio with 95% confidence intervals (CI), χ^2 test and Fisher's exact probability test for categorical (qualitative) variables; parametric tests (Student's *t* test, analysis of variance and correlation coefficient) for numeric (quantitative) variables; and non-parametric tests (Mann–Whitney *U* test, Wilcoxon two-sample test and Spearman rank correlation coefficient) for those quantitative variables that did not satisfy the necessary requirements for the *t* test, i.e. abnormal distribution or statistically significant difference in standard deviations.

Table 1 *Primary diagnoses for which neuroleptics were used in 107 patients with tardive dystonia*

Diagnosis	Patients (%)
Psychiatric disorders	
Schizophrenia	**42 (39)**
Mood disorder	**23 (21)**
(Bipolar)	16 (15)
(Monopolar)	7 (6.5)
Schizoaffective	**15 (14)**
Anxiety disorder	**7 (6.5)**
Somatoform disorder	**3 (3)**
Tic disorder (Tourette's)	**3 (3)**
Delusional paranoid disorder	**2 (2)**
Personality disorder	**1 (1)**
Mental retardation	**1 (1)**
Non-psychiatric disorders	
Vertigo	**6 (6)**
Gastrointestinal symptoms	**4 (4)**

Table 2 *Numbers of the most frequently used and 'offending' neuroleptics in 107 patients with tardive dystonia*

Frequency of use		'Offending' drug frequency*	
Drug	Patients (*n*)	Drug	Patients (*n*)
Trifluoperazine	40	Trifluoperazine	16
Chlorpromazine	34	Fluphenazine	16
Fluphenazine	33	Flupenthixol	14
Flupenthixol	21	Chlorpromazine	8
Haloperidol	21	Haloperidol	8
Thioridazine	12	Thioridazine	4
Pimozide	7	Perphenazine	4
Perphenazine	5	Prochlorperazine	4
Prochlorperazine	4	Zuclopenthixol	2
Sulpiride	3	Metaclopromide	1
Metoclopramide	2	Pimozide	1
Zuclopenthixol	2	Pipothizine	1
Droperidol	2	Sulpiride	1
Pipothiazine	1	Unknown	29
Fluspirilene	1		
Chlorprothixene	1		
Promazine	1		
Promethazine	1		

*The 'offending' neuroleptic was the drug being taken at dystonia onset.

Results

Demographics, primary diagnosis and drug-related data

There were 57 males and 50 females (1.14 : 1). Eighty-two were Anglo-Saxon, five Jewish (two Ashkenazi origin), three Pakistani, three Greek, three Black African, two Indian, two Iranian and two Polish, and there was one each of Afro-Caribbean, Portuguese, Turkish, Arabian and Chinese origin. Their mean age (± SD) at last follow-up was 46.3 ± 15.7 years (range 15–80 years).

The primary diagnoses that led to the use of DRAs are shown in Table 1.

All classes of DRAs were implicated (Table 2). Trifluoperazine was the most frequently used and also the

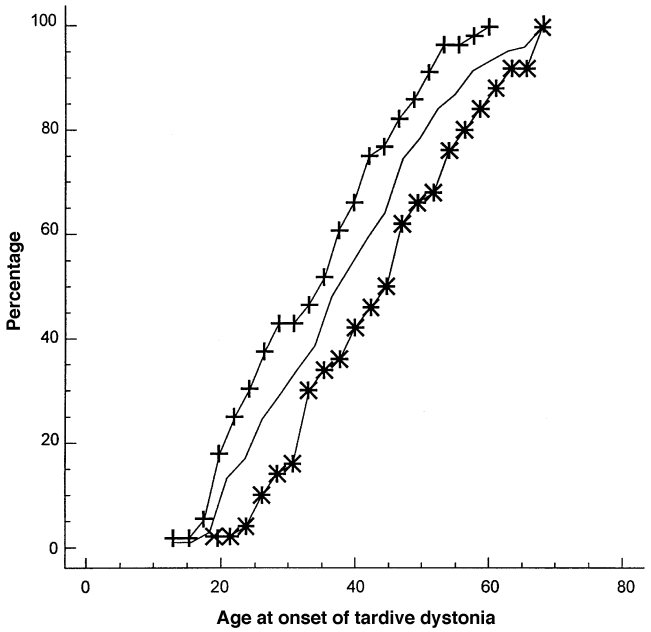

Fig. 1 The cumulative percentage of tardive dystonia patients increases linearly with age at dystonia onset. Males (+) are younger at onset of dystonia than females (*); curve without symbols = all patients.

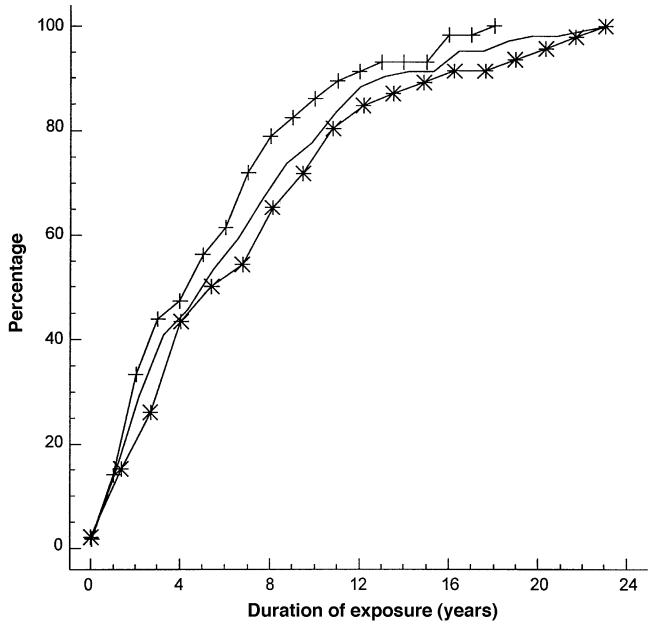

Fig. 2 Cumulative percentage of tardive dystonia patients as a function of duration of exposure to neuroleptics prior to dystonia onset. Males (+) have shorter exposure time than females (*); curve without symbols = all patients. There was no 'safe' duration of exposure.

most frequent 'offending' drug (e.g. the drug that had been used alone concurrently with, or just prior to dystonia onset). Forty patients had used only one DRA prior to dystonia onset, 26 had used two and 41 used three or more. Depot preparations had been used in 46 patients (data for 89, 52%). Seventy-seven patients had received DRAs continuously, and 25 intermittently, before the onset of dystonia (n = 102). DRAs had been taken alone in 52 patients. Of the remaining, 28 used one additional drug, and 27 used two or more. Anticholinergic agents were used prior to dystonia onset in 20 patients, lithium in 15, antidepressant drugs in 27 and anxiolytics in 22.

