Drug-Induced Extrapyramidal Syndromes

M. H. LADER, PhD, MD, Member, MRC External Staff,
Institute of Psychiatry, University of London

Drug-induced extrapyramidal syndromes are usually clinically indistinguishable from their non-iatrogenic counterparts. The production of complex and varied neurological reactions so consistently by such a variety of compounds has excited continued interest. These effects were first noted nearly 20 years ago: reports of such adverse reactions are published regularly (Shepherd *et al.*, 1968).

Extrapyramidal syndromes induced by drugs, chiefly major tranquillisers, can be divided for convenience into two groups, the reversible and the generally irreversible (Ditfurth, 1967). The former comprise Parkinsonian reactions, akathisia and dystonia; the latter are the dyskinesias, the majority of which, despite some assertions to the contrary (Kline, 1968), persist for months or years.

REVERSIBLE SYNDROMES

Parkinsonism

Although this drug-induced extrapyramidal effect is often dubbed 'pseudo-Parkinsonism', the clinical features closely resemble those of idiopathic Parkinsonism. The mildest form presents as bradykinesia and loss of associated movements, with weakness especially marked in those muscles used in repetitive movements such as walking. Hesitant speech may be noted (Bockner, 1964). In moderate cases the classical triad of tremor, rigidity, and akinesia is present together with facial and pharyngeal immobility, drooling of saliva, 'pill-rolling' movements, and seborrhoea. The characteristic 'simian' postural abnormalities are seen in the drug-induced syndrome, together with festinant gait and impairment of righting responses. Monotony of speech, faint voice, and dysarthria occur; changes in handwriting (micrographia) are sensitive measures of drug-induced Parkinsonism (Haase, 1965; Kemperdick *et al.*, 1967). In severe cases complete immobility may occur.

Akathisia

This syndrome of motor restlessness is sometimes termed 'tasikinesia' (Borenstein *et al.*, 1962). The patient appears agitated, experiences a compulsion to

move about and may complain of anxiety or of the 'jitters'. He constantly shuffles his feet, paces up and down, stands up and sits down repeatedly, changing his position. When standing, he rocks continuously back and forward, shifting from one foot to the other. Wringing of the hands, twisting and interlocking of the fingers, and smacking of the lips may also occur. The condition may be misdiagnosed as an exacerbation of the psychosis for which the drug was originally prescribed, and the dosage raised instead of lowered. The distinguishing characteristic is that only agitation and motor restlessness are increased in akathisia whereas other features of a pre-existing psychosis increase *pari passu* in a spontaneous exacerbation.

Acute Dystonic Reactions

These reactions, sometimes termed acute dyskinesias, are the most dramatic of the extrapyramidal syndromes. There is an abrupt onset of features such as torticollis, retrocollis, facial grimacing and distortions, dysarthria, and laboured respiration. Other phenomena include scoliosis, lordosis, opisthotonus, tortipelvis, and sinuous writhing movements resembling those seen in dystonia musculorum deformans. Bizarre movements of the tongue ('fly-catcher') and jaw may occur; trismus, severe tongue injuries and dislocation of the temporomandibular joint have occurred. Spasms may be very widespread, involving most muscle groups including the bladder. In children, periocular twitches ('winking spasms') may occur. Patients with dystonia may be very distressed indeed (Chaitin, 1968). Most dystonic reactions subside within a few hours or a day or two but occasional severe reactions have been accompanied by hyperpyrexia, disorientation, electrolyte disturbance with marked hyponatraemia, shock and even death (Haan and Tilsner, 1966). Rare cases of persistent dystonias have been recorded (Angle and McIntire, 1968; Chateau *et al.*, 1966).

Another form of this reaction is the oculogyric crisis. The attack begins with a fixed stare, soon followed by upward and sidewards rotation and fixation of the eyeballs. The head is tilted backwards, the mouth opened wide and the tongue protruded. Attacks last a few minutes to several hours. Oculogyric crises used to be considered pathognomonic of post-encephalitic Parkinsonism. That they can be drug induced is a major change in the interpretation of physical signs. The combination of dysarthria, trismus, torticollis, spasm of the muscles of mastication, protrusion of the tongue and, often, oculogyric crises is usually termed the 'neck-face' syndrome.

The differential diagnosis of drug-induced dystonias is difficult and misdiagnosis has been frequent. The trismus and meningismus often simulate tetanus (Gott, 1966), and other diagnoses that have been considered include

meningitis, encephalitis, cerebrovascular accident, catatonic schizophrenia, and strychnine poisoning. The movements are not typical of post-rheumatic or Huntington's chorea ('Therapeutic Dilemmas', 1969). The most abused misdiagnosis is 'hysteria'. In this respect a physician should no more diagnose hysteria from physical signs alone than a psychiatrist should diagnose a neurological complaint from the mental state. Abuse of trifluoperazine by teenagers in the mistaken belief it was amphetamine has resulted in multiple simultaneous cases of dystonia (Fitzgerald and Fitzgerald, 1969). Positive features in favour of a diagnosis of drug induced dystonia are: (*a*) history of ingestion of an appropriate drug; (*b*) repeated spasms without hypertonicity between attacks; (*c*) muscle groups involved varying from attack to attack; (*d*) relatively painless spasms; (*e*) ocular signs commonly present. An injection of an anti-parkinsonian agent may be used as a diagnostic test (Berger and Mackinnon, 1966).

Mixed Clinical States

From the descriptions of the clinical features of the main drug extra-pyramidal reactions, it can be seen that often no clear cut boundaries exist between them. Furthermore, combinations of syndromes are frequent, parkinsonism and akathisia commonly occurring together.

FACTORS AFFECTING INCIDENCE

In common with many unwanted effects of drugs, the more diligent the search, the greater the number of cases found. In the most frequently cited survey, 38·9 per cent of 3,775 patients treated for major psychoses with phenothiazines developed extrapyramidal reactions (Ayd, 1961). With respect to the individual syndromes, 15·4 per cent showed Parkinsonian syndromes, about 21 per cent akathisia, and 2·3 per cent dystonias.

Type of Drug (Table 1)

Reserpine and its analogues are more prone to cause Parkinsonism than the other syndromes. However, the most obvious differences are to be found among the various phenothiazines. The piperazine compounds are the most likely to produce extrapyramidal reactions, especially akathisia and dystonia; the aliphatic side-chain compounds such as chlorpromazine are more likely to produce Parkinsonism; the piperidine group are least likely to induce any such adverse effects (Cohen, 1966). In one study of the comparative effectiveness of phenothiazines in newly admitted schizophrenics, among patients on moderate dosages of chlorpromazine (mean 650 mg/day), the incidence of Parkinsonism was 15 per cent, of akathisia 6 per cent, and dystonia 4 per cent.

TABLE 1. Drugs Causing Extrapyramidal Reactions

Type	*Examples*	*Trade Name*
Rauwolfia alkaloids	Reserpine	Serpasil
Benzoquinolizines	Tetrabenazine	Nitoman
Phenothiazines		
Dimethylaminopropyl	Chlorpromazine	Largactil
Piperazine	Prochlorperazine	Stemetil
	Fluphenazine	Moditen
	Trifluoperazine	Stelazine
	Perphenazine	Fentazin
Piperidine	Thioridazine	Melleril
Thioxanthenes	Chlorprothixene	Taractan
	Thiothixene	Navane
Butyrophenones	Haloperidol	Serenace
	Trifluperidol	Triperidol
Tricyclic antidepressives (dibenzazepines)	Imipramine	Tofranil
	Desipramine	Pertofran
Alphamethyldopa	Methyldopa	Aldomet
L-dopa	L-dopa	

The corresponding percentages for fluphenazine (mean dosage 6 mg/day) were 24, 12 and 7, and for thioridazine (700 mg/day) 4, 5 and 1 (National Institute of Mental Health, 1964). The figures for placebo were not zero but approximated to those for thioridazine, illustrating the subjective and inaccurate nature of the assessments rather than the rate of spontaneous occurrence of these neurological conditions.

The thioxanthenes resemble thioridazine in their paucity of extrapyramidal reactions; the butyrophenones, especially triperidol, are similar to the piperazine-type phenothiazines (Hollister *et al.*, 1965); methyldopa and the dibenzazepines (tricyclic antidepressives) induce only Parkinsonism.

Dosage and Mode of Administration

Chlorpromazine and reserpine, and more recently tetrabenazine, given in small doses have been used in the treatment of idiopathic Parkinsonism. Closely related phenothiazines, diethazine and ethopropazine, are, of course, effective anti-parkinsonian agents. Similarly, small doses of imipramine have ameliorated Parkinsonism although the improvement may be due to a therapeutic effect on co-existent depression.

The incidence of extrapyramidal reactions tends to be dose-related, increasing steeply with rising dosage. However, the variation in dosage required to induce syndromes varies enormously. In one study in which deliberate attempts were made to produce reactions the dosage of trifluoperazine required ranged from 20 to 480 mg/day and presumably reflected individual

differences in pharmacokinetics (Simpson and Kunz-Bartholini, 1968). Dystonic reactions, however, may occur after quite small doses (Gardner-Thorpe, 1969).

Administration of the drug by intramuscular injection is particularly liable to produce extrapyramidal reactions which may be severe and prolonged after injection of one of the depot fluphenazine preparations, the enanthate or decanoate, especially if the patient has not previously had his drug levels gradually increased by some weeks of oral medication. Reactions usually start on the second day after the injection, become worse over the next few days, and then decrease (Hsu *et al.*, 1967).

Patients who develop reactions to low doses of one drug tend to do so with low doses of other neuroleptic compounds (Ayd, 1968; Bhaskaran and Antony, 1965). Moreover, exposure to a previous course of a phenothiazine may result in a higher incidence of reactions at the same dosage levels during a second course of the drug (Simpson and Laska, 1968).

Duration of Treatment

As a general rule, acute dystonic reactions are the earliest extrapyramidal reactions to appear, occurring within a few hours to a week after the start of treatment; at least three-quarters occur within 72 hours. Akathisia usually appears after a week of treatment, but its onset may be delayed. Parkinsonism may not become evident for several weeks. Increase in dose, as expected, often precipitates reactions. Exceptions to the usual times of onset are not unusual, e.g., Parkinsonism has occurred after 24 hours of treatment.

Age and Sex of Patients

As a very rough rule, dystonias tend to occur in the young, akathisia in the middle-aged, and Parkinsonism in the elderly. Although to some extent the age-distribution of drug-induced Parkinsonism mirrors that of idiopathic Parkinsonism, it can be seen at all ages including the neonate (Tamer *et al.*, 1969), and dystonias are not unusual in the middle-aged. The differences in age-incidence of the forms of extrapyramidal syndromes may also partly reflect the varying uses of the different types of tranquillisers in patients of different age groups. For example, dystonic reactions have been frequently reported in children given piperazine phenothiazines in relatively high doses.

In general, males more commonly develop dystonias than females, whereas women appear to be more susceptible than men to Parkinsonism and akathisia. Hormonal factors may be relevant, as oestrogen administration has apparently precipitated Parkinsonism in patients on phenothiazines (Gratton, 1960).

Other Predisposing Factors

There is an increased frequency of extrapyramidal reactions in brain-damaged patients. Leucotomised schizophrenics had a greater incidence of extrapyramidal reactions to butaperazine than a matched group of non-operated patients (Holden *et al.*, 1969).

It has been postulated that there is a genetically determined susceptibility to develop Parkinsonian reactions on major tranquilliser therapy (Myrianthopoulos *et al.*, 1962). This was on the basis of data, not entirely conclusive, that idiopathic Parkinsonism was more common among the relatives of patients who developed drug-induced Parkinsonism than among the relatives of those that did not. In this connexion the experiments of Knopp and his co-workers (1966) are of interest: patients who were taste-sensitive to quinine developed extrapyramidal effects more readily than their taste-insensitive colleagues.

Patients with hypoparathyroidism and hypocalcaemia are especially susceptible to dystonic reactions to prochlorperazine: when normocalcaemic, milder reactions occur to challenge doses. The sensitivity may be related to generalised hypocalcaemia or due to vascular calcifications in the basal ganglia (Schaaf and Payne, 1966).

Relationship between Extrapyramidal Syndromes and Therapeutic Response

All effective major tranquillisers are capable of inducing extrapyramidal effects. At one time controversy existed between those who regarded extrapyramidal effects as an essential prerequisite for an adequate therapeutic response (Deniker, 1960; Flügel, 1956) and those who regarded such responses as irrelevant (Bishop *et al.*, 1965; Hollister, 1967). In other words, is the adverse effect necessary or unnecessary? Various clinicians have concluded that there is no correlation between clinical response and the presence of extrapyramidal signs (Cole and Clyde, 1961; Tetreault *et al.*, 1968) or even that extrapyramidal reactions are accompanied by clinical deterioration (Zolotnitsky, 1968). That thioridazine, although of the same order of clinical effectiveness as fluphenazine, induces far fewer extrapyramidal reactions suggests that such reactions are unnecessary.

Mattke (1968) studied the relationship between therapeutic response to a major tranquilliser and the incidence of both gross and minimal extrapyramidal reactions. He concluded 'that the upper limit of optimal neuroleptic therapy is set by the occurrence of extrapyramidal coarse motor symptoms, but that, on the other hand, psycho-neuroleptic action will not be achieved unless extrapyramidal fine motor inhibition is present as measured by handwriting changes'.

The conjunction of major tranquillising and extrapyramidal reaction-inducing effects may be an historical accident. The novel psychotropic actions of chlorpromazine were discovered accidentally and *ad hoc* animal tests were improvised to screen all further new compounds of this class. As some of the effects which the test compounds are expected to show, e.g. the induction of a 'cataleptic' state, may be detecting extrapyramidal system effects, it is not surprising that all newer compounds have resembled chlorpromazine in this respect. Although it may eventually transpire that major tranquillisers must inevitably interfere with motor function, there is no evidence at the moment to support this conclusion.

Prophylaxis and Treatment

If gross extrapyramidal reactions are unwanted effects, such reactions should be avoided, or treated if they develop. There is a widespread practice of routinely prescribing anti-parkinsonian agents in the mistaken belief that they can prevent the onset of Parkinsonism. These drugs have psychotropic effects in their own right, e.g. orphenadrine is euphoriant, their anticholinergic effects summate with those of the phenothiazine, and, in large doses, toxic confusional states may occur (Bolm, 1969). Consequently, anti-parkinsonian agents should not be indiscriminately prescribed (Hollister, 1969; Raskin, 1968).

There is a wide choice of drugs for the treatment of drug-induced Parkinsonism. Orphenadrine (150–300 mg/day), benztropine (0·5–2 mg at night), benzhexol (2–20 mg/day), and procyclidine (7·5–30 mg/day) appear to be most widely used. The therapeutic effect is usually greater than in non-drug-induced Parkinsonism especially if the condition is mild. If the symptoms are marked the dose of the causative drug should be lowered (Dynes, 1968). Akathisia is more difficult to treat: dosage of the drug responsible should be reduced and sometimes the simultaneous administration of an anti-Parkinsonian agent and a barbiturate is beneficial.

Acute dystonic reactions have been treated with an astonishing variety of drugs, apparently to good effect, including barbiturates, benztropine, biperiden, caffeine sodium benzoate, diphenhydramine, methylphenidate, pethidine, and procyclidine. Biperiden lactate, 2 to 5 mg i.v. or i.m. is usually effective as is diphenhydramine (25 mg i.m.). The offending drug should be discontinued, and another drug less prone to cause dystonic reactions substituted if possible. If the dystonic patient is a child, careful re-assessment of the appropriate dosage is advisable (Melnick and Berger, 1967).

Biochemical and Physiological Mechanisms

There is now much evidence relating idiopathic Parkinsonism to imbalance of dopaminergic and cholinergic mechanisms in the pathways subserving motor control, with cholinergic preponderance (Hornykiewicz, 1966). Similar mechanisms appear to be implicated in drug-induced Parkinsonism. Reserpine, its related compounds, and benzoquinolizines such as tetrabenazine lower the levels of cerebral amines, including dopamine, by interfering with intra-neuronal storage (Shore, 1962). Similarly, α-methyldopa, is known to reduce dopamine levels in rats' brains (Sourkes *et al.*, 1961), probably because its metabolite α-methyldopamine displaces the endogenous amine.

The mechanism involved with the other drugs such as the phenothiazines and butyrophenones is less clearly understood. Although the levels of dopamine in the brain are not altered by chlorpromazine and its congeners, these drugs cause a pronounced rise in the excretion of homovanillic acid, a dopamine metabolite (Pletscher and Da Prada, 1967). This may reflect a compensatory increase in dopamine metabolism due to an inhibition of the transport of amines into the brain cell, possibly at the site of the outer cell membrane. Haloperidol, in large doses, was found to induce tremor of the head in dogs, and a reduction in dopamine concentration in the caudate nucleus (Himwich and Glisson,1967).

If dopamine is involved in drug-induced Parkinsonism then, as in idiopathic Parkinsonism, L-dopa should be beneficial: however, the literature is inconsistent. In view of the greatly increased interest in the therapeutic effects of L-dopa further studies on drug induced Parkinsonism will undoubtedly be carried out.

At the physiological level, chlorpromazine decreases the spontaneous firing rate in most pallidal units but increases the discharge in response to sciatic nerve stimulation (Adey and Dunlop, 1960), suggesting an enhancement and even 'release' of pallidal function by the drug. Increased alpha motor neurone activity has been noted in animals treated with reserpine and chlorpromazine (Roos and Steg, 1964) and presumed from H-reflex studies in man (Zakrzewska, 1966).

GENERALLY IRREVERSIBLE SYNDROMES

Persistent Dyskinesia

This disorder of movement, variously termed persistent, permanent or complex dyskinesia or the terminal insufficiency syndrome has been receiving much attention recently as a late effect of major tranquillisers (Paulson, 1968). The clinical features consist of postural changes such as clumsiness in walking, lordosis, and abduction of the arms together with repeated restless movements

especially of the extremities. Extension, flexion, and spreading apart of the fingers and toes is commonly seen, especially when the patient is not walking or talking. Orofacial movements are common with repeated protrusion of the tongue and smacking of the lips. Or the tongue may remain in the mouth but show writhing, athetoid movements. Grimacing and a fixed stare may be noted. The movements usually cease during sleep but even when awake the patient is often unaware of them (Lowther, 1969). Secondary problems may occur such as inability to retain dentures, dryness of the tongue, and oral sordes.

The incidence of persistent dyskinesias is so dependent on the characteristics of the patient population that is is difficult to produce a meaningful estimate. From a review of the world literature, Paulson (1968) suggested that, at least in the milder form, it is present in 15 to 25 per cent of chronic institutionalised patients on phenothiazines although some prevalence rates reported have been lower (Degwitz *et al.*, 1967; Demars, 1966; Hunter *et al.*, 1964; Pryce and Edwards, 1966).

Persistent dyskinesias may occur in patients on prolonged treatment with reserpine, the phenothiazines, the butyrophenones or the thioxanthenes, and very similar, but reversible dyskinesias, have been reported in patients with idiopathic Parkinsonism treated with L-dopa (Mawdsley, 1970; Peaston and Bianchine, 1970).

With persistent dyskinesias the total amount of drug ingested is more important than the dosage level; many patients have had over a kilogram of chlorpromazine (or its equivalent in other drugs); however, there seems little correlation with the presence of oculocutaneous pigmentation (Wheeler *et al.*, 1968).

One problem is in attempting to relate the condition to prolonged drug usage and age. Women are more prone to develop this condition, especially the aged. However, elderly people who have not received phenothiazines may show similar dyskinesic phenomena of the mouth and tongue especially if they are edentulous. In one survey of the inhabitants of old-age homes, 2 per cent showed mild dyskinesias (Heinrich *et al.*, 1968). It has been suggested that this represents the sucking reflex of the infant reappearing with senile brain disease (Paulson and Gottlieb, 1968). Nevertheless, these restricted movements are dissimilar to the full-blown dyskinetic syndrome. Furthermore, chronically psychotic patients, especially if long-institutionalised, display a variety of stereotyped movements and mannerisms of the face ('schnauzekrampf'). Nonetheless, in one detailed survey, the incidence in drug-treated chronic patients was 12·3 per cent of male and 20·2 per cent of females; age was not a predisposing factor (Heinrich *et al.*, 1968). The total amount of

administered drug was decisive and, as a rule, older patients would have tended to have had more drug. Direct examination of patient populations on drugs has suggested that the incidence of dyskinesias increase with higher dosage. In one study, carried out in the USA and Turkey, the incidence was much higher in the heavily drug-treated American patients than in the relatively drug-free Turkish ones (Crane, 1968).

A more recent controlled evaluation of phenothiazine intake and dyskinesia showed a higher incidence in brain-damaged patients but electroconvulsive therapy was not a factor (Edwards, 1970). No such relationship was evident in two previous surveys (Pryce and Edwards, 1966; Heinrich *et al.*, 1968).

The condition frequently worsens when the phenothiazines are withdrawn, suggesting that the drugs mask the condition. Remission of the syndrome occurs in less than half the cases, but in the remainder further progression is exceptional. Thus, it is unlikely that the condition is related to Huntington's chorea which it closely resembles.

Post-mortem examinations of three dyskinetic patients revealed no specific abnormalities although in a larger series, gliosis of the cortex and degeneration of the substantia nigra was reported (Hunter *et al.*, 1968). No biochemical abnormalities have been detected.

Apart from stopping the drug therapy, if feasible, there is no established therapy, specific or general, appropriate to the condition. Anti-parkinsonian agents are ineffective or may exacerbate the movements. However, thiopropazate dihydrochloride, 30 to 60 mg daily, was extremely effective in treating two patients with well-established dyskinesia; this recent report, if confirmed, offers new hope for the therapy of this condition (Roxburgh, 1970).

CONCLUSIONS

Drug-induced extrapyramidal syndromes present a fascinating picture of a pharmacological lesion. The existence of this very common effect of tranquillisers raises many questions regarding their specificity and mode of action. In some respects, possibly crucial, the resemblance to idiopathic syndromes, especially Parkinsonism, is so close that study of the drug-induced states should be profitable in understanding the physiological and biochemical mechanisms involved in motor control and its pathology. But, at the very least, patients on major tranquillisers merit careful attention to their motor difficulties. Reversible, unwanted drug effects are unpleasant, probably unnecessary, but not catastrophic. Irreversible dyskinesias, on the other hand, are a serious drawback to long-term tranquilliser therapy. Repeated assessment of patients on these drugs is essential and the need for them to continue to receive tranquillisers should be continually reviewed.

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A Latent Scholar

Both Richard Bright and Thomas Addison learnt a lot of their medicine from a failed school boy, a classical late developer who would never have passed the eleven plus examination. Their teacher at the Public Dispensary had stumbled through schools in his native Whitby, silent, unresponsive and never known to open a book of his own volition. After three years with a local apothecary this young man, Thomas Bateman, came south to St George's Hospital, later taking his Edinburgh MD. He came under the influence of Dr Willan, who managed to get him on to the staff of the London Fever Hospital, and he eventually took over Willan's teaching commitments at the Public Dispensary. His essay on the diseases of London and the state of the weather brought him fame and he was consulted by many as the leading authority on diseases of the skin. In 1817 he published *Delineations of Cutaneous Disease*, using Willan's classification, and the book was an immediate best-seller. It became known to the Czar of Russia who asked for a copy of it and any subsequent publications by Bateman to be sent to St Petersburg. In return the Czar sent Bateman a diamond ring worth one hundred guineas.

In the full flood of success Bateman's health gave way. He suffered from severe digestive symptoms, fearful headaches, and blindness in one eye. He was treated with heroic doses of mercury from whose toxic effects he never recovered and he went home to Whitby to die at the age of forty-two years.