Article abstract—It is not widely recognized that antipsychotic drugs can cause late-onset and persistent dystonia. This dystonia, which we call tardive dystonia, is to be distinguished from acute dystonic reactions, which are transient, and from classic tardive dyskinesia, which is a choreic disorder that predominantly affects the oral region. We present 42 patients with tardive dystonia. The age of onset of dystonia was 13 to 60 years. Symptoms began after 3 days to 11 years of antipsychotic therapy. Younger patients tended to have more generalized dystonia. In a few patients, spontaneous remission occurred, but dystonia persisted for years in most. Therapy was rarely a complete success. The most frequently helpful medications were tetrabenazine (68% of patients improved) and anticholinergics (39% improved).

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Tardive dystonia: Late-onset and persistent dystonia caused by antipsychotic drugs

Robert E. Burke, Stanley Fahn, Joseph Jankovic, C. D. Marsden, Anthony E. Lang, Stephen Gollomp, and Joyce Ilson

That antipsychotic drugs can cause persistent dyskinesias has been recognized since the 1950s.[1,2] The term "tardive dyskinesia" has been applied,[3] because the movements usually occur as a late complication of antipsychotic drug therapy, unlike acute dystonia or parkinsonism, which typically occur earlier. The first reports of the condition described choreic movements affecting predominantly the oral region: tongue protrusion, lip smacking and puckering, and chewing.[4-8] These movements are now recognized as the predominant and characteristic feature. The oral movements are often accompanied by chorea of the hands and feet.[5-9] There may also be myoclonus[10] or dystonia,[9-12] including hyperextension and abduction of the arms, exaggerated lordosis, and pelvic rotation.

There have been a few reports of dystonia as the predominant late and persistent movement disorder caused by antipsychotic drugs. Opisthotonos,[13-15] retrocollis,[5,16,17] torticollis and scoliosis,[18-20] and isolated dystonia of limbs[21] have been described. The dystonia may persist for 4 years without remission.[16] There is little epidemiologic information about ages at risk, predisposing factors, or drugs responsible. The clinical presentation and course are not known. It is not clear whether or how persistent tardive dystonia is related to acute dystonic reactions or other forms of spontaneous chronic dystonia, either idiopathic or secondary.

We report our experience with 42 patients who developed persistent tardive dystonia during or immediately after (within 2 months) treatment with antipsychotic drugs. We call this condition "tardive dystonia" to distinguish it from choreic tardive dyskinesia, which differs clinically. (A similar term was used by Keegan and Rajput[20] for a single patient. The term "tardive dystonia" has been used also to describe the appearance of dystonia months or years after static cerebral injury.[22] We prefer the term delayed-onset dystonia for these cases.[23]) We do not, by this terminology, wish to advocate that tardive dystonia is a separate entity from oral choreic tardive dyskinesia. Both are types of tardive dyskinesia, as they are persistent movement disorders that follow chronic antipsychotic use. We define dystonic movements as sustained, involuntary twisting movements, generally slow, which may affect the limbs, trunk, neck, or face.[24]

From the Department of Neurology, Columbia University (Drs. Burke, Fahn, Gollomp, and Ilson), the Department of Neurology, Baylor College of Medicine (Dr. Jankovic), and University Department of Neurology of the Maudsley and King's College Hospitals (Drs. Marsden and Lang).

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Address correspondence and reprint requests to Dr. Burke, Neurological Institute, 710 West 168th Street, New York, NY 10032.

Focal dystonia refers to dystonia that remains confined to its site of onset; segmental dystonia involves more than one body region; generalized dystonia involves all four limbs and axial structures.[21] In all cases, other causes of secondary dystonia were excluded by clinical course and laboratory studies. By using the temporal relationship between antipsychotic treatment and appearance of dystonia as the criterion for the diagnosis of tardive dystonia, we may have included some cases that represent the chance occurrence of idiopathic dystonia developing during antipsychotic drug treatment. However, the likelihood of this coincidence is small.

We present two cases of tardive dystonia in detail to illustrate the clinical spectrum. Data from these and the remaining 40 cases as well as 15 cases from the literature are presented in tabular form.

Case reports. Patient 1. This man developed persistent dystonia at age 19 years. The parents were non-Jewish, and there was no family history of dystonia. Birth was abnormal in being 2 weeks premature with a breech presentation. Developmental milestones were delayed; he did not walk until age 2 years. He was diagnosed to be mentally retarded at age 6 years. At age 17, he was placed in an institution because of aggressive behavior. During this time, he was treated with haloperidol 15 mg daily and chlorpromazine 450 mg daily, but it is not known for how long. He was again admitted at age 19 and treated with unknown doses of haloperidol, chlorpromazine, and thioridazine when he developed facial grimacing and abnormal trunk postures that persisted.

