TARDIVE DYSKINESIA

by

Anthony John Blowers  J. P.

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ABSTRACT

Tardive dyskinesia is now widely recognised as a neurological disorder associated with the administration of antipsychotic drugs. Prevalence is higher among the elderly. The cause is unknown but the hypothesis of hypersensitivity of post-synaptic dopamine receptors is currently generally accepted. Many therapeutic approaches have been suggested but there is no completely satisfactory treatment at present.

The main purpose of this study was to undertake a survey of the prevalence of the disorder in a sample of elderly subjects who were resident in local authority homes for the elderly, and to determine what drugs were associated with the condition. A total of 500 elderly subjects were examined for dyskinetic movements and a prevalence rate of 15 per cent was identified. Association of tardive dyskinesia with antipsychotic agents, antiparkinsonian agents and the benzodiazepines was investigated.

Preliminary work to the main subject included an evaluation of the various rating procedures, followed by a pilot study in a group of long-stay mental handicap patients.

Following earlier reports of the success of co-dergocrine in treating tardive dyskinesia, a double-blind study was carried out in a group of 43 patients who had been hospitalised for many years and in whom the disorder was firmly established.

The implications for psychiatry of tardive dyskinesia are discussed and the current practices for management of the syndrome are considered. Research strategies are reviewed and, finally, recommendations are made for both the strategy to limit the incidence of tardive dyskinesia and the management of the problem if it arises.
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CHAPTER 1

INTRODUCTION

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1.8 SUMMARY
1.1 **BACKGROUND TO THE STUDY**

"One of the first things I noticed about Old Granny Trill was that she always seemed to be chewing, sliding her folded gums together in a daylong ruminative cud. I took this to be one of the tricks of age, a kind of slowed-up but protracted feasting. I imagined her being delivered a quartern loaf - say, on a Friday night - then packing the lot into her rubbery cheeks and chewing them slowly through the week".

From: *Cider with Rosie*, by Laurie Lee

The tardive dyskinesia syndrome was overlooked for many years, probably because abnormal movements have been common in chronic psychiatric patients for centuries. A senile chorea manifested by chewing movements was observed in the elderly long before phenothiazines were ever used; and the line between some of the abnormal movements seen in patients with presumed tardive dyskinesia and the rocking movements seen in chronically institutionalised mental handicap patients and chronically psychotic patients in the predrug era is hard to define (Cole, 1976).

This project arises because of the concern over the association of tardive dyskinesia with long term antipsychotic medication, and the subsequent effect that this might have on the drug treatment of mental illness. The need for further research in this field has been advocated by many authors (Cole, 1976; Marsden, 1976a; Davis & Casper, 1978; Sovner, 1978; Lancet, 1979). The main objectives of this research are to establish further the relevance of tardive dyskinesia to antipsychotic drug therapy, to determine which antipsychotic drugs are associated with the disorder, and whether any particular drug is less likely to cause tardive dyskinesia.
It is also necessary to establish the extent to which established tardive dyskinesia can be treated, and one such therapeutic agent is investigated and reported. Recommendations are also made in respect of minimising the risks of producing tardive dyskinesia.

1.2 THE PREVALENCE OF ANTIPSYCHOTIC MEDICATION

From the introduction of chlorpromazine in 1952, antipsychotic medication has played a key role in the transformation that has taken place in the treatment of mental illness. Patients previously so unmanageable that they would perhaps have been immured in a mental institution for the rest of their lives have responded to drug treatment and, with suitable rehabilitation measures and adequate domiciliary support, have returned to the community to lead relatively normal lives (Norton, 1978).

George (1978) stated that most doctors would agree that modern antidepressants and tranquillisers have revolutionised the management of psychiatric illness. Because of their effectiveness, and the frequency of mental illness in the community, antipsychotic drugs are now among the most widely prescribed groups of drugs in practice. Parkes (1976) estimated that 250 million prescriptions for antipsychotic drugs, antidepressants and minor tranquillisers are issued yearly in the United States, where 20 per cent of the population use them once or more each year.
1.3 **ADVERSE EFFECTS OF ANTIPSYCHOTIC DRUGS**

"You cannot have therapeutic roses without therapeutic thorns"

Sir Derrick Dunlop

Since their introduction into psychiatry in the early 1950's the antipsychotic drugs have been shown to be remarkably safe compounds. Hall (1977) stated that serious drug side effects are rare and are perhaps the only instances of which journals will publish a single case report. Certain antipsychotic drugs do occasionally cause serious side effects such as agranulocytosis and jaundice, and those of a less serious nature such as oculocutaneous changes, galactorrhoea, amenorrhoea, weight gain, constipation, and disturbances of the central nervous system which include somnolence, Parkinsonism, akathisia, dystonia and persistent dyskinesias (Shepherd, Lader & Lader, 1972; Davis & Casper, 1978).

In considering unwanted effects of antipsychotic drugs, Edwards (1977) observed that most treatment, whether medical or surgical, carries risks, and the price paid for progress in psychopharmacology has been a wide range of adverse effects. Hall (1977) in discussing the choice of medical treatment in schizophrenia concluded that treating a common, chronic and extremely crippling and tragic mental illness with an appalling untreated morbidity and, at times, mortality rate, justifies some therapeutic risks.
1.4 MOVEMENT DISORDERS ASSOCIATED WITH ANTIPSYCHOTIC MEDICATION

Antipsychotic drugs, known also as neuroleptics, have been shown to produce a variety of movement disorders. These may be divided into the extrapyramidal side effects, such as hypokinesia, hyperkinesia, dystonia and myoclonus, and the delayed onset abnormal movements known as tardive dyskinesia.

1.4.1 Hypokinesia, Hyperkinesia, Dystonia and Myoclonus

Extrapyramidal reactions are the most dramatic of the CNS side effects of antipsychotic drugs. The characteristic syndromes which these drugs produce, probably by acting on higher EP centres, are as follows:

hypokinesia associated with rigidity and tremor, as seen in the classical Parkinsonian syndrome;

hyperkinesias of different kinds; choreiform, athetoid and ballistic movement disorders;

dystonia and other dyskinetic states similar to those found in dystonia musculorum deformans (torsion dystonia) and myoclonus (Hornykiewicz & Klawans, 1978).

These side effects are discussed in greater detail in Chapter 2 (2.5.2), and generally speaking they occur within the first few days of treatment and most can be controlled by the addition of anti-parkinsonian drugs (benztropine, procyclidine, diphenhydramine, trihexyphenidyl, orphenadrine, chlorphenoxamine, etc.) (Davis & Casper, 1978).
More recently considerable attention has been focussed on a long-term extrapyramidal syndrome which occurs late in the course of treatment with antipsychotic drugs, and because of the delay in onset of involuntary movements the term "tardive dyskinesia" has been applied.