The mean age (± SD) at first exposure to DRAs was 31.8 ± 12.5 years (range 11–66 years; n = 102). Males had a younger mean age at first exposure than females (males, mean = 27.9 ± 11 years; females, mean = 36.4 ± 12.7 years; t = 3.6, P = 0.0005).

Onset of dystonia, clinical picture and clinical course

The cumulative percentage of patients who developed tardive dystonia after receiving DRAs increased linearly with age at onset, as shown in Fig. 1. The mean age (± SD) at onset of dystonia was 38.3 ± 13.7 (median = 38, range 13–68 years; n = 106). Men were significantly younger at onset of dystonia (33.5 ± 12.2 years) than women (43.7 ± 13.4 years) (t = 4.1, P = 0.00008).

Usually, tardive dystonia developed insidiously or subacutely over a period of weeks or months, so that patients could only determine the month or the year of onset. The interval between age at first exposure to DRAs and age at onset of tardive dystonia (duration of exposure to neuroleptics) was known in 103 patients and ranged from 4 days to 23 years with a median of 5 years and a mean of 6.2 ± SD 5.1 years. Thirty patients developed dystonia within 2 years after their first exposure to DRAs. Six had been exposed to DRAs for ⩽6 months. The cumulative percentage of patients who developed tardive dystonia after receiving DRAs, as a function of duration of exposure, is shown in Fig. 2.

In 15 patients the onset of tardive dystonia occurred 2 weeks to 4 months after some change in drug treatment; switching to another DRA in six patients, adding a new DRA in two, decreasing the dose in two, discontinuing DRAs in three (dystonia followed after 1–3 weeks), discontinuing procyclidine in one and adding lithium in another patient. However, in the remaining patients no apparent change in medication was recorded in the 6 months preceding the onset of dystonia.

Younger patients had a shorter exposure to neuroleptics at onset of tardive dystonia (r = 0.35, P = 0.0004 by Spearman rank correlation coefficient test).

A few patients reported that sensory symptoms or strange somatic sensations preceded the onset of tardive dystonia. Neck pain was reported by at least four patients who subsequently developed cervical dystonia after weeks or months, and three others reported odd somatic sensations heralding their tardive dystonia.

Table 3 shows the distribution and frequency of tardive dystonia when it first developed. Usually it presented as a focal dystonia, most commonly blepharospasm (with or without oromandibular dystonia) or torticollis. Other, less

Table 3 *Distribution and frequency of tardive dystonia by site, at onset and when the condition was fully developed*

Feature	At onset (%)		When fully developed (%)	
Distribution				
Focal	89	(83)	17	(16)
Segmental	15	(14)	64	(60)
Generalized	2	(2)	25	(23)
Hemidystonia	1	(1)	–	
Multifocal	–		1	(1)
Dystonia sites				
Cervical	40	(37)	71	(66)
Cranial	35	(33)	64	(60)
One or both arms	16	(15)	67	(63)
Trunk	15	(14)	47	(44)
One or both legs	13	(12)	28	(26)
Cervical dystonia	(pattern known in 38/40)		(pattern known in 69/71)	
Pure rotatory torticollis	16		12	
Retrocollis	6		5	
Antecollis	2		3	
Laterocollis	1		4	
Complex	13		45	
Trunk involvement	(pattern known in 14/15)		(pattern known in 47)	
Hyperextension	5		16	
Forward flexion	1		5	
Lateral flexion	2		3	
Rotation	1		3	
Complex or variable	5		20	

common, initial modes of presentation included pharyngeal dystonia causing dystonic dysphagia, oromandibular dystonia presenting with severe speech disturbance, dystonia of the tongue and lips and unilateral blepharospasm years before developing bilateral blepharospasm and generalized dystonia. Presentation with dystonia of the arms, trunk or legs was less common. Nine patients presented with a disturbance of gait which in five was very bizarre.

The pattern of cervical dystonia at onset was known in 38 patients, and the pattern of trunk involvement in 14 (Table 3).

No relationship was found between the distribution of dystonia at onset and age at onset or duration of drug exposure. However, there was a relationship between the site of onset and age at onset of dystonia; the site of onset ascended from lower limbs (at 34 $\pm$ 12 years) to the upper limbs (at 31 $\pm$ 10 years) to the trunk (at 37 $\pm$ 18 years) then to the neck (at 38 $\pm$ 13 years), and finally to the face (at 43 $\pm$ 13 years) as the mean age at onset of dystonia increased.

Once developed, the dystonia often progressed over months or years, usually in a stepwise fashion, subsequently involving other parts of the body.

Data on the rate of progression of tardive dystonia to maximum severity were available for 46 patients, whose characteristics were representative of the total study population; their mean time for progression was 1.8 years (range 1 month to 14 years); only three patients progressed to maximum after >5 years. In 23, dystonia spread to its maximum after <1 year. These patients with rapid spread were significantly younger at onset of dystonia (32.3 $\pm$ 11 years) than those with a slower (>1 year) progression (42.8 $\pm$ 16 years, $P = 0.02$ by Mann–Whitney test). They also had a shorter duration of exposure to DRAs before the onset of dystonia (median 3 versus 7 years, $P = 0.03$ by Mann–Whitney test); and they tended to be younger at first exposure (median = 29 versus median = 35 years, $P = 0.15$ by Mann–Whitney test). The patients with more rapid progression to maximum severity had a mean follow-up time of 5.5 years, whereas it was 9.1 years for those with slower progression. Only three patients progressed to maximum after >5 years. These rapid and slow progression groups did not differ significantly with respect to sex ratio, diagnosis, DRA use, distribution of dystonia, response to treatment or outcome of dystonia at the last follow-up.

Table 3 shows the distribution and frequency of the sites involved at the time of maximum severity of the tardive dystonia. Dystonia remained focal in only 17 patients (16%), and all but two of these had cranial or cervical regions involved. Overall, cranial or cervical regions were involved in the large majority of patients (93, i.e. 87%). The pattern of cervical dystonia, when fully developed, had been recorded for 69 patients, and that of trunk involvement for all 47 such patients.

Patients with generalized tardive dystonia (at maximum severity) tended to be younger at onset of dystonia (mean onset age 34.2 years) than those with segmental (39.4 years)

Table 4 *Other drug-induced disorders in the 107 patients with tardive dystonia*

Disorder	No. of patients (%)		Male : female
Characteristic oral stereotypies of tardive dyskinesia	32	(30)	17 : 15
Akathasia	24	(22)	18 : 6
Parkinsonism	29	(27)	14 : 15
Prior acute dystonic reaction	10	(9)	6 : 4
Neuroleptic malignant syndrome	1	(1)	1 : 0
Tardive Tourettism	1	(1)	0 : 1
Tardive facial pain	1	(1)	1 : 0

Table 5 *Additional past or associated medical problems in the 107 patients with tardive dystonia*

Past medical problems	No. of patients (%)	
Prior trauma	27	(25)
Surgical procedure	14	
Injury (head 6, peripheral 6 and both 2)	13	
ECT	22	(21)
Autoimmune disorders or atopy (psoriasis 1, vitiligo 1, eczema 1 and asthma 2)	5	(5)
Mental retardation	5	(5)
Seizures	4	(4)
'Essential' tremor	2	(2)
Dysmorphic facies	2	(2)
Short stature	2	(2)
Hearing loss	4	(4)
Insulin therapy for depression	1	(1)

or focal (38.9 years) dystonia. Similarly, generalized dystonia tended to develop more frequently in those with an earlier first exposure to DRAs (mean age at first exposure was 27.5 years for generalized dystonia, versus 33 years for segmental and focal dystonia). However, none of the above differences were significant. There was no relationship between the distribution of dystonia at maximum severity and duration of exposure to DRAs.

There was also a relationship between the site of involvement at maximum severity and age at onset of dystonia. The mean age at onset of dystonia increased as the site of involvement ascended from the legs (at 35 $\pm$ 15 years) to the trunk (at 33 $\pm$ 13 years) then to the arms (at 36 $\pm$ 14 years) to the neck (at 38 $\pm$ 14 years) and finally to the face (at 40 $\pm$ 14 years).

Phenomenology of tardive dystonia

We also compared the clinical picture of these patients with tardive dystonia with our cases of primary dystonia (unpublished observations); 36% of patients (25 out of 69) with tardive cervical dystonia had retrocollis compared with 19% of patients (61 out of 316) with primary cervical dystonia (odds ratio = 2.37, 95% CI = 1.35–4.17, P = 0.0037 by χ^2 test). Antecollis was also more frequent in tardive than in primary cervical dystonia; 33% (23 out of 69) versus 10% of patients (32 out of 316), respectively (odds ratio = 4.438, 95% CI = 2.39–8.24, $P < 0.0001$ by χ^2 test). Another finding was the right-sided predominance of torticollis in tardive cervical dystonia (32 out of 46, 70%) compared with the left-sided predominance in primary cervical dystonia [166 out of 275, 60%: odds ratio = 3.48 (95%CI = 1.78–6.82), P = 0.0002].

Other drug-induced movement disorders

Besides tardive dystonia, 70 patients (65%) had, at some time, developed other drug-induced movement disorders (Table 4). Most common were the typical stereotypies of classical tardive dyskinesia, akathisia and parkinsonism.

The patients with a history of orobuccolingual tardive dyskinesia in addition to tardive dystonia tended to be older at the onset of dystonia than patients without such a history. In a parallel analysis, 75 patients with tardive dystonia without orofacial tardive dyskinesia were compared with 58 patients with classical orofacial tardive dyskinesia, but without tardive dystonia, seen in the same clinic over the same period of time. The mean age at onset of classic tardive dyskinesia was 56.6 $\pm$ 15 years, significantly higher than that of tardive dystonia [37 $\pm$ 13.2 years, $t(130) = 7.96$, $P < 0.0001$].

Past medical history, family history (Table 5)

In eight of the 27 patients with a history of trauma prior to the dystonia onset, the dystonia appeared first in the injured body part, but in only three of them was there a close temporal relationship. One developed dystonia in both legs a few weeks after bilateral leg fractures; another developed a dystonic left arm a week after a fracture of that arm; the third developed torticollis 2 days after a wasp sting to the neck.

The vast majority of patients had a CT or MRI scan of the brain at some point. Mild, generalized brain atrophy—the only reported abnormality—was found in six patients.

Thirty-eight first-degree relatives of 25 (23%) of the index patients had a history of psychiatric disorder. Twenty of these relatives, of 16 index patients, also had a history of DRA exposure. Four relatives, of separate index patients, had a tardive syndrome (two tardive dystonia and two tardive dyskinesia). A history of a movement disorder was present in 13 first-degree relatives of 11 (10%) index patients. One had 'parkinsonism'; two had 'tics'; two were reported to have 'head jerking'; two 'abnormal facial movements'; one 'intermittent shoulder movements'; and one 'hand jerking'. Although none of these relatives was personally examined, there is no evidence that any of them had primary dystonia.

Treatment, outcome

Patients were followed for a mean of 8.3 $\pm$ 6.2 years (range 1 month to 29 years, median 7 years) after the onset of

tardive dystonia. Twenty-seven patients were followed for >10 years, 17 for >15 years and six for >20 years.

After the development of tardive dystonia, changes in medication were made in almost all patients. Efforts were made to discontinue all DRAs if the patient's psychiatric condition permitted. This was done immediately after the onset of dystonia (within the first few weeks) in 10 patients and at some later stage in 57 other patients. Of these 67 patients, 13 had to restart DRAs, 0.5 to 8 (mean 2.7, median 2) years after discontinuation. Therefore, at the last follow-up, 54 patients were off all DRAs (for a mean of 4.3 years, range 1 month to 18 years) and 52 were still on them ($n = 106$). Patients off all DRAs at the last follow-up had a diagnosis of major psychiatric disorder less frequently (62%) than patients still on DRAs (93%).

Where withdrawal from DRAs was impossible, substitution of the 'offending' drug(s) with another DRA was frequently undertaken. Overall, 97 patients used DRAs for some period after the onset of dystonia. Fourteen of them used the so-called atypical neuroleptics, clozapine (seven patients) and risperidone (seven patients). Four of the seven on clozapine derived some (two mild and two moderate) benefit, and three of the seven on risperidone derived mild benefit. During the course of their tardive dystonia many patients reported an improvement or worsening, usually following a change in their medication. However, in the vast majority of cases, this improvement was transient, usually lasting for a few weeks.

Therapeutic agents other than DRAs were given to treat the tardive dystonia in 96 patients. Tetrabenazine, a dopamine-depleting agent, was used in 45 patients. The response to treatment was known in 30 of them; 16 (53%) derived some benefit (10 mild, five moderate and one marked). Anticholinergic agents were used in 84 patients. The response to treatment was known in 54 of them; 24 (44%) derived some benefit (16 mild, six moderate and two marked). Benzodiazepines were used in 67 patients. The response to treatment was known in 38 of them; 20 (53%) derived mild benefit.. The response to treatment with baclofen, used in 18 patients, was known in nine of them; five (56%) derived some benefit (four mild and one moderate). Several other drugs were used with occasional benefit (L-dopa, dopamine agonists, amantadine, β-blockers, anticonvulsants, choline and vitamin E). Two patients reported significant benefit in their dystonia after using cannabis.

Botulinum toxin A was used in 31 patients with tardive dystonia. Among patients who had botulinum toxin A treatment for cervical dystonia, 83% reported improvement (Kiriakakis *et al*., 1997) and 80% had considerable relief from neck pain, and 86% of those treated for blepharospasm reported improvement.

Bilateral thalamotomy resulted in moderate improvement in one patient and unilateral thalamotomy produced a mild improvement in another. Other treatments (physiotherapy, speech therapy, homoeopathy, hypnotherapy and relaxation techniques) were tried by some patients without benefit.

Many patients had considerable fluctuations in their status not related to changes in the medication. Of particular interest were four patients with bipolar affective disorder who reported marked improvement or partial remission of their dystonia during the hypomanic or manic phase of their illness. Also, two schizophrenic patients reported worsening of their tardive dystonia during exacerbation of their psychosis.

More important and informative is the overall change in tardive dystonia at the time of last follow-up. Comparing the clinical picture at the last follow-up with that at the time of maximum severity, and considering the patients' subjective evaluation of their status, we made an overall estimation of the outcome of tardive dystonia in our cohort. We rated the outcome on a 0–4 subjective scale: 0 = no improvement in dystonia, stable or worse; 1 = mild improvement in dystonia, no change in function; 2 = moderate improvement, better function; 3 = marked improvement, minimal residual dystonia without symptoms and with almost full function (partial remission); and 4 = complete remission of dystonia (no symptoms of dystonia and no dystonic movements at last follow-up examination). We defined remission as sustained (>1 month) disappearance of dystonic symptoms, either spontaneously or with treatment, regardless of whether or not the patient was still taking DRAs. Overall, at the last follow-up, 15 patients (14%) were in remission (seven complete and eight partial), 42 (39%) were improved, and 50 patients (47%) had been stable or had worsened.

Comparisons of the characteristics of 15 remitting and 92 non-remitting patients are shown in Table 6**.** There was no significant difference in the age at follow-up, or in the mean duration of follow-up between the two groups, and therefore comparisons are valid.

No significant difference was found between remitting and non-remitting patients with respect to sex, distribution of dystonia at onset and at maximum severity, affected body part, history of other drug-induced movement disorder, history of ECT before the onset of dystonia, history of trauma before the onset of dystonia, family history of psychiatric or movement disorder, primary diagnosis or use of drugs before the onset of dystonia. However, there was a significant negative association between benzodiazepine treatment and occurrence of remission.

Patients who remitted were more likely to have had their DRAs discontinued ($P = 0.023 < 0.05$). Remitting patients tended to be younger (Table 7A), had a significantly shorter mean duration of exposure to DRAs before the onset of dystonia ($P = 0.02 < 0.05$; Table 7B), and tended to have less continual neuroleptic exposure after the onset of their tardive dystonia (Table 7C). Overall those patients whose tardive dystonia remitted had a significantly ($P = 0.03 < 0.05$) shorter total exposure to DRAs than those whose dystonia persisted (Table 7D). Remission occurred a mean of 5.2 years (range 1.5–12, median 4 years) after the onset of dystonia. At the time remission was achieved, 12 of the 15 patients (80%) had been off all DRAs for 2 months to 9 years (mean 2.4, median 2 years). On the

Table 6 *Remitting and non-remitting patients with tardive dystonia*

	Remitters		Non-remitters	
	n	(%)	*n*	(%)
Patients	15	(14)	92	(86)
Male : female	10	(67) : 5 (33)	47	(51) : 45 (49)
Neuroleptics discontinued	12	(80)	42	(46)[i]
Primary diagnosis				
Schizophrenia	5	(33)	37	(40)
Schizoaffective disorder	3	(20)	12	(13)
Mood disorder	2	(13)	21	(23)
Other	5	(33)	22	(24)
Drugs before tardive dystonia onset				
Neuroleptics only	6	(40)	46	(50)
Single neuroleptic	9	(60)	31/76	(41)
Depot neuroleptics	10	(71)	36/75	(48)
Anticholinergics	5	(33)	15	(16)
Lithium	1	(7)	14	(15)
Distribution of dystonia at onset				
Focal	14	(93)	75	(82)
Segmental	1	(7)	14	(15)
Generalized	0	(0)	2	(2)
Distribution of dystonia at maximum				
Focal	2	(14)	14	(15)
Segmental	10	(67)	55	(60)
Generalized	3	(21)	22	(24)
Other drug-induced movement disorder				
Acute dystonic reaction	2	(13)	8	(9)
Parkinsonism	6	(40)	24	(26)
Akathisia	4	(27)	20	(22)
Tardive dyskinesia	6	(40)	26	(28)
History of ECT prior to tardive dystonia onset	4	(27)	18	(20)
History of trauma prior to tardive dystonia onset	2	(13)	25	(27)
Family history of:				
Psychiatric disorder	3	(20)	26	(29)
Movement disorder	4	(27)	15	(16)
Treatment of tardive dystonia				
Tetrabenazine	8	(53)	37	(41)
Anticholinergics	13	(87)	71	(78)
Benzodiazepines	5	(33)	62	(68)[ii]
Botulinum toxin	3	(20)	28	(31)
Age at last follow-up (years; mean ± SD)	44.5 ± 15.2		46.6 ± 16.0	
Duration of follow-up (years; mean ± SD)	9.5 ± 6.8		8.0 ± 6.1	
Duration of tardive dystonia (years; mean ± SD)	5.2 ± 3.5		8.0 ± 6.1[iii]	
Age at onset of tardive dystonia (years; mean ± SD)	35.3 ± 12.7		38.8 ± 13.9	
Pre-tardive dystonia NL duration (years; median)	3.0		5.9	
Post-tardive dystonia NL duration[iv] (years; median)	2.7		3.2	
Total NL duration (years; median)	5.5		10.0[v]	
Duration of discontinuation after tardive dystonia onset (years; median)	1.5[vi]		2.0[vii]	

[i]Odds ratio (OR) = 4.67 (95% CI, 1.23–17.66), $P = 0.024$ (Fisher's test); [ii]OR = 0.23 (CI, 0.07–0.74), $P = 0.018$ (Fisher's test); [iii]$P = 0.036$, Mann–Whitney test; [iv]NL = neuroleptics; in case of remitters up to remission onset; [v]$P = 0.02$, Mann–Whitney test; [vi]for patients off neuroleptics when remission achieved; [vii]for patients off neuroleptics, but without remission.

other hand, 42 of 91 (46%) non-remitting patients were off all DRAs at the last follow-up for even longer (mean 4.7, median 2 years, range 1 month to 18 years). The remitting patients were followed for 1 month to 17 years (mean 4.3, median 3 years) after the remission occurred. At the last follow-up, 10 of the 15 remitting patients were off DRAs but all 15 were still in remission.

The characteristics of improved patients (including those with remission) and of non-improved patients are compared in Table 8. There was no significant difference in the mean age or duration of follow-up between the two groups and therefore comparisons are valid.

Most of the improved patients (53%) were off all DRAs at last follow-up, as were 44% of the non-improved patients, but the difference was not significant. No significant difference was found with respect to various numeric variables and most of the categorical variables. A positive association with a history of orofacial tardive dyskinesia

Table 7A *Remission and age at onset of tardive dystonia*

Age at onset (years)	No. of patients	No. of remitting patients (%)	
13–20	14	1	(7.1)
21–30	18	5	(27.8)
31–40	30	6	(20.0)
41–50	22	1	(4.5)
51–60	15	1	(6.7)
>60	7	1	(14.3)
Unknown	1	0	(0.0)

χ^2 (for trend) = 0.9, P = 0.34.

Table 7B *Remission and duration on DRAs before tardive dystonia onset*

Time on DRAs after onset (years)	No. of patients	No. of remitting patients (%)	
0–4	47	11	(23.4)
>4	56	4	(7.1)
Unknown	4	0	(0.0)

Odds ratio = 3.97 (95% CI = 1.2–13.4), P = 0.02 by Fisher's test.

Table 7C *Remission and time on DRAs after tardive dystonia onset*

Time on DRAs after onset (years)	No. of patients	No. of remitting patients (%)	
0–5	65	12	(18.5)
>5	38	3	(7.9)
Unknown	4	0	(0.0)

Odds ratio = 2.6 (95% CI = 0.7–10), P = 0.16 by Fisher's test.

Table7D *Remission and total time on DRAs*

Time on DRAs after onset (years)	No. of patients	No. of remitting patients (%)	
0–5	27	6	(22.2)
>5–10	29	7	(24.1)
>10–15	18	1	(5.6)
>15–20	12	0	(0.0)
>20–30	14	1	(7.1)
Unknown	7	0	(0.0)

χ^2 (for trend) = 4.7, P = 0.03.

was noted, improved patients having developed this more frequently than non-improved patients. A significant negative association was found with a history of use of DRAs only (before the onset of dystonia).

Discussion

Today, tardive dystonia is established as a syndrome separate from, but sometimes co-existent with, classical orobuccolingual tardive dyskinesia. Its phenomenology has been explored in previous case series involving small numbers of subjects with a short follow-up time. Our study also has limitations because of its retrospective design and its tertiary referral centre setting which can cause a referral bias. Nevertheless, it has provided some clues to the frequency, predisposing risk factors, response to treatment and outcome of tardive dystonia.

Epidemiology

There have been nine cross-sectional studies on tardive dystonia in psychiatric in-patients (Friedman *et al*., 1987; Gureje, 1989; Sethi *et al*., 1990; Inada *et al*., 1991; Chiu *et al*., 1992; Micheli *et al*., 1993; Pourcher *et al*.,1995; Raja, 1995; Van Harten *et al*., 1996), one study in psychiatric out-patients (Sachdev, 1991) and one with a mixed (out-patient and in-patient) psychiatric population (Yassa *et al*., 1986). The reported prevalence of tardive dystonia has ranged from 0.5% to 21.6%, with only three studies reporting a prevalence above 5%. Out of a total of 4166 psychiatric patients exposed to DRAs in all these 11 studies, 113 (2.7%) had developed tardive dystonia.

Sex and age differences

Male predominance (average 1.2 : 1) has been a consistent finding in almost all case series. This difference could simply reflect the sex difference in age at onset of schizophrenia and schizoaffective disorder, which in our cohort were the most frequent diagnoses in patients who developed DRA-related dystonia. Both these disorders (but not affective psychoses) occur earlier in men, and men are given DRAs earlier than women (Loranger, 1984; Hare, 1987; Angermeyer and Kuhn, 1988; Channon, 1993). This could explain why men develop tardive dystonia earlier than females, and to some extent after a shorter duration of exposure to DRAs. Sex and age may therefore be risk factors for developing tardive dystonia.

Psychiatric diagnoses

The role the primary diagnosis may play in the development of tardive dystonia has not been explored in previous studies. In a total of 249 tardive dystonia patients from seven studies (including ours, Burke *et al*., 1982; Gimenez-Roldan *et al*., 1985; Kang *et al*., 1986; Gardos *et al*., 1987*a*; Wojcik *et al*., 1991; Sachdev, 1993*a*), 51% had schizophrenia or schizoaffective disorder, 30% mood disorders and 19% minor psychiatric disorders (e.g. anxiety disorders and personality disorders), or non-psychiatric disorders. Thus, the development of tardive dystonia is not exclusively restricted to patients with major psychiatric disorders.

Schizophrenic patients have accounted for only half of the tardive dystonia cases in the reported series. Its overall prevalence among 835 schizophrenics in four studies (Gureje, 1989; Inada *et al*., 1991; Sachdev, 1991; Raja, 1995) was

Table 8 *Improved*[1] *and non-improved tardive dystonia patients at last follow-up*

	Improved *n* (%)	Non-improved *n* (%)
Patients	57 (53)	50 (47)
Gender		
Male	30 (53)	27 (54)
Female	27 (47)	23 (46)
Neuroleptics discontinued	30 (53)	22 (45)
Primary diagnosis		
Schizophrenia	20 (35)	22 (44)
Schizoaffective disorder	9 (16)	6 (12)
Mood disorder	16 (28)	7 (14)
Other	12 (21)	15 (30)
Drugs before tardive dystonia onset		
Neuroleptics only	22 (39)	30 (60)*
Single neuroleptic	25/50 (50)	15/41 (37)
Depot neuroleptics	29/48 (60)	17/41 (41)
Anticholinergics	13 (23)	7 (14)
Lithium	9 (16)	6 (12)
Distribution of dystonia at onset		
Focal	50 (88)	39 (78)
Segmental	6 (11)	9 (18)
Generalized	1 (2)	1 (2)
Distribution of dystonia at maximum		
Focal	9 (16)	7 (14)
Segmental	36 (63)	29 (58)
Generalized	12 (21)	13 (26)
Other drug-induced movement disorder		
Acute dystonic reaction	8 (14)	2 (4)
Parkinsonism	15 (26)	15 (30)
Akathisia	13 (23)	11 (22)
Tardive dyskinesia	22 (39)*	10 (20)**
History of ECT prior to tardive dystonia onset	14 (25)	8 (16)
History of trauma prior to tardive dystonia onset	15 (26)	12 (24)
Family history of		
psychiatric disorder	16 (28)	13 (26)
movement disorder	13 (23)	6 (12)
Treatment of tardive dystonia		
Tetrabenazine	25 (44)	20 (40)
Anticholinergics	44 (77)	40 (80)
Benzodiazepines	37 (65)	30 (60)
Botulinum toxin	18 (32)	13 (26)
Age at last follow-up (years; mean ± SD)	46.7 ± 16.3	45.9 ± 15.3
Total duration of follow-up		
from tardive dystonia onset (years; mean ± SD)	9.1 ± 6.4	7.1 ± 5.8
Duration of tardive dystonia (years; mean ± SD)	8.0 ± 6.0	7.1 ± 5.8
Age at onset of tardive dystonia (years; mean ± SD)	37.9 ± 13.3	38.8 ± 14.2
Duration on neuroleptics		
prior to tardive dystonia onset (years; median)	4.2	6.0
Duration on neuroleptics		
after tardive dystonia onset (years; median)	3.5	2.7
Total duration on neuroleptics (years; median)	9.0	10.0
Duration of discontinuation	3.0	2.0
after tardive dystonia onset (years; median)		

[1]All patients with improvement (mild, moderate) or remission (partial, complete) at last follow-up.
*$P = 0.04$, odds ratio = 0.42 (95% CI, 0.19–0.91); **$P = 0.056$, odds ratio = 2.5 (95% CI, 1.05–6.02).

2.8% (range 2–5.6%), which is the same as that among psychiatric patients in general. Mood disorders may predispose patients to develop classical tardive dyskinesia (Davis *et al*., 1976; Rosenbaum *et al*., 1977; Rush *et al*., 1982; Wolf *et al*., 1982; Yassa *et al*., 1984, 1992; Mukherjee *et al*., 1986; Gardos *et al*., 1987*b*; Casey, 1988;), and it has been speculated that they may also predispose patients to develop tardive dystonia (Yadalam *et al*., 1990; Gabellini

et al., 1992). However, none of 114 patients with mood disorders in three prevalence studies (Gureje, 1989; Inada *et al*., 1991; Raja, 1995) developed tardive dystonia. Raja (1995), in a study of 200 psychiatric in-patients, concluded that psychiatric diagnosis was not associated with an increased risk of developing classical tardive dyskinesia or tardive dystonia.

Neuroleptic drugs and duration of exposure

Many different drugs were implicated in the development of tardive dystonia in our patients. We cannot conclude that certain drugs are more toxic than others, since the order of frequency we found may simply reflect the frequency of their prescription. However, even neuroleptics conventionally considered 'safe' (e.g. sulpiride or thioridazine) were among the 'offending' drugs. Sulpiride-induced tardive dystonia has been reported previously in a single case (Miller and Jankovic, 1990), and antiemetic drugs such as prochloperazine (four cases) and metoclopramide (two cases), frequently prescribed in the non-psychiatric population for vertigo, nausea, vomiting or other gastrointestinal complaints, were also 'offending' drugs in our series. Both prochlorperazine and metoclopramide individually and in combination have been reported to cause tardive dystonia (Chateau *et al*., 1966; Kang *et al*., 1986; Miller and Jankovic, 1989; Factor and Matthews, 1991). In five of our patients, the 'offending' drug was a formulation of a neuroleptic (fluphenazine or perphenazine) combined with an antidepressant ('Minipress' and 'Minitran' are the common trade names).

No individual classical DRA appears to be without risk of provoking tardive dystonia. This is an important issue, since 22 (21%) of our patients were prescribed neuroleptics for conditions, psychiatric or other, for which there was no indication for their use (e.g. anxiety disorder), or when alternative drugs were available (e.g. vertigo and nausea) and only three of them remitted.

Our findings are also consistent with the observation of Burke *et al*. (1982) and Kang *et al*. (1986) that there is no safe period after the introduction of DRAs regarding the risk for developing tardive dystonia.

Phenomenology of tardive dystonia

The phenomenology of tardive dystonia can be indistinguishable from that of primary (idiopathic) dystonia (Kang *et al*., 1986). However, these authors suggested that retrocollis and trunk hyperextension seemed to occur more frequently in tardive than in primary dystonia. We found that retrocollis and antecollis were more frequent in tardive than in primary cervical dystonia. Another intriguing, but unexplained, finding was the right-sided predominance of torticollis in tardive cervical dystonia. Also, trunk hyperextension seems to occur more commonly in tardive dystonia than in patients with adult onset primary axial dystonia, who commonly have flexion spasms (Bhatia *et al*., 1997). Thus, differences in the clinical pictures of tardive and primary dystonia seem to exist.

Outcome of tardive dystonia

One aim of our study was to provide data on the long-term prognosis of this disorder and to identify factors possibly related to outcome.

Unfortunately, once developed, tardive dystonia is usually persistent. After a mean of ~8.5 years follow-up, only 15 (14%) of our patients had a remission. Only four of the 15 patients remitted after $>$8.5 years from onset. Similar remission rates of 12% and 7.5% were reported by Burke *et al*. (1982) and Kang *et al*. (1986), respectively, but with much shorter follow-up times. Putting together all the reported case series (Table 9), the overall remission rate is ~10% (21 out of 231 patients) after an mean follow-up period of 6.6 years.

The discontinuation of all DRAs seems to be the most important factor related to remission, although the statistical association was not very strong in our series. Permanent discontinuation of DRAs increased the chances of remission fourfold; 12 out of 54 patients (22%) in whom DRAs were withdrawn remitted versus three out of 52 patients who continued them. Even discontinuation of DRAs for any period after the onset of their tardive dystonia, increased the patient's chances of remission compared with those who continued to take neuroleptics.

Another factor related to remission was the total duration of DRA treatment (Table 7D). Patients with $\leqslant$10 years on DRAs had five times more chance to remit than those with $>$10 years exposure. Tardive dystonia is likely to be permanent in patients who continue on DRAs for $>$10 years. Almost half of our patients had experienced no improvement of dystonia at last follow-up as also noted in all previous studies. A few of our patients had worsened many years later, despite the conventional belief that tardive dystonia progresses over months to a few years but remains static thereafter.

None of the various treatments used in our patients seemed to influence the final overall outcome of tardive dystonia. It is debatable whether clozapine has any special therapeutic effect in tardive dystonia as some reports have claimed (Van Putten *et al*., 1990; Lieberman *et al*., 1991; Lamberti and Bellnier, 1993; Trugman *et al*., 1994; Friedman, 1994; Adityanjee and Estrera, 1996); instead the withdrawal of other neuroleptics may account for the improvement at least in some of these reported cases (Friedman, 1994). Botulinum toxin seems to exert the same symptomatic relief in tardive as in primary focal dystonia (Kiriakakis *et al*., 1997). The significant negative association between the occurrence of remission and use of benzodiazepines was probably due to reverse causality, since non-remitting patients were more likely to use benzodiazepines as a second line treatment.

The persistence of tardive dystonia, and the association of remission with duration of neuroleptic use and withdrawal

Table 9 *Remission rates of tardive dystonia reported in various studies*

Study	Patients (*n*)	Follow-up from onset (years)*	Follow-up from DRA withdrawal (years)*	Remitting patients (*n*)
Burke *et al*. (1982)	42 (9[†])	3.1	1.5	5 (1[‡])
Gimenez-Roldan *et al*. (1985)	9	4.7	n.s.	0
Kang *et al*. (1986)	67	~4.8	2.8	5
Gardos *et al*. (1987*a*)	10	~5.2	n.s.	0
Wojcik *et al*. (1991)	29	7.3	n.s.	0
Kiriakakis *et al*. (1997)	107	8.3	3.9	15

*Means. [†]Excluding 16 and 17 patients followed up later by Kang *et al*. (1986) and Kiriakakis *et al*. (1997), respectively. [‡]Excluding one and three patients followed-up later by Kang *et al*. (1986) and Kiriakakis *et al*. (1997), respectively. Approximation (~) = not stated explicitly, but calculated by us; n.s. = not stated at all.

of DRAs, suggests that the pathogenic changes causing tardive dystonia may be rendered irreversible after long-term use of such drugs. There is some evidence that DRAs may exert toxic effects on neurons and interference with cell membrane function and inhibition of respiratory chain enzymes (Desci, 1961; Richter, 1965). Recent findings point to a relationship between DRAs and free radicals, indicated by products of enhanced lipid peroxidation in the CSF of some patients taking phenothiazines (Pall *et al*., 1987; Halliwell and Gutteridge, 1989). Prolonged neuroleptic use could lead to increased free radical formation, by increased catecholamine metabolism and production of hydrogen peroxide or by increasing brain iron (Borg and Cotzias, 1962; Rajan *et al*., 1974; Lohr *et al*., 1987, 1988; Cadet and Lohr, 1989; Lohr, 1991; Halliwell and Gutteridge, 1989; Ben-Shachar *et al*., 1994). Increased caudate nucleus iron and manganese concentrations have been demonstrated in guinea pigs treated chronically with chlorpromazine (Weiner *et al*., 1977). Neuropathological studies (Campbell *et al*., 1985) and MRI findings (Bartzokis *et al*., 1990) have indicated increased basal ganglia iron levels in tardive dyskinesia patients. Finally, clinical studies have suggested the efficacy of vitamin E, an antioxidant and a free radical scavenger, in the treatment of classical tardive dyskinesia (Lohr *et al*., 1987; Elkashef *et al*., 1990; Egan *et al*., 1992; Dabiri *et al*., 1994).

Pathological evidence for the neurotoxicity of neuroleptics has been found in some animal studies. Striatal cell loss (Nielsen and Lyon, 1978) and altered striatal synaptic patterns (Benes *et al*., 1985) have been reported in rats after prolonged treatment with neuroleptics. Neuropathological studies in tardive dyskinesia patients have shown neuronal loss and gliosis in areas of the basal ganglia (Roizin *et al*., 1959, Hunter *et al*., 1968; Christensen *et al*., 1970; Jellinger, 1977; Kaufman, 1977). Brain CT (Bartels and Themelis, 1983) and MRI studies (Bartzokis *et al*., 1990; Mion *et al*., 1991) have been reported to show various basal ganglia structural changes in patients with tardive dyskinesia, and a recent PET study revealed altered basal ganglia metabolic patterns (Pahl *et al*., 1995).

Is DRA treatment alone sufficient to cause chronic, persistent dystonia, or is tardive dystonia the chance occurrence of primary dystonia in a population of psychiatric patients? A related question is whether DRAs trigger the development of tardive dystonia in individuals who are in some way predisposed to develop this disorder. For example, do these patients carry a gene for primary dystonia, with DRAs triggering the condition? The prevalence of all primary dystonias in the general population of Rochester, Minn., USA has been reported to be 329 per million (Nutt *et al*., 1988) which can be doubled to 658 per million given the fact that in a UK genetic study of primary dystonia, half of identified cases with secondary dystonia were previously unrecognized (Fletcher *et al*., 1990). The lowest reported prevalence of tardive dystonia in psychiatric patients exposed to neuroleptics is 1.5% (Friedman *et al*., 1987), far higher than that in the general population, suggesting a causal role of DRAs in the aetiology of tardive dystonia.

However, the fact that tardive dystonia is not a common side effect of DRAs suggests some underlying vulnerability. Sachdev (1993*b*) found that tardive dystonia patients more frequently had a history of a prior acute dystonic reaction (40% of his 15 patients) and 'essential' tremor (26.7% of his patients) than patients with classical tardive dyskinesia. However, out of 198 patients from our present study and those of Burke *et al*. (1982), Kang *et al*. (1986) and of Sachdev (1993*a*), only 10% had a history of an acute dystonic reaction, a figure similar to that reported for the general psychiatric population (Comaty, 1993). A history of 'essential' tremor prior to dystonia onset was noted in only 3.5% of the 198 patients.

One hypothesis is that these patients with tardive dystonia may be carrying a gene for dystonia whose expression is triggered by DRAs. Since the genetic contribution to adult-onset primary dystonias is not clear, it is difficult to examine this hypothesis. However, if one assumes that all adult-onset idiopathic dystonia cases are genetic, the calculated crude prevalence of dystonia gene(s) carriers would be <6000 per million (0.6%) of the general population. Even this figure is lower than the prevalence of dystonia in DRA-treated psychiatric patients, suggesting that a genetic predisposition to primary dystonia cannot wholly explain the occurrence of tardive dystonia. Moreover, a recent genetic study found that none of 15 Ashkenazi Jewish patients with tardive dystonia

carried the founder mutation of the DYT1 gene (Bressman *et al*., 1997).

However, from our study, there are some hints suggesting that an underlying vulnerability, and possibly a genetic predisposition, may exist, at least in some patients. (i) Two out of 20 first-degree relatives with psychiatric illness who had used DRAs, had also developed tardive dystonia, giving a 10% prevalence, which is higher than that estimated in the general psychiatric population. There are no other reports in the literature of familial occurrence of tardive dystonia. Two other first-degree relatives had a history of classical tardive dyskinesia. Familial-genetic predisposition for classical tardive dyskinesia has been suggested because of reports of patient–relative pairs (Yassa and Ananth, 1981; Weinhold *et al*., 1981;Waddington and Youssef, 1987). Also, familial occurrence of acute dystonic reactions has been reported (Guala *et al*., 1992). (ii) There was a history of trauma just before the onset of dystonia in three of our patients. We know that trauma may precipitate dystonia in patients with a pre-existing liability which is likely to be genetic (Fletcher *et al*., 1991). Therefore it remains possible that another dystonia gene is involved in at least some of the tardive dystonia patients.

Conclusions

The main conclusions from our study can be summarized as follows. (i) Tardive dystonia can develop at any time between 4 days and 23 years after exposure to DRAs and there is no 'safe' period. (ii) Young males seem to be particularly predisposed. (iii) Tardive dystonia occurs in those with psychiatric illness but also in those with other conditions. (iv) The nature of the psychiatric illness does not seem to predispose to the development of tardive dystonia. (v) There are no 'safe' DRAs, as all classes were implicated in causing tardive dystonia. (vi) Although the majority had a focal onset involving the craniocervical region, tardive dystonia tended to spread over the next 1–2 years and resulted in segmental or generalized dystonia in most cases. Patients with a younger onset had a higher chance of the dystonia spreading to involve their legs. (vii) Retrocollis, antecollis and torticollis to the right were significantly more common in tardive dystonia than in primary cervical dystonia. (viii) Once developed, tardive dystonia is a very persistent disorder with a low remission rate of only 14%. (ix) Discontinuation of DRAs increases the chances of remission fourfold. (x) Tardive dystonia is probably irreversible in patients who have been on neuroleptics for >10 years. (xi) Except for botulinum toxin injections, which offered symptomatic relief, none of the various drug treatments tried were found to be consistently beneficial. (xii) Only a very small proportion of patients receiving DRAs develop tardive dystonia, but whether they have an underlying susceptibility and whether that is genetic or due to other factors remains unanswered.

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