On our examination, at age 21 years, he was mentally retarded. There were no Kayser-Fleischer rings on slit-lamp examination. There was intermittent, sustained facial grimacing affecting predominantly the lower face, retrocollis, and opisthotonic trunk extension that was exacerbated by walking, and intermittent, sustained extension movements of the arms. The opisthotonus tended to force him off a chair, and he could not sit. There was no oral chorea. Withdrawal of antipsychotics did not diminish the movement disorder. Treatment with carbamazepine and valproate in succession was without benefit. Tetrabenazine caused sustained, forced jaw opening and oculogyric crisis, and so it was discontinued. Ethopropazine 25 mg four times daily improved the dystonic movements. At most recent examination, age 22 years, he remained much improved on ethopropazine 150 mg each day.

Patient 19. At age 40 years, this man developed anxiety and was treated with fluphenazine 25 mg intramuscularly every month for 12 months. Two months after the cessation of the therapy he noted posterior neck stiffness, and in the next 6 months he noted involuntary pulling of the head backward, making it impossible for him to drive. In the next year, there was involuntary pulling of the head to the left with painful spasms on the right side of the neck and right shoulder. He developed tremor of both hands. As a result of the constant neck muscle spasms, his neck size increased from 15 ½ to 18 inches in 1 year. Loxapine provided some relief of the spasms. Haloperidol and chlorpromazine did not affect the neck dystonia. Examination was unremarkable except for marked hypertrophy of the sternocleidomastoid muscles with retrocollis and slight torticollis to the left. There was mild dysarthria and involuntary right shoulder shrugging. When he walked, there was dystonic posturing of the hands, more on the right. At rest, there was involuntary sustained extension of the left foot. There was a 8- to 10-Hz postural of the hands, arms and shoulders. There were no Kayser-Fleischer rings on slit-lamp examination. Copper studies, serum ceruloplasmin, CSF, and CT were normal. Trihexyphenidyl 10 mg daily improved the painful neck pulling, but he continued to have right shoulder spasms 3 years after the onset of the dystonia.

Results. The age at onset of tardive dystonia ranged from 13 to 60 years in our 42 patients, with a mean of 34 years (tables 1 and 2). Cases in the literature extend the age range from 5 to 89 years.

The age of onset and distribution of dystonia seem to be related (figure). Generalized dystonia tends to occur in younger individuals; segmental or focal dystonias restricted to face, neck, or arms tend to occur in older individuals. The mean age of onset in patients with generalized dystonia was 22.5 years, significantly less than the mean age of 34 years in patients with segmental dystonia ($p = 0.05$; Student t test) or 41.4 years in patients with focal dystonia ($p < 0.005$). The difference in age of onset between patients with segmental and patients with focal dystonia was not significant ($p < 0.1$).

There were 26 men and 16 women in our series, a ratio of 1.6:1. The mean age of dystonia onset for men was 29.0 years, significantly less than the mean age of 41.5 years for women ($p < 0.005$), but there were no definite sex differences for severity of dystonia. Although five of the six patients with generalized dystonia were men, this number was too small to draw conclusions. Sixteen men and 11 women had segmental dystonia (1.45:1), and 5 men and 4 women had focal dystonia (1.25:1).

All classes of antipsychotic drugs were implicated. Aliphatic, piperazine and piperidine phenothiazines, butyrophenones, molindone, and thioxanthines (often in combination) were responsible. Promethazine, a phenothiazine used clinically as an antiemetic, was the offending drug in one case.

It usually was impossible to determine exactly when dystonia started during a particular course of antipsychotic drug treatment, nor could we determine total cumulative doses of drugs prescribed, because either the complete institutional records were unavailable or the patient had unknown access to antipsychotics as an outpatient. However, for each patient we could document when antipsychotic drugs were first prescribed. The interval between that time and the onset of dystonia was recorded (tables 1 and 2).

The average duration of exposure to antipsychotic drugs was 3.7 years. In the younger patients (table 1), the average duration of exposure was 2.8 years

Table 1. Epidemiologic data: Patients with onset of dystonia ≤ 30 years of age

Pt.	Age at onset	Sex	Birth/ development	Primary diagnosis	Antipsychotic drugs	Ethnic	Interval of exposure to antipsychotic drugs prior to dystonia onset
1	19	M	Premature Delayed milestones	Aggressive behavior	Haloperidol Thioridazine Chlorpromazine	A - S	2 years
2	21	M	Premature Minimal brain dysfunction	Anxiety	Trifluoperazine Thioridazine Chlorpromazine	Jewish, Ashkenazic	1 year
3	27	M	Normal	Schiz.	Haloperidol	Jamaican	7 years
4	25	F	Normal	Hyperemesis gravidarum	Promethazine	A - S	3 days
5	17	M	Normal birth Delayed milestones Mental retardation	Aggressive behavior	Haloperidol Thioridazine	A - S	?
6	20	F	Normal	Schiz.	Trifluoperazine Haloperidol	Jewish, Ashkenazic	2 years
7	18	M	Normal	Anxiety	Thioridazine Fluphenazine Haloperidol Chlorpromazine	Jewish	1½ years
8	21	M	? (adopted)	Schiz.	Haloperidol Chlorpromazine Trifluoperazine Molindone	?	1 year
9	26	M	Birth 4 wks overdue Forceps Normal developmental milestones	Schiz.	Chlorpromazine Trifluoperazine Thioridazine Fluphenazine Haloperidol Perphenazine	Jewish	11 years
10	13	M	Normal birth Delayed developmental milestones	Aggressive behavior	Thioridazine Haloperidol Fluphenazine	Italian	1 month
11	18	M	?	Schiz.	Chlorprothixene Trifluoperazine Thioridazine	A - S	10 months
12	22	F	Normal	Schiz.	Trifluoperazine Thioridazine Perphenazine Amitriptyline	?	1 year
13	20	M	Normal birth Delayed development	Acute schizophreniform psychosis	Trifluoperazine Haloperidol Chlorpromazine	Greek	1½ years
14	20	M	Normal	Schiz.	Chlorpromazine Fluphenazine	A - S	3 years
15	22	M	Normal	Acute schizophreniform psychosis	Chlorpromazine Fluphenazine Haloperidol Trifluoperazine	A - S	1 yr, 3 months
16	26	M	Normal	Acute schizophreniform psychosis	Trifluoperazine	A - S	3 years
17	28	M	Normal	Schiz.	Flupenthixol	A - S	10 years
18	13	M	Normal birth Delayed development	Aggressive behavior	Chlorpromazine Thioridazine	A - S	2 years
a*	27	F	?	Acute psychosis	Prochlorperazine	?	5 months
b†	5	M	?	Accidental ingestion	Unknown phenothiazines	?	?
c‡	10	F	Delivered at home Delayed milestones Mental retardation	Accidental ingestion	Unknown phenothiazines	Black	?
d§	5	F	?	Sydenham chorea	Haloperidol	?	1 month
e¶	25	M	?	Schiz.	Trifluoperazine	?	1½ yrs
	25	M	?	Schiz.	Trifluoperazine	?	6 yrs

* Chateau et al (1966).
† Dabbous et al (1966).
‡ Angle and McIntire (1968).
§ Shields and Bray (1976).
¶ Tarsy et al (1974).
? Unknown.
Schiz. Schizophrenia.
A - S Anglo-Saxon.

Table 2. Epidemiologic data: Patients with dystonia > 30 years of age

Pt.	Age at onset	Sex	Primary diagnosis	Antipsychotic drugs	Ethnic	Interval of exposure to antipsychotic drugs prior to dystonia onset
19	41	M	Anxiety	Fluphenazine	Black	1 year, 2 months
20	50	F	Depression	Perphenazine Thiothixene Thioridazine	A - S*	8 years
21	47	F	Anxiety	Haloperidol Others unknown	Hispanic	14 years
22	37	M	Schiz.	Trifluoperazine Haloperidol	Chinese	6 years
23	32	M	Schiz.	Haloperidol	Italian	5 years
24	53	F	Depression	Trifluoperazine	Hispanic	5 years
25	41	F	Schiz.	Fluphenazine Haloperidol	A - S	1 year
26	40	M	Anxiety	Perphenazine	Hispanic	4 months
27	41	F	Depression	Chlorpromazine Thioridazine	?	3 years
28	31	M	Schiz.	Trifluoperazine Thioridazine Haloperidol Thiothixene	Jewish, Ashkenazic	14 years
29	48	F	Schiz.	Chlorpromazine	A - S	1 year
30	52	F	Depression	Perphenazine	?	Years
31	48	F	Depression	Haloperidol Trifluoperazine	A - S	7 months
32	54	F	Schizoaffective disorder	Tricyclic anti-depressants Phenothiazines	A - S	4 years
33	35	F	Schiz.	Fluphenazine; Other phenothiazines	A - S	Many years
34	41	M	Schizoaffective disorder	Fluphenazine Flupenthixol	Jewish, Ashkenazic	1½ years
35	47	M	Schiz.	Unknown antipsychotics	A - S	many years
36	34	M	Schiz.	Flupenthixol Pimozide	Jewish	1½ years
37	47	M	Schiz.	Flupenazine Flupenthixol	A - S	9 months
38	39	F	Schiz.	Trifluoperazine	A - S	3 years
39	34	M	Schiz.	Chlorpromazine Thioridazine Flupenthixol	A - S	7 years
40	32	F	Schizo-affective	Pimozide	A - S	4 years
41	57	F	Depression	Fluphenazine Amitriptyline	A - S	10 years
42	60	M	Manic-depressive	Haloperidol Chlorpromazine Thioridazine	?	1 year
a†	46	M	Depression	Chlorpromazine Other unknown tranquilizers	?	3 years
b‡	74-89	F	?	'Neuroleptics'	?	"A long time"
c§	40	F	Schiz.	Chlorpromazine Trifluoperazine Thioridazine	?	20 years
d¶	34	F	Schiz.	Trifluoperazine	Jewish	10 months

* A - S Anglo-Saxon.
† Druckman et al (1962).
‡ Harenko (1967), 6 cases.
§ Keegan and Rajput (1973).
¶ Crane (1973).

(range, 3 days to 11 years); in the older patients, the average duration was 4.4 years (range, 4 months to 20 years). This tendency for earlier onset in younger patients was not significant ($p < 0.3$). Although tardive dystonia usually developed after years of antipsychotic drug treatment, it occurred within 3 days in patient 4 and 1 month in patient 10. We included these patients as examples of tardive dystonia, because their dystonia was chronic.

The duration of drug therapy did not correlate with severity of dystonia. The average duration of drug exposure was 2.4 years for generalized dystonia, 3.4 years for segmental dystonia, and 5.7 years for focal dystonia. There was no difference in duration of exposure in men (3.5 years) and women (4.0 years).

Several primary diagnoses were represented. Some patients had conditions for which antipsychotic drugs are not indicated, such as anxiety (n = 5) or "aggressive behavior" (n = 4). Other conditions included schizophrenia (n = 18), acute schizophreniform psychosis (n = 3), depression (n = 7), schizo-affective disorders (n = 4), and hyperemesis gravidarum (n = 1).

Among the younger patients, information about birth and development was available in 16. At least one was abnormal in six patients (38%). No patient had a family history of dystonia. Ethnic backgrounds included: Anglo-Saxon (n = 20), Jewish (n = 8), Italian (n = 2), Greek (n = 1), Pakistani (n = 1), Hispanic (n = 3), Chinese (n = 1), and Jamaican (n = 1). Five (12%) had a history of acute dystonic reactions early in the course of antipsychotic drug treatment.

In general, dystonia was insidious in onset, progressive for months or years, and then persistent but static for years (tables 3 and 4). A few patients, such as patient 4, were maximally disabled in a few weeks, but most progressed for a longer time while they continued to receive antipsychotics. All but three patients had the onset of their dystonia during antipsychotic treatment. Patients 24 and 19 developed dystonia 2 months after antipsychotic drugs were discontinued; patient 30 developed dystonia "shortly after" treatment. Three patients (patients 11, 22, and 25) developed torticollis after prolonged antipsychotic treatment; movements resolved when drugs were discontinued but recurred and persisted after a later course of treatment.

Usually, a single body region was affected with dystonia at the onset but occasionally, multiple sites were involved; consequently, the number of body regions initially involved in the following data exceeds the number of patients. For all 42 patients, the face or neck was the first region affected in 29 of 43 instances; among the younger patients, face or neck was first affected in 11 of 20 instances.

The clinical appearance of dystonia was identical to that seen in idiopathic torsion dystonia or secondary dystonia. For example, patients with focal tardive dystonia (torticollis, blepharospasm, or oromandibular dystonia) were identical in appearance to patients with idiopathic focal dystonia. The pattern of dystonia distribution in our younger patients was distinctive, affecting face or neck in 16 of 18; none had dystonia of the leg or trunk without face or neck involvement (fig). Face, neck, arms, or trunk often were involved when the legs were normal. Six patients (14%) had generalized dystonia; most (27 of 42; 64%) had segmental dystonia; the remainder (9 of 42; 21%) had focal dystonia, usually restricted to face or neck. Only patient 17 became bedridden because of tardive dystonia. In 16 patients, there were other movement disorders in addition to dystonia. Eight had an oral chorea with masticatory movements typical of tardive dyskinesia; three young patients had myoclonus, and one of these patients had oral chorea as well; two patients had chorea of the hands; four older patients had tremor.

Patients were followed from 9 months to 11 years after the onset of dystonia, with a mean of 3.1 years. Antipsychotic medication (excluding tetrabenazine) was stopped in 29 patients, and these patients have been followed from 1 month to 6 years since discontinuation of antipsychotic drugs, with a mean of 1.5 years. Dystonia persisted in 37 of the 42 patients, including 24 of the 29 patients who stopped taking antipsychotic medication. The longest time that tardive dystonia persisted after discontinuation of antipsychotic drugs was 6 years (patient 30).

In several patients, there was a transient remission of symptoms when the dose of antipsychotic drug was increased. We have not, however, considered such cases as remissions, because none of them had prolonged relief of symptoms. Five patients had true remissions of dystonia (patients 4, 15, 26, 34, and 36). They had been treated with antipsychotic drugs for 3 days, 1.25 years, 4 months, 1.5 years, and 1.5 years, respectively, before the onset of dystonia. The interval from onset of dystonia to remission was determined by our definition of remission, which included cessation of all drug therapy. Remission was achieved at 1, 4, 1.5, 1.5, and 4 years, respectively, after the onset of dystonia.

There were no consistent abnormalities in diagnostic studies. Ten patients had examination of CSF; one showed a slightly increased protein (85 mg per deciliter). Seventeen patients had CT scans. Five showed cerebral atrophy (patients 2, 25, 29, 39, and 42); one showed slight cerebellar atrophy (patient 32). Fourteen patients had EEGs, all of which were normal.

Dystonia was treated with several drugs (tables 3 and 4). Therapy was often difficult and rarely a complete success. No single class of drugs emerged as universally helpful. An increase in dose of an-

Table 3. Clinical data: Patients with age of onset ≤ 30 years

Pt.	Other movements	Duration of dystonia; status at follow-up	Interval of follow-up after discontinuation of antipsychotics**	Treatment	
				No benefit	Benefit
1	No	3 yrs; persistent	2 yrs	Tetrabenazine Carbamazepine Valproate	Ethopropazine
2	Oral chorea, Myoclonus	3 yrs; persistent	1.5 yrs	Clozapine Diphenhydramine Trihexyphenidyl	Haloperidol Tetrabenazine
3	No	1.5 yrs; persistent	4 mos	—	Carbamazepine
4	No	1.5 yrs; minimal dystonia	6 mos	Diphenhydramine Diazepam	Benztropine Haloperidol
5	Chorea arms	4 yrs; persistent	1 mo	Deanol	—
6	Oral chorea	5 yrs; persistent	None; remains on antipsychotics	Deanol Lithium Clonazepam Choline Reserpine Baclofen Diazepam Tetrabenazine	Ethopropazine
7	Myoclonus	2.5 yrs; persistent	2 yrs	Propranolol Reserpine Baclofen Choline Lecithin Clonidine Trihexyphenidyl	Tetrabenazine plus α-methyltyrosine
8	No	9 mos; persistent	None; remains on antipsychotics	Deanol Choline Diazepam	—
9	Oral chorea	2 yrs; persistent	1.5 yrs	Deanol Choline Lecithin Lithium Diazepam	—
10	No	4 yrs; persistent	None; remains on antipsychotics	Clonazepam	Tetrabenazine
11	No	5 yrs; persistent	3 yrs	Diphenhydramine Choline Diazepam	Trihexyphenidyl
12	Myoclonus (levodopa-induced)	1 yr; persistent	6 mos	Deanol Trihexyphenidyl Diphenhydramine Carbamazepine Physostigmine Reserpine Bromocriptine	Tetrabenazine plus Cyclobenzaprine plus Chlorazepate

continued

Table 3. (continued)

Pt.	Other movements	Duration of dystonia; status at foplow-up	Interval of follow-up after discontinuation of antipsychotics**	Treatment	
				No benefit	Benefit
13	Oral chorea, Chorea hands and feet	3 yrs; persistent	3 yrs	Pimozide plus Tiapride	Tetrabenazine
14	No	11 yrs; persistent	yrs	Pimozide L-dopa Lithium Oxiperamide	Diazepam Tetrabenazine R Thalamotomy
15	No	4 yrs; minimal residual (90% improved)	None; remains on antipsychotics	Tiapride Benztropine Clonazepam	Pimozide
16	No	2 yrs; persistent	14 mos	Phenobarbital Diazepam Choline	Procyclidine Tetrabenazine
17	No	Dystonia persistent until death by suicide 6 years after onset	None; remained on antipsychotics	Tetrabenazine Amantadine Valproate Deanol Clonazepam Lorazepam Flurazepam Choline	Pimozide Bilateral thalamotomy
18	No	1.5 yrs; persistent	1 mo	—	—
a*	Tremor	?	?	—	—
b†	No	2 yrs; persistent	2 yrs	Diphenhydramine Benztropine	—
c‡	No	7 yrs; persistent	7 mos	—	Diphenhydramine Benztropine
d§	No	5 yrs; persistent	5 mos	Diphenhydramine Benztropine Deanol Physostigmine Reserpine L-dopa	—
e¶	General restlessness	1 yr; persistent	None	Diphenhydramine Benztropine Dantrolene Propranolol Deanol	Haloperidol
	Chorea arms, tongue	3 yrs; persistent	None	Diphenhydramine Trihexyphenidyl Diazepam L-dopa	Haloperidol

* Chateau et al (1966).
† Dabbous et al (1966).
‡ Angle and McIntire (1968).
§ Shields and Bray (1976).
¶ Tarsy et al (1974).
** Excluding reserpine and tetrabenazine.

Table 4. Clinical data: Patients with age of onset > 30 years

Pt.	Other movements	Duration of dystonia; status at follow-up	Interval of follow-up after discontinuing antipsychotics*	Treatment	
				No benefit	Benefit
19	No	3 yrs; persistent	3 yrs	Haloperidol Chlorpromazine	Trihexyphenidyl Propranolal
20	No	2 yrs; persistent	1 yr	Deanol α-methyltyrosine	Haloperidol Tetrabenazine
21	No	2 yrs; persistent	None; remains on antipsychotics	Barbiturate L-dopa Tetrabenazine	—
22	No	1 yr; persistent	None; remains on antipsychotics	Haloperidol Trihexyphenidyl	—
23	No	10 months; persistent	None; remains on antipsychotics	Haloperidol Benztropine Ethopropazine Tetrabenazine	
24	Oral chorea Tremor	2 yrs; persistent	None; remains on antipsychotics	Haloperidol Pimozide Reserpine α-methyltyrosine Deanol Valproate Baclofen Amantadine Diazepam	Clonazepam Lecithin
25	Chorea arms	9 mos; persistent	None; remains on antipsychotics	α-methyltyrosine Trihexyphenidyl	Haloperidol
26	No	Dystonia remitted; 2 yrs	Dystonia remitted in 1 yr after discontinuation	—	—
27	Oral chorea	2 yrs; persistent	1½ yrs	Haloperidol Reserpine Deanol Diphenhydramine	Trihexyphenidyl Ethopropazine
28	No	4 yrs; persistent	None; remains on antipsychotics	Pargyline Clonazepam Propranolol Diazepam Biperiden	Tetrabenazine
29	Tremor	5 yrs; persistent	?	—	—
30	No	6 yrs; persistent	6 yrs	—	—
31	No	3 yrs; persistent	2 yrs	Tetrabenazine L-dopa Diazepam Haloperidol Trihexyphenidyl Carbamazepine	
32	No	6 yrs; persistent	2 yrs	Trihexyphenidyl Diazepam Procyclidine Lithium	—

continued

Table 4. (continued)

Pt.	Other movements	Duration of dystonia; status at follow-up	Interval of follow-up after discontinuing antipsychotics*	Treatment	
				No benefit	Benefit
33	No	7 yrs; persistent	None; remains on antipsychotics	Procyclidine Lorazepam	Pimozide
34	No	1½ yrs; minimal residual (90% improved)	6 mos	—	—
35	No	2 yrs; persistent	None; remains on antipsychotics	—	—
36	Oral chorea	4 yrs; minimal residual	6 mos	—	—
37	Tremor L arm	4 yrs; persistent	2 yrs	Thiopropazate Valproate Phenytoin	Tetrabenazine Choline
38	Oral chorea	2 yrs; persistent	1 mo	L-dopa Amantadine	Thiopropazate Tetrabenazine
39	No	10 mos; persistent	10 mos	Diazepam Benztropine Orphenadrine Procyclidine Pimozide	Valproate Tetrabenazine
40	Tremor (prior to drug treatment)	1 yr; persistent	1 yr	—	—
41	Tremor	3 yrs; persistent	2 yrs	Diazepam Clonazepam Temazepam	Orphenadrine
42	Tremor	3 yrs; persistent	2 yrs	Nitrazepam	Tetrabenazine
a†	"Restless" movements	2 yrs; persistent	2 yrs	Benztropine Phenobarbital Chlordiazepoxide Trihexyphenidyl Amobarbital Mepiridine	Thalamotomies (transient relief)
b‡	?	?	?	?	?
c§	No	5 yrs; persistent	5 yrs	L-dopa	—
d¶	Tics Chorea	4 yrs; persistent	3½ yrs	—	—

* Excluding reserpine and tetrabenazine.
† Druckman (1962).
‡ Harenko (1967).
§ Keegan and Rajput (1973).
¶ Crane (1973).

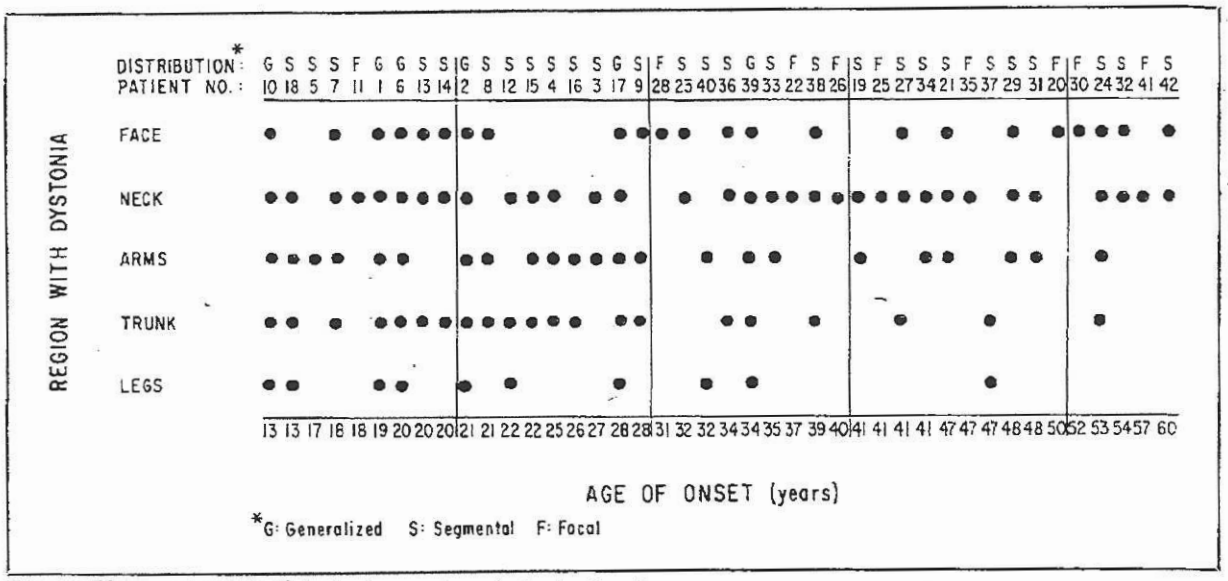

Figure. The effect of age of dystonia onset on dystonia distribution.

tipsychotic drugs commonly suppressed dystonia, and we occasionally used haloperidol, for example, in the acute management of particularly severe cases. However, they did not help in every case. Most of our experience has been with tetrabenazine and anticholinergics. Of 19 patients treated with tetrabenazine, 13 (68%) showed some benefit. Of 18 patients treated with anticholinergic drugs (trihexyphenidyl, benztropine, procyclidine, and ethopropazine), 7 (39%) were helped. Occasionally these drugs had considerable benefit. Patient 1 showed marked improvement with ethoproprazine; patient 2 showed substantial, prolonged benefit from tetrabenazine. Twenty-seven patients were treated with drugs intended to diminish central dopaminergic transmission, either by dopamine depletion (tetrabenazine) or dopamine receptor blockade (e.g., phenothiazines). Improvement occurred in 12 (44%) patients, worsening in six (22%). In nine patients (33%), there were mixed results with these agents, some causing improvement and others worsening dystonia. Thirteen patients were treated with drugs intended to enhance central cholinergic transmission (deanol, lecithin, and choline), and two (15%) showed some benefit.

Discussion. Our criteria for the diagnosis of tardive dystonia were: (1) the presence of chronic dystonia, (2) a history of antipsychotic drug treatment preceding or concurrent with the onset of dystonia, (3) exclusion of known causes of secondary dystonia by appropriate clinical and laboratory evaluation, and (4) a negative family history for dystonia. The clinical course and diagnostic studies did not support a diagnosis of any of the known causes of secondary dystonia, including Huntington disease, Parkinson disease, Hallervordern-Spatz disease, cerebral lipidosis, or mass lesions.[25] Wilson disease was ruled out in each case by laboratory studies of copper metabolism and slit-lamp examination. Tardive dystonia cannot be distinguished from Wilson disease on clinical grounds alone, and so appropriate diagnostic studies must be done, regardless of exposure to antipsychotic drugs.

Some of these patients could be examples of idiopathic torsion dystonia appearing coincidentally with antipsychotic drug use. The clinical features of idiopathic dystonia are variable; the family history may be negative in autosomal-recessive cases and in autosomal-dominant cases where formes fruste go unrecognized by family members.[26] Nevertheless, these cases of tardive dystonia considered collectively seem likely to be distinct from idiopathic dystonia, implying that long-term antipsychotic drug treatment may induce chronic dystonia. Some clinical differences between tardive dystonia and idiopathic dystonia can be discerned. Tardive dystonia is characterized by early involvement of the face or neck, even in younger patients. None of the young patients had leg or trunk involvement in the absence of dystonia of the face or neck. In contrast, idiopathic torsion dystonia commonly begins in the limbs (80% of patients in Marsden and Harrison's series[27]), particularly in younger patients, and not uncommonly it affects legs or trunk in the absence of face or neck movements. There is a tendency for tardive dystonia to be less often generalized than idiopathic dystonia. Among our young patients (≤ 30 years at onset), 5 of 18 (28%) developed generalized dystonia. In idiopathic dystonia, among patients with onset at 11 to 30 years (the group that is most comparable by age to our tardive dystonia patients), 6 of 13 (46%) developed generalized dystonia.[27] Tardive dystonia led to a chronic bedridden state in only 1 of our 42 patients, whereas 33% of patients

with idiopathic dystonia become so disabled.[27] A final distinguishing feature of tardive dystonia is the occasional presence of other abnormal involuntary movements such as oral chorea or myoclonus, which occurred in 11 of our patients. These movements are not usually seen in idiopathic dystonia.

In spite of these clinical differences between tardive and idiopathic dystonia, it will be impossible in many cases to distinguish between them, especially in older individuals with tardive dystonia restricted to face or neck. Except for a history of antipsychotic drug use, these individuals may be identical to patients with idiopathic torticollis or blepharospasm-oromandibular dystonia (i.e., Meige syndrome. We prefer to reserve use of this eponym for idiopathic cases of facial dystonia, since Meige's report antedated use of antipsychotic drugs).

Among our six patients with abnormal birth or development, it was also not possible on clinical grounds to exclude delayed-onset dystonia resulting from perinatal injury coincident with use of antipsychotic drugs.[23] The latter diagnosis would be suggested by unilateral dystonia or focal abnormalities on EEG or CT. In the absence of such features, however, these two conditions may be clinically indistinguishable. The difficulty of distinguishing between tardive dystonia, delayed-onset dystonia, and idiopathic dystonia is compounded, because they might act synergistically in an individual to cause dystonia. There is no adequate control group for our series of patients; therefore, we cannot conclude that birth injury is a predisposing factor for the development of tardive dystonia. It may be simply an associated factor. However, other authors[18] have suggested that birth injury may predispose to the development of dystonia, and our findings are at least compatible with that belief. Birth injury also has been implicated as a predisposing factor for dystonia induced by phenytoin[28] and carbamazepine.[29] Birth injury may also influence the expression of inherited dystonia. In Eldridge's[26] extensive survey of individuals with dystonia in the United States, three categories of patients seemed likely to have inherited dystonia; category IA (typical dystonia, Jewish descent), category IIA (typical dystonia, Jewish descent, parent and child affected), and category VA (typical dystonia, non-Jewish, with parent and child affected). Among the 93 patients in these categories, 23 (25%) had abnormal birth or developmental histories where that information was available.

Some other characteristics of tardive dystonia deserve comment. Younger patients with tardive dystonia, idiopathic dystonia,[27] and acute dystonic reactions[30,31] are more likely to develop generalized dystonia. Aging may confer protection against generalized dystonia, but the nature and mechanism of this protection is unknown. Most of our older patients were women, and dystonia was usually restricted to the face or neck; tardive dyskinesia is also more common in older women.[7-13,30,32,33] However, female preponderance among tardive dyskinesia patients has been questioned,[34] and our findings may also be due to bias in a series of referred patients, undoubtedly selected for severity and persistence of dystonia. Female sex may be a risk factor for tardive dyskinesia only in older and more severe cases.[35-37] It is premature to suspect that endocrine factors associated with female aging are relevant to the pathogenesis of tardive dystonia.

Like oral choreic tardive dyskinesia, tardive dystonia is caused by chronic treatment with any of the antipsychotic drugs, and it occurs in patients with various psychiatric and nonpsychiatric illnesses. Although these two types of tardive dyskinesia are clinically distinct, they may occur in combination in the same patient. They both can be persistent. It is possible that children are more likely to get tardive dystonia than oral choreic tardive dyskinesia, because the latter is rare in children.[38] However, our patients are a referred group, and we cannot draw conclusions about the relative prevalence of these two forms of tardive dyskinesia in any age group.

Our retrospective review of therapeutic trials among these patients fails to provide a clear picture of the clinical pharmacology of tardive dystonia. Oral choreic tardive dyskinesia is usually suppressed by dopamine depleting or blocking agents,[39] but tardive dystonia was improved by these agents in only 44% of patients. On the other hand, anticholinergic drugs often exacerbate tardive dyskinesia,[39] but 39% of our patients with tardive dystonia improved with anticholinergic drugs, some remarkably. Without an understanding of the pharmacology of tardive dystonia, treatment is difficult and often unsuccessful. Because therapy often is unsuccessful, and because tardive dystonia can be incapacitating and sometimes persistent, attention must be focused on preventive measures. Tragically, many of these patients were treated with antipsychotics inappropriately for disorders such as anxiety or aggressive behavior. Even if antipsychotics are indicated and a patient develops tardive dystonia, the indications for treatment must be reviewed, especially in younger patients. We believe that early recognition of the syndrome and withdrawal of antipsychotics may permit remission of the condition. In three of our patients, dystonia remitted when antipsychotics were stopped, but the disorder became permanent when antipsychotics were resumed. In addition, the five patients in our series who had remissions of dystonia were exposed to antipsychotic drugs, on the average, for briefer periods than other patients.

If antipsychotic drugs can be stopped, they should be. If the psychiatric illness, untreated, is incapacitating, antipsychotic therapy may need to be

continued in spite of the risk of inducing severe tardive dystonia. In these circumstances, the patient or family should be informed of the possible permanent consequences. If antipsychotics can be stopped and if the motor symptoms are not too severe, we follow the course of the dsytonia for several months without treament, because spontaneous remission may occur. If remission does not occur or if dystonia is severe and causes disabling incapacity, we use tetrabenazine; a second choice is an anticholinergic drug, alone or in combination with tetrabenazine. The existence of tardive dystonia suggests that the neurochemical changes associated with chronic antipsychotic drug treatment may be relevant to idiopathic dystonia. In addition, animal models of drug-induced movement disorders may be relevant to chronic dystonia, for which there is still no animal model.

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