1.4.2 Tardive Dyskinesia

In a leading article, (Lancet, 1979) tardive dyskinesia is described as a syndrome, or several syndromes, of involuntary movement arising in psychiatric patients taking antipsychotic drugs; in order to meet the definition the disorder must be persistent and must not have preceded the onset of antipsychotic medication. Most of the patients are chronic schizophrenics and the condition begins insidiously with exaggerated and persistent chewing movements, or variations such as sucking and smacking movements, tongue protrusion, grimacing and grunting.

Whilst the cause of tardive dyskinesia is unknown (Task Force, 1980) it has been suggested that antipsychotic drugs produce a chronic blockade of post-synaptic dopamine receptors which increases sensitivity of these receptors to a hyper or supersensitivity state (Rubovits & Klawans, 1972; Klawans 1973a; Gerlach, Reisby & Randrup, 1974; Curzon, 1976; Lader, 1978).

Clinical reports began to appear in the middle 1950's describing involuntary movement disorders in psychiatric patients undergoing treatment with antipsychotic drugs (Ey, Faure & Rappard, 1956; Hall, Jackson & Swain, 1956; & Schonecker, 1957). A review of these reports, and the increasing number of publications reporting many further cases, follows in Chapter 2. Despite the frequency of reports little attention was given to the syndrome.
1.5 THE EFFECT OF TARDIVE DYSKINESIA ON THE USE OF ANTIPSYCHOTIC DRUGS

An editorial in the Lancet (1979) observed that although tardive dyskinesia was first described more than 20 years ago, for a long time recognition of the syndrome had little impact on prescribing habits. Some psychiatrists seemed reluctant even to accept that the mainstay of the treatment of schizophrenia, the antipsychotic drugs, might have irreversible side-effects; others saw the dyskinesia as a reasonable price to pay for good control of psychosis.

Gibson (1978a) mentioned that in treating nearly 400 patients with depot antipsychotics over a 5 year period, 63 of them developed tardive dyskinesia. He observed that depot injections had allowed many people to lead reasonably normal lives outside hospital and that it was surely better to have involuntary movements of the lower face and tongue than to suffer the disturbing perceptions of uncontrolled schizophrenia.

Lader (1970) observed that irreversible dyskinesias are a serious drawback to antipsychotic therapy. This is emphasised by the fact that a wide variety of drugs have been used to treat the symptoms of tardive dyskinesia, and the results have been disappointing (Lancet, 1979).

The relative lack of appreciation of their symptoms by patients suffering from tardive dyskinesia was mentioned in a review article by Granacher (1978), who stated that most chronically psychotic or institutionalised patients showed little or no concern for their malady. The patients who were most likely to be embarrassed by the movements were the neurotic or those with personality disorders. Some individuals were likely to have sufficient truncal and extremity dyskinesia to interfere with their jobs.
This opinion was supported by Gibson (1978b) who in reporting a 22 per cent prevalence of tardive dyskinesia in a study of 374 psychiatric out-patients, stated that in three-quarters of those affected, symptoms were mild and that whilst mild tardive dyskinesia may pass unnoticed among the socially handicapped population of a long-stay hospital ward, its presence in a patient in the community can be distressing to observers.

Paulson (1968) in an investigation involving nearly 500 patients, observed that complex dyskinasias despite their unpleasant appearance rarely disturb patients. The movements usually continue in the absence of awareness and are often worse after exertion. Secondary difficulties may arise such as the inability to retain dentures, or erosion and dryness of the tongue.

Sovner (1978) in presenting filmed records of patients showing tardive dyskinesia, commented that the disorder was one of the most critical problems facing psychiatry in the coming decade. He drew attention to the fact that several law suits were pending in the United States, initiated by people who had become alarmed at the appearance of tardive dyskinesia in their relatives who had been treated with antipsychotic drugs. In conclusion he stated that if the therapeutic gains which have been made in the treatment of psychosis over the past 20 years were not to be undone, then the entire mental health community must address the clinical issues of tardive dyskinesia.

1.6 TARDIVE DYSKINESIA AND SPONTANEOUS DYSKINESIA

One criticism of the concept of tardive dyskinesia is that dyskinesia frequently occurs spontaneously among chronic psychiatric patients, especially the elderly - the group that is also most prone to develop tardive
dyskinesia (Jeste & Wyatt, 1981). Abnormalities of posture and movement were reported in schizophrenic patients before the use of antipsychotic drugs (Marsden, Tarsy & Baldessarini, 1975).

In reviewing 12 major studies, involving a total of 4340 patients comparing the prevalence of dyskinesia among antipsychotic-treated and non-antipsychotic-treated patients, Jeste & Wyatt (1981) reported that 10 of these 12 studies found a significantly higher prevalence among antipsychotic-treated patients. All of the studies were done with chronic patients in psychiatric hospitals or nursing homes. When all 12 studies were taken together, the overall weighted mean prevalence of dyskinesia for chronically institutionalised individuals was 3.25 times greater in the antipsychotic-treated patients.

1.7 STUDY OBJECTIVES

In view of the impact of tardive dyskinesia on the use of antipsychotic medication in the treatment of mental illness, the purpose of the studies described in this thesis was to study methods of assessing tardive dyskinesia, determining prevalence rates in the non-hospitalised elderly and evaluating the effectiveness of a drug in the treatment of the syndrome.

1.7.1 Review of Literature

Chapter 2 outlines the impact of antipsychotic drugs on the treatment of mental illness. The range of effects and side effects observed following administration of these compounds is presented. The emergence of tardive dyskinesia as a late and gradually appearing neurological side effect syndrome is reviewed and its
importance concerning the future use of antipsychotic medication is considered.

1.7.2 Methods of Assessing Tardive Dyskinesia

The fact that there is no currently accepted standard for diagnosis of tardive dyskinesia has meant that it has been nearly impossible to specify precise prevalence rates (Task Force, 1980). In Chapter 3, the various methods employed in assessing tardive dyskinesia are considered. The use of videotapes to test inter-rater and intra-rater reliability is described, and the technique chosen for subsequent studies is detailed, together with a small pilot study to test its reliability.

1.7.3 Pilot Study to Test Rating Technique

Chapter 4 reports on a pilot study carried out in a ward for mentally handicapped patients by two raters in order to establish the reliability and validity of the rating technique for subsequent work.

1.7.4 Prevalence of Tardive Dyskinesia in the Elderly

The aim of this part of the study (Chapter 5) was to examine 500 elderly subjects who were either resident in or attending each day a home for the elderly to establish the prevalence rate of tardive dyskinesia in a moderate sized population sample, and to determine the difference between those treated with antipsychotic drugs and the non-antipsychotic treated group.
1.7.5 Evaluation of Co-d ergocrine in the Treatment of Tardive Dyskinesia

Chapter 6 describes a double-blind evaluation of co-d ergocrine in the treatment of 43 patients showing signs of tardive dyskinesia. This was an attempt to confirm earlier promising open, uncontrolled studies with the compound (Gomez, 1977; Hajioff, 1978).

1.7.6 General Discussion and Recommendations

The implications of these studies are outlined in Chapter 7 together with suggestions for further work. Recommendations are made for preventing tardive dyskinesia, and progress in the development of compounds less likely to cause the syndrome is discussed.

1.8 SUMMARY

This chapter introduces the subject of the study. It outlines the importance of antipsychotic medication in the treatment of mental disorders, and how the antipsychotic drugs have contributed to the rehabilitation of the mentally ill from isolated institutions to the community. The safety of antipsychotic drugs is described and their serious and less serious side effects are listed. The emergence of tardive dyskinesia as a major problem in the long-term use of antipsychotic medication is introduced and its effect on current and future use of antipsychotic drugs is considered.

The main study objectives are set out and the reasons stated as to why they should be undertaken.
# CHAPTER 2

## REVIEW OF LITERATURE

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2.9 SUMMARY.
2.1 HISTORICAL BACKGROUND TO THE TREATMENT OF MENTAL ILLNESS

Disorders of the mind have been the subject of study throughout recorded history and there have been many theories on both the causes and treatment. For the most part these theories have been based on a combination of ignorance and fear of the unknown, and it is only very recently that rational thought has been applied to psychiatric problems.

From Neolithic times when trepanning involving the drilling of holes in the skulls of insane patients to let out evil spirits, the history of psychiatry in Western civilisation has been characterised by the imposition of physical suffering on the patient - whether the approach was active, for example whipping; or passive, such as manacling and the use of the strait-jacket (Sargant 1967; Hamilton, 1978).

The mentally ill were subjected to treatments which included blood letting, dousing with cold water, and centrifugation, and evidence of these latter methods is to be seen in the museum set up at Brookwood Hospital, Surrey. Restraint was frequently used and many of those responsible for the care of "the insane" were concerned only with ensuring custody and control, often by crude physical restraint (Office of Health Economics, 1979). In a lecture at the Institute of Psychiatry, Allenderidge (1979) observed that from at least 1348 it was lawful to beat one's mad kinfolk with a rod if with nothing else; and that from some time before 1482 it was lawful to imprison a lunatic provided you could be fairly sure he was going to burn down a house; and that from the end of the sixteenth century these two circumstances began to appear in the Justices' manuals. In the manual
of 1581 it is stated that "Every man also may take his kinsman that is mad, and may put him in a house, and bind him and beat him with rods, without breach of the Peace" (Lambard, 1581). Allderidge added that the beating with rods was considered to be one of the appropriate remedies for insanity at that time. In suggesting that the care of the mentally ill has been going round in circles for at least the last 750 years, Allderidge (1979) observed that the received version of the history of the care of the insane consists largely of myth and folklore, tempered by a strong dash of wilful ignorance, and is capable of absorbing any number of incongruous features. Depending on where the version was received, nothing happened at all, or the mentally disordered were indiscriminately exorcised, or burnt, or left to wander at will, or chained up and beaten, or all four.

The modern approach can be said to have its beginning in the early 19th century, and it is significant that the main feature of the methods used by Tuke in England and Pinel in France was an attitude of humane sympathy. In 1835 Dr. Gardiner Hill began to remove mechanical restraints in Lincoln Asylum and Dr. John Conolly abolished all mechanical restraint in Hanwell Asylum, Middlesex in 1839 (Hamilton, 1978). An Act of Parliament in 1845 provided legislation for the establishment of County Asylums. These were generally built in rural areas, out of sight and out of mind of a supposedly respectable community (Norton, 1978). The complex of five hospitals to the west of Epsom illustrates this philosophy as three of these had catchment areas in London. Many of these asylums were built on the tops of hills e.g. Epsom Common, because this was believed to lessen the incidence of tuberculosis which decimated the 19th century institutional occupants (Lader, 1981). These asylums each built to accommodate more than 1,000 patients were essentially custodial and wards were securely locked to prevent escape. Patients who were less disturbed were engaged
in agricultural work which was both therapeutic to the patient and beneficial in terms of produce to the hospital. Additionally patients were involved in work in the asylum launderies, bakeries and workshops, and the asylums themselves were practically self-sufficient. Most of these Victorian asylums are our major psychiatric hospitals of today.

Figure 2.1 illustrates how the numbers of patients resident in psychiatric hospitals steadily rose from 1860 when the 1845 Act was coming to fruition, to a peak in the mid-1950s. A steady decline then occurred following the introduction of the antipsychotic drugs and changes in attitudes to the treatment of mental illness.

The Office of Health Economics (1979) commented that the close conjunction of the availability of the antipsychotic drugs and drops in the number of people in hospital both in this country and abroad is reasonably firm evidence in favour of the hypothesis that medicines were of considerable significance around the start of this transition from closed to open care. There is clearly a degree of correlation between these two factors, although many would dispute this.

The Department of Health and Social Security, White Paper (1975) "Better Services for the Mentally Ill", in setting out further long-term plans for the mentally ill, recognised that although most of the mental hospitals were old, treatment methods had been revolutionised, and a considerable part had been played by antipsychotic drugs discovered in the 1950s. Hordern (1961) mentioned that in mental hospitals, these drugs have reawakened the interest of the staff in the whole resident population. He added that as a result staff morale in mental hospitals has improved, and treatments always considered by some as punishments have been replaced by remedies of a demonstrably "medical" nature.
Figure 2.1

In-patients resident in mental illness hospitals, England and Wales 1860–1978 (Office of Health Economics, 1979)
Cohen and Pillsbury (1960) treated 200 'deteriorated' schizophrenics, who had been continuously hospitalised for an average of over 15 years, with the phenothiazine, thioridazine and 39.5 per cent improved sufficiently to be discharged, sent to foster homes or to reside on open wards. In a four year study Leger (1966) treated 1225 mainly chronic psychiatric patients with thioridazine and was able to discharge 477 from hospital.

2.2 THE DISCOVERY OF THE ANTIPSYCHOTIC DRUGS

In the latter third of the last century in the city of Heidelberg, two events occurred that were destined to revolutionise psychiatry. In 1883, August Bernthsen synthesised phenothiazine, the progenitor of a group of drugs that have since been demonstrated to be of value in the treatment of schizophrenia; and, in 1896, Emil Kraepelin defined the psychiatric syndrome which he called "dementia praecox", and which is now called "schizophrenia". These important discoveries were made in the same city within 13 years of each other, and yet it was some 70 years later when they came together when the phenothiazine drug chlorpromazine was first used in the treatment of schizophrenia. The identification and synthesis of phenothiazine took place in the course of a series of chemical analyses that Bernthsen was conducting on two dyes that had been synthesised in 1876, Lauth's violet and methylene blue (Swazey, 1974).

In a description of the development of phenothiazines, Swazey (1974) noted that in 1937, Daniel Bovet and A.M. Staub, at the Institut Pasteur, demonstrated the antihistamine properties of compound 929F (thymoxyethylidiethylamine), one of a series of phenolic ether amines first synthesised in 1910 by E. Fourneau. The development of synthetic antihistamines rested on three decades of research, notably by Sir Henry
Dale and his colleagues, that had defined the pharmacologic actions of histamine. The first synthetic antihistamine both powerful and nontoxic enough for therapeutic use in the treatment of allergies was phen benzamine, an aniline derivative developed by Mosnier and Halpern at Rhône-Poulenc in 1942. Two years later a Rhône-Poulenc chemist, Paul Charpentier, synthesised a new line of phenothiazine amines in an unsuccessful effort to obtain a series of antimalarial, trypanocidal or anthelmintic drugs. Phenothiazine itself was used as a veterinary vermifuge (Knipling, 1938; Taylor & Sanderson, 1940).

Phenothiazine chemistry merged with research on synthetic antihistamines in 1945 when Halpern and Ducrot discovered the strong antihistamine properties of compound 3015 RP, one of the phenothiazine amines that Charpentier had synthesised the previous year.

A French surgeon, Henri Laborit, in a personal interview (Swazey, 1974) described how in 1949 he was doing what every other surgeon was doing - trying to protect or substitute for the organism's natural defences. He had first used a combination of four drugs to combat shock by lowering or inhibiting the activity of the autonomic nervous system; procaine, a local anaesthetic; curare; atropine; which blocked the action of acetylcholine on muscarinic effector organs; and tetraethylammonium, the ganglion blocking drug. Then, after his experimental study of the irritation syndrome, a fifth type of drug, antihistamines, was added to his pharmacodynamic regimen. In fact Laborit was so struck with how effectively promethazine relieved anxieties that he asked an army psychiatrist to watch him operate on some of his tense, Mediterranean type patients. The psychiatrist agreed that after surgery, the patients were remarkably calm and relaxed.
In October 1950, Dr. Pierre Koetschet of Rhône-Poulenc drafted a research memorandum which set in motion the work which culminated in the synthesis of 4560 RP - chlorpromazine - in December 1950. The compound was subjected to a test in rats involving conditioned avoidance response to stimuli. The loss of response to stimuli without impairment of muscular strength was considered to indicate consistent central activity (Swazey, 1974). In considering the lines of influence that first led psychiatrists to test chlorpromazine, Swazey (1974) observed that Henri Laborit, through informal personal contacts, and through his publications on artificial hibernation played a pivotal role. Soon after he began working with chlorpromazine, Laborit sought to implement his belief that the drug would find applications in psychiatry. On April 6th 1951 the first clinical trial of chlorpromazine began and the compound was marketed in November 1952 under the trade name of Largactil.

2.3 THE CHEMISTRY AND ANIMAL PHARMACOLOGY OF THE ANTI-PSYCHOTIC DRUGS

By definition these are drugs that are used in the treatment of the psychoses. They have many other names and Lader (1977) suggested that this demonstrates the lack of consensus on their clinical action. The following list shows the variety of synonyms used in describing anti-psychotic drugs.

<table>
<thead>
<tr>
<th>Antischizophrenics</th>
<th>Neutrotopics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataractics</td>
<td>Psycholeptics</td>
</tr>
<tr>
<td>Major tranquillisers</td>
<td>Psycholytics</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Psychoplegics</td>
</tr>
<tr>
<td>Neuroplegics</td>
<td>Psychotropics</td>
</tr>
</tbody>
</table>
The term "tranquilliser" appears to have developed from the early observations of the French surgeon Henri Laborit, who noted that patients who had received phenothiazines were more tranquil after surgery than other comparable surgical patients. Delay and Deniker (1957) proposed the term "neuroleptic" on the basis of their clinical observations of the action of chlorpromazine and related compounds, in that the drugs produced a reduction in nervous activity rather than a paralysis.

The antipsychotic drugs are divided into three main classes, viz the phenothiazines, the thioxanthenes and the butyrophenones.

2.3.1 The Phenothiazines

This group of antipsychotic drugs was developed following the discovery of the tranquillising activity of chlorpromazine. Several hundred phenothiazine compounds have been synthesised and there are twelve phenothiazines currently available for routine prescription as antipsychotics in Britain. There are others, e.g. promethazine and thiethylperazine, which are not antipsychotics. They all have the same basic three ringed structure in which two benzene rings are linked by a sulphur and a nitrogen atom. The structure is numbered as shown in Figure 2.2.

The basic structure has been modified by substitutions at position 10 ($R_1$) and position 2 ($R_2$) e.g. (Figure 2.3) with the objective of achieving safer and more effective antipsychotic compounds. Whilst the former objective has been met (Sandison, Whitelaw & Currie (1960) in a two year study involving 174 patients concluded that thioridazine had fewer side-effects than any other of the phenothiazine compounds) there has been some debate on the
Figure 2.2

Basic structure of the phenothiazine molecule.
Figure 2.3

Substitutions at positions 2 and 10 of the phenothiazine nucleus

Chlorpromazine

Thioridazine
latter as some workers consider that the antipsychotic potency of the many phenothiazines is equivalent (Cole, 1976).

### 2.3.2 The Thioxanthenes

The synthesis and pharmacology of the first thioxanthen compounds was reported by Petersen, Lassen, Holm, Kopf & Møller Nielsen (1938), and although Møller Nielsen, Hougs, Lassen, Holm & Petersen (1962) described the pharmacological properties of 66 new thioxanthenes, only 4 have been marketed in Britain.

The basic structure of the thioxanthenes is very similar to the phenothiazine nucleus except that the nitrogen atom at position 10 in the phenothiazine nucleus is replaced by a carbon atom (Figure 2.4).

As with the phenothiazines, substitutions can be made at positions 2 and 10 of the basic thioxanthen structure to produce different antipsychotic compounds (Figure 2.5).

The profile of the thioxanthenes is similar to those of other antipsychotic compounds in terms of pharmacological variables that include decreased mobility, selective inhibition of conditioned avoidance responses, antagonism of amphetamine-induced stereotypies and of apomorphine-induced emesis, production of catalepsy, potentiation of analgesics and hypnotics and a taming effect (Simpson & Lee, 1976).

### 2.3.3 The Butyrophenones

The synthesis of the butyrophenone, haloperidol (Figure 2.6) resulted from the search for a pethidine-like analgesic. The
Figure 2.4

Basic structure of the phenothiazine and thioxanthene molecules

Phenothiazine Nucleus

Thioxanthene Nucleus
Figure 2.5

Substitutions at positions 2 and 10 of the thioxanthene nucleus

Chlorprothixene

\[
\begin{array}{c}
\text{S} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{CH(CH}_2\text{)}_2\text{N(CH}_3\text{)}_2
\end{array}
\]

Flupenthixol

\[
\begin{array}{c}
\text{S} \\
\text{C} \\
\text{C} \\
\text{CF}_3 \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N} \\
\text{N-CH}_2\text{CH}_2\text{OH}
\end{array}
\]
Figure 2.6

Structure of the butyrophenone, haloperidol
compound induced cataleptic immobility, inhibited exploratory and self-stimulating behaviour, interfered with apomorphine-induced vomiting and amphetamine-induced stereotyped chewing, and Janssen (1970) suggested that the compound could therefore have antipsychotic properties.

The butyrophenones are monophenylbutylpiperidines. Replacement of the carbonyl in the propylene chain of the butyrophenone structure by a fluorophenyl resulted in a chemically new group of drugs, usually referred to as diphenylbutylpiperidines. Common characteristics of this class of antipsychotic drugs are their long duration of action, and the best known of the diphenylbutylpiperidine series is the oral antipsychotic pimozide (Figure 2.7) which has a duration of action of 24 hours (Ban & Pecknold, 1976).

2.4 THE CLINICAL USE OF ANTIPSYCHOTIC DRUGS

2.4.1 Use in Non-Psychiatric Indications

The antipsychotic drugs, and in particular the phenothiazines, have been used in a number of non-psychiatric indications:

i) Use in Vomiting

In patients with psychogenic vomiting, considerable symptomatic relief followed treatment with phenothiazines (Hill, 1968). The phenothiazines, notably chlorpromazine and prochlorperazine, inhibit vomiting caused by stimulation of the chemoreceptor trigger zone which is situated on the surface of the medulla. They are thus indicated in the symptomatic treatment of vomiting in hypertensive
Figure 2.7

Structure of pimozide, a diphenylbutylpiperidine compound
encephalopathy, cerebral tumour, and certain other conditions such as encephalitis, meningitis and subarachnoid and cerebral haemorrhage (British Medical Journal, 1970).

ii) **Use in Alcoholism**
Chlorpromazine and mesoridazine each produced improvement which was most marked in the first week, in a controlled study of 40 patients in alcohol withdrawal states. Agitation, tremor, anxiety and hallucinations were relieved or reduced (Frost, 1973). In addition to its property of not suppressing vomiting, another favourable aspect of the use of thioridazine in chronic drinkers with severe liver disease, is its low hepatotoxicity (Cohen, 1964). The use of thioridazine in treating alcohol withdrawal symptoms has also been reported (Huot, 1966; Ehik, 1968) and Acton (1968) treated more than 11,000 prison hospital alcoholics with thioridazine until a regular eating pattern was established.

iii) **Use in Premedication**
A total of 173 patients with duodenal ulcer were premedicated with chlorpromazine, atropine and phenobarbitone, prior to gastric freezing (Hitchcock, Ruiz, Sutherland & Bitter, 1966).

iv) **Use in Dentistry**
The phenothiazine derivative promethazine, is often used in dentistry. Its property of H₁ receptor antagonism, potentiation of barbiturate action and/or sedative effects, and antiemetic action partially explain its popularity in i/v sedation combined with analgesics which are known histamine releasers (Hayden, 1978).
2.4.2 **Use in Psychiatric Indications**

The antipsychotic drugs have been widely prescribed over the past twenty years for a variety of mental and emotional disturbances, particularly where anxiety, tension and agitation are presented. They have been used in acute, sub-acute and chronic schizophrenia, manic depressive psychoses, acute and chronic neuroses, confusional states, especially in the elderly, the disturbed mentally handicapped, and behaviour disorders in children with epilepsy.

i) **Use in Schizophrenia**

The target symptoms of the schizophrenic states are the prime indication for the phenothiazines. Disturbances of thought, emotion, perception and behaviour are all moderated. The acute psychoses are most quickly influenced, but chronic processes can also be ameliorated (Cohen, 1964).

Some of the best designed, most carefully controlled, large sample studies have been the Veterans Administration inter-hospital cooperative projects and those carried out by the National Institute of Mental Health. In one project (Lasky, Klett, Caffey, Bennett, Rosenblum & Hollister, 1962) 512 chronic schizophrenics were given one of six drugs "blind" over a 24 week period. At the end of the study fluphenazine, thioridazine and chlorpromazine were superior to reserpine at the 5 per cent level of statistical significance or better. The National Institute of Mental Health (1964) reported a double-blind study involving over 400 acutely ill schizophrenic patients treated at 9 collaborating hospitals. The
results demonstrated the clinical efficacy of drug therapy in acute schizophrenic psychoses. Ninety-five per cent showed some degree of improvement within six weeks - over 75 per cent showed marked to moderate degrees of improvement.

Core symptoms of schizophrenia (e.g. apathy, withdrawal, retardation, hebephrenic giggling and grimacing) show the greatest drug-placebo differences in acute studies, whilst secondary symptoms (e.g. delusions, hallucinations, hostility) show some change on placebo but substantially more on antipsychotic drugs (Cole, 1976). The degree of overall improvement in drug-treated patients is nevertheless greater for the secondary symptoms (Goldberg, Klerman & Cole, 1965).

ii) Use in Other Psychiatric Indications

Leger (1966) reported impressive results in mania using thioridazine and there is good evidence that chlorpromazine and thioridazine may be effective in some kinds of depression. Chlorpromazine seems to be particularly effective in agitated depressions (Klein & Davis, 1969) and thioridazine in anxious depressions (Hollister, 1973). In the neuroses, thioridazine was compared with diazepam in 27 patients under double-blind conditions. Significantly more patients receiving thioridazine experienced relief from tension (Loftt & DeMars, 1974).

There is modest evidence that phenothiazines are better than placebo in the treatment of geriatric patients with such psychotic behaviour as agitation, restlessness, delusions or
hallucinations, or thought disorder (Cole & Stotsky, 1974). Felger (1966) found that thioridazine had a calming effect without dulling or extrapyramidal effects in eight geriatric patients suffering from behaviour disorders, and Kral (1961) reported that confusion of thought, restlessness and agitation were improved by thioridazine in 29 out of 37 patients resident in an old peoples home. In treating paranoid syndromes in the elderly with thioridazine, only 6 of 71 patients failed to show any beneficial effects: 22 improved and 43 achieved complete immediate remissions (Post, 1965). In the management of disturbed, mentally handicapped patients the phenothiazines can be used in the control of behaviour disorders (Bicknell & Blowers, 1980a), and thioridazine was found to be effective in controlling symptoms of senseless physical overactivity, aggressiveness, rage and tantrum outbursts, disturbance of sleep rhythm, agitation, self-injury and noisiness (Le Vann, 1961). Where behaviour disorders were present in epileptic children, 61 of 100 randomly selected patients showed a marked improvement in behaviour, and moderate improvement was seen in a further 28 following treatment with thioridazine. There was a decrease in the number of seizures in 41 patients and in a further 23 patients no seizures were recorded after the addition of therapy (Pauig, Deluca & Osterheld, 1961).
2.5. **SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS**

There are many side effects of antipsychotic drugs and whilst this work concentrates on one aspect of the CNS side effects, the non-CNS side effects are also of importance.

2.5.1 **Non-CNS Side Effects**

i) **Allergic Reactions**

(a) **Jaundice**

Chlorpromazine-induced jaundice was one of the earliest noted and more dramatic of the phenothiazine-induced side effects. The jaundice generally occurs within 1 - 5 weeks after initiation of therapy, and on a clinical basis it is difficult to differentiate from infectious hepatitis (Davis & Casper, 1978). Sherlock (1962) observed that about 1 per cent of patients receiving chlorpromazine develop intra-hepatic obstructive jaundice, usually within 4 weeks of starting the drug and unrelated to dosage. Over recent years there has been a steady decline in chlorpromazine-induced jaundice, and the present incidence is probably well under 0.5 per cent (Davis & Casper, 1978). The decline is unexplained.

(b) **Agranulocytosis**

This is a serious, though rare, side effect of phenothiazines. It is not dose related and generally occurs within the first 6 - 8 weeks of treatment. Its onset is extremely abrupt, consisting of the sudden appearance of sore throat, ulcerations and fever (Davis & Casper, 1978). If a fall in the
leucocyte count is found, the drug must be stopped immediately and a full course of antibiotic treatment commenced.

(c) Skin Reactions

Davis & Casper (1978) noted that a variety of skin eruptions have been associated with chlorpromazine treatment, including the urticarial, maculopapular, petechial and eczematous type. These reactions usually occur during the first 5 weeks of treatment. Allergic skin reactions due to chlorpromazine were reported by Tszycka (1961) following a survey of three neuropsychiatric hospitals. This revealed allergic reactions in both patients and staff. Sixteen members of staff developed contact dermatitis and this presented either in the form of scarlatiniform rash, local oedema, or small, itchy vesicles on the hands, forearms, face or eyelids. Davis & Casper (1978) also referred to the occurrence of a contact dermatitis in personnel who handle chlorpromazine. Chlorpromazine is unique among the phenothiazines for causing marked photosensitivity. Patients receiving chlorpromazine in the summer are likely to develop severe sunburns after relatively short exposure to the sun (Cole, 1976). Acute photosensitivity with chlorpromazine has been the subject of a number of reports (Greiner & Berry, 1964; Feldman & Freirson, 1964; Greiner & Nicholson, 1964; Cairns, Capoore & Gregory, 1965; Satanove, 1965). Treatment consists of protecting the patient from sunlight, either by use of barrier creams, protective clothing, or by restriction of patients to wards or covered areas.
ii) **Autonomic Side Effects**

(a) **Antiadrenergic**

Postural (orthostatic) hypotension can occur during phenothiazine therapy and when it does appear it usually does so in the first few days of treatment. Tolerance of this side effect generally develops quickly (Davis & Casper, 1978). Phenothiazines, particularly thioridazine, can postpone, or eventually prevent, ejaculation without interfering initially with erectile potency (Cole, 1976). This side effect responds to a reduction in dosage (Davis & Casper, 1978).

(b) **Anticholinergic**

A variety of anticholinergic side effects occur in patients treated with phenothiazines, including dry mouth and throat, blurred vision, nasal congestion and constipation (Davis & Casper, 1978).

iii) **Long Term Skin and Eye Effects**

Long-term high dosage chlorpromazine therapy has occasionally produced skin and eye changes (Davis & Casper, 1978). The skin changes consist of a blue-grey metallic discolouration of the skin over areas exposed to sunlight, such as the face and nose, the neck and collar area of the chest, and the dorsum of the hand. Eye changes are described as bilateral whitish-brown granular deposits concentrated in the subcapsular area, which in more severe cases may also be found in the anterior lens cortex as well as in the posterior cornea. Retinal damage is not seen and, in general, vision is not impaired.
Thioridazine has produced a pigmentary retinopathy in patients who were receiving 1,600 mg or more per day, and to provide a margin of safety the dose level has been restricted to 800 mg per day. This side effect can be produced by other phenothiazines in very rare instances, and this effect is different from ocular deposits and not related to the anterior lens opacities (Davis & Casper, 1978).

iv) **Endocrine and Other Side Effects**

Weight gain is a well-documented side effect of phenothiazines, particularly of chlorpromazine. The aetiology of this weight gain, which often occurs rapidly when the drug is started and comes to a halt on continuous treatment, remains obscure (Davis & Casper, 1978). Phenothiazines can produce galactorrhoea and gynaecomastia, most commonly in premenopausal women, although it does occur in postmenopausal women and in men. It can occur as early as the first or second week of antipsychotic therapy. This side effect was first described in patients being treated with chlorpromazine, but also can occur with other phenothiazines, such as thioridazine, trifluoperazine, prochlorperazine and fluphenazine. It has been suggested that phenothiazines block the inhibitory action of dopamine on prolactin secretion, thus accounting for the galactorrhoea. Amenorrhoea, a frequent occurrence with psychiatric patients, has been reported in a small percentage of schizophrenic patients under phenothiazine treatment (Davis & Casper, 1978).
An electrocardiographic abnormality of uncertain significance, consisting of broadened, flattened, or inverted T-waves, has been observed in patients treated with phenothiazines, particularly thioridazine. Although not associated with clinical electrolyte disturbance, it is said to be reversible by potassium supplements, discontinuation of the drug, isorbide dinitrate and ergotamine tartrate. S-T segment depression has also been observed in patients treated with phenothiazines. In addition, bradycardia, tachycardia or palpitations may occur. A cardiomyopathy consisting of a thickening of cardiac vessels less than 0.1 mm in diameter has been found in patients treated with phenothiazines for long periods, including some patients who died suddenly or unexpectedly whilst on these drugs. It is unclear whether sudden death occurs more frequently in phenothiazine treated patients than in non-drug patients (Davis & Casper, 1978).

2.5.2 CNS Side Effects

i) Extrapyramidal Side Effects

Drug induced extrapyramidal side effects may be divided into two groups, the reversible syndromes and the generally irreversible syndromes. The former comprise Parkinsonian reactions, akathisia and dystonia, and the latter are the dyskinesias (Lader, 1970).

(a) Reversible Syndromes

Parkinsonism: Although this drug induced extrapyramidal effect is frequently called '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 (Lader, 1970). 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 (Lader, 1970).

Tremor is both one of the main signs and one of the main symptoms of Parkinsonism, and usually affects distal muscle groups such as those of the hand, forearm and foot. It is characteristically present at rest, and it is made worse by nervousness, excitement, or fatigue. It is sometimes seen when the patient is walking (Pallis, 1971). Rigidity is another common feature and is detected clinically as resistance to passive manipulation of the limbs and trunk. The examiner encounters uniform resistance throughout the range of passive movement, hence the terms "plasticity" and "lead-pipe rigidity". When tremor is present the rigidity is broken up, producing "cog-wheel rigidity" - a jerking sensation often experienced by the examiner on passively stretching a hypertonic Parkinsonian muscle (Pallis, 1971; Marsden, 1977).

Postural abnormalities also occur and rigidity contributes to the characteristic flexed posture. However, other abnormalities of postural stability are evident, such as the festinating (hurrying) gait, the inability to withstand a push or pull, and frequent falls without attempts to avoid injury (Marsden, 1977). As far as the patient is concerned, akinesia is the most disabling of all the main features of
Parkinsonism. A slowness of initiation and execution of movements, and a general poverty of spontaneous and automatic or associated movements, are characteristic. Akinesia is not merely the result of rigidity; it is an inability to generate movement. Along with rigidity and postural abnormalities it accounts for many of the characteristic features of Parkinsonism - the masked face, the loss of blinking, the absence of arm swinging when walking, the small handwriting, the soft monotonous speech (Marsden, 1977).

The incidence of extrapyramidal side effects caused by antipsychotic drugs varies considerably. Cohen (1966) mentioned that fluphenazine and trifluoperazine had a high incidence of extrapyramidal side effects and that there was a lower incidence with thioridazine. Cole & Clyde (1961) estimated the relative incidence figures to be 36 per cent for fluphenazine and 3 per cent for thioridazine. The thioxanthenes resemble thioridazine in their paucity of extrapyramidal reactions, and the butyrophenones are similar to the piperazine-type phenothiazines (e.g. trifluoperazine) (Lader, 1970).

The true incidence of extrapyramidal side effects is masked by the administration of antiparkinsonian drugs. Researchers typically administer antiparkinsonian agents with antipsychotic drugs routinely, thus clouding the statistics on side effect incidence which are usually based on the entire time period of the study (Davis & Casper, 1978).
Akathisia: This syndrome is characterised by motor restlessness. 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 forwards, 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 (Lader, 1970).

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 ("flycatcher") and jaw may occur; trismus, severe tongue injuries and dislocation of the temporo-mandibular joint have occurred. Spasms may be very widespread, involving most muscle groups including the bladder (Lader, 1970).

Another form of dystonic reaction described by Lader (1970) is the oculogyric crisis, in which the attack begins with a fixed stare, soon followed by upwards and sideways 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.
Other CNS Effects: In normal subjects, high doses of the more sedative phenothiazines such as chlorpromazine cause sedation. In patients, mild or moderate drowsiness usually disappears after the first or second week, and patients should be cautioned about driving or operating machinery while taking phenothiazines. If the effect proves troublesome, it can be controlled by lowering the dosage (Davis & Casper, 1978). Occasionally disturbed body temperature, paroxysmal or focal EEG slowing, and respiratory depression may be seen with phenothiazine therapy (Davis & Casper, 1978), though variations are seen with individual phenothiazines. Taeschler & Cerletti (1958) found that thioridazine reduced the body temperature of rats only when given at 10 times the dosage required for a similar effect with chlorpromazine.

(b) Generally Irreversible Syndromes

Tardive Dyskinesia: The syndrome of antipsychotic-induced tardive dyskinesia includes a variety of abnormal movements, from lingual-facial-buccal dyskinesias to dyskinesias and choreiform movements of the limbs and trunk. The subject is considered in greater detail in this chapter (See 2.7)

2.6 PHARMACOLOGY OF ANTIPSYCHOTIC DRUGS

"The value of a hypothesis lies not so much in whether it is right or wrong, but in its capacity to stimulate attempts to refute it".

Karl Popper.
This can be truly said of the Dopamine Hypothesis of Schizophrenia. The hypothesis states that, since many behavioural effects of the amphetamines are due to increased central dopamine release, and since most neuroleptic compounds are antagonists at central dopamine receptors, the symptoms of schizophrenia may be due to an abnormal increase in central dopamine release and the effects of this increase are diminished by partial blockade of the receptor site (Crow, Deakin, Johnstone & Longden, 1976).

The observations that led to the hypothesis are:-


ii) The drugs that control schizophrenic symptoms can be shown to decrease brain dopamine activity (Crow, Deakin, Johnstone & Longden, 1976; Iversen, 1977; Snyder, 1978).

2.6.1 Dopamine Receptor Blockade

The majority of the drugs that have been found to be effective in the treatment of schizophrenic symptoms act by blocking receptors for the CNS transmitter dopamine. Reserpine and oxypertine
however, prevent dopamine storage. The dopamine neurones are arranged in two principal systems, one originating from cells in the substantia nigra and innervating various regions of neostriatum, and a second originating from cells in the ventral tegmentum (the so-called A10 group) whose fibres project to various limbic structures, including nucleus accumbens, olfactory tubercle, medial frontal cortex and cingulate cortex (Iversen, 1977). The physiology of dopamine in the main brain dopamine tracts is illustrated in Figure 2.8.

Dopamine blockade of various central systems has a number of different consequences, e.g. in the nigrostriatal system, Parkinsonism and other extrapyramidal effects may result; in the tubero-infundibular system, elevation of plasma prolactin occurs; in the mesolimbic and mesocortical system, dopamine blockade may underlie antipsychotic actions. There is much evidence to suggest that various antipsychotic drugs have differential actions on these various systems. For example, clozapine and thioridazine have a much stronger effect on dopamine turnover in the limbic system than in the striatum, relative to haloperidol; clinically these drugs are associated with a low incidence of extrapyramidal effects. Conversely haloperidol and perphenazine seem to affect the striatum more than the limbic system with a correspondingly high incidence of Parkinsonian symptoms (Brain Biochemistry, 1980) Figure 2.9 illustrates the balance relating to the increase or decrease of Parkinsonian symptoms resulting from dopamine blockade.
Physiology of brain dopamine tracts

Source: Brain Biochemistry, Mental Disorders and Antipsychotic Agents (1980)
Evidence from dopaminergic blockade: extrapyramidal effect

Decrease acetylcholine: cholinolytics eg antiparkinsonian drugs

Worse
Tremor
Rigidity
Akinesia

Better
Decrease dopamine: antipsychotics (spontaneous in idiopathic Parkinsonism)

Increase acetylcholine: physostigmine

Ach=acetylcholine DA=dopamine

Source: Brain Biochemistry, Mental Disorders and Antipsychotic Agents (1980)
Whereas the antipsychotic effects and the elevation in plasma prolactin concentrations persist as long as the drug is continued, the extrapyramidal effects tend to diminish. This has been attributed to diminution in the feedback response. The other long-term effect is receptor supersensitivity which refers to variations of receptor response according to the availability of the neurotransmitter. Thus, dopamine-receptor blockade by antipsychotic agents increases the number of receptors, an adaptive mechanism to overcome the blockade. Such a mechanism is believed to underlie tardive dyskinesia which appears to be due to dopaminergic overactivity in the striatum. Drugs which increase dopamine, such as levodopa or amphetamine, exacerbate tardive dyskinesia whereas reserpine and the antipsychotic drugs (in the short-term) ameliorate the condition by blocking the extra receptors. On the other hand, physostigmine and deanol, drugs which increase acetylcholine, improve the condition, whereas anticholinergics, including the antiparkinsonian drugs, exacerbate it. The benzodiazepines and sodium valproate can help alleviate the dyskinesia by increasing GABA inhibition on the nigrostriatal dopaminergic neuron (Brain Biochemistry, 1980). Figure 2.10 illustrates the balance situation in tardive dyskinesia resulting from dopamine blockade.

Dopamine released within the CNS acts on specific dopaminergic postsynaptic receptors. CNS dopamine receptors are potently stimulated by the drug apomorphine and are not antagonised by \( \alpha \) or \( \beta \) adrenoceptor antagonist drugs. Amphetamine appears to elicit many of its behavioural effects indirectly by causing a release of endogenous dopamine in the brain, since selective lesions of CNS dopaminergic pathways abolish its behavioural effects (Creese and Iversen, 1975).
Evidence from dopaminergic blockade: tardive dyskinesia

Better

Decrease acetylcholine: cholinolytics e.g. antiparkinsonian drugs

Worse

Decrease dopamine: increase antipsychotics give reserpine

Increase acetylcholine: physostigmine, deanol

Increase dopamine: levodopa, amphetamines withdraw antipsychotics

Ach = acetylcholine  DA = dopamine

Source: Brain Biochemistry, Mental Disorders and Antipsychotic Agents (1980)
Amphetamine psychosis is alleviated by drugs known to be effective in the treatment of schizophrenia (Iversen, 1977) and such drugs also block the behavioural stimulant effects of amphetamine in animals and this is such a consistent property that this test has been used to predict new compounds likely to exhibit antipsychotic actions in man (Randrup & Munkvad, 1974). The hypothesis that antipsychotic drugs of many different chemical classes share a common ability to block CNS dopamine receptors is supported by other lines of evidence (Iversen, 1977). All such drugs cause a selective stimulation of the rate of synthesis and metabolism of dopamine in the animal brain, apparently as an adaptive response to dopamine receptor blockade (Sedvall, 1975).

The most direct evidence for dopamine-blocking properties of antipsychotic drugs has come from studies of CNS dopamine receptor mechanisms in vitro. Many antipsychotic drugs act as potent inhibitors of the ability of dopamine to stimulate cyclic AMP formation in homogenates of dopamine-rich areas of brain (Iversen, 1975). The actions of antipsychotic drugs on the dopamine stimulated adenylate cyclase are, however, anomalous, in that certain potent antipsychotic drugs (notably pimozide and the related butyrophenone series) are only weakly active on this test (Iversen, 1977).

There is evidence for Dopamine_1 and Dopamine_2 receptor sites (Kebabian and Calne, 1979), and it has been shown in animal experiments that continuous administration of neuroleptics to rats for up to a year induces behavioural and biochemical supersensitivity of striatal dopamine mechanisms, including an enhanced
response of striatal adenylate cyclase to dopamine, which persists for a further six months after drug withdrawal. Adenylate cyclase is linked with $D_1$ dopamine receptor systems, and selective $D_1$ receptor antagonists such as flupenthixol certainly cause tardive dyskinesia (Jenner & Marsden, 1979), and whilst it is suggested that $D_2$ antagonists such as the substituted benzamides sulpiride, tiapride and oxiperomide should theoretically reduce the likelihood that tardive dyskinesia will ensue (Lancet, 1979), there are so far no data to support this hypothesis (Jenner & Marsden, 1979).

A more recently developed test system depends on measurements of the saturable high affinity binding of the radioactively labelled butyrophenones, haloperidol or spiroperidol to specific membrane sites in brain homogenates (Creese, Burt & Snyder, 1976). Such sites occur only in dopamine-rich areas of brain and appear to represent CNS dopamine receptors. There is good correlation between the rank order of potencies of various antipsychotic drugs in clinical use and their potencies in competing for the binding of labelled haloperidol or spiroperidol in vitro (Iversen, 1977). Spiroperidol also binds to 5-HT receptors which complicates interpretation of binding studies.

2.6.2 **Dopamine Receptor Actions**

Long term therapy with any drug which causes dopaminergic blockade can give rise to the risk of tardive dyskinesia (see 2.7.5). Blockade of dopamine receptors can give rise to a number of actions additional to antipsychotic activity.
i) **Antiemesis**
Blockade of dopamine receptors in the chemoreceptor trigger zone located in the area postrema of the medulla oblongata can cause antiemetic effects (Richelson, 1980), and most phenothiazines have been used to control vomiting.

ii) **Prolactin Rise**
Any substance with dopamine-blocking actions elevates the secretion of prolactin. Substantial parts of these effects are exerted directly at pituitary level although there may also be dopaminergic inhibition at the hypothalamic level, possibly mediated by a polypeptide (Horrobin, 1977). Thus treatment of patients with antipsychotic drugs results in increased levels of prolactin, which may result in galactorrhea accompanied by amenorrhoea (Sachar, 1978).

iii) **Parkinsonism**
Drugs which block dopaminergic receptors such as the phenothiazines, butyrophenones and diphenylbutylpiperidines can induce Parkinsonism (Calne, 1976). Because of the clinical analogy between the neurological syndrome of akinesia, muscular rigidity and tremor produced by dopaminergic antagonists and other antipsychotic drugs and that seen in Parkinson's disease, the former has been regarded as a classic example of drug-induced Parkinsonism, serving as one of the experimental models for the latter (Hornykiewicz, 1975).

iv) **Body Temperature Regulation**
The evidence that dopamine plays a role in thermoregulation was demonstrated by Fuxe & Sjoqvist (1972) who injected
mice with apomorphine. Falls in body temperature of about 3
to 4°C were observed after 15 minutes, and after 2 hours the
body temperature was still below its normal level. The
apomorphine action was completely prevented by the
dopamine receptor agonist pimozide. Similar findings were
obtained in the rat (Kruk, 1972).

v) Sleep Induction and Sedation
Intramuscular administration of apomorphine to 12 human
volunteers produced sedation in 8 subjects, 4 of whom also
showed sound sleep. The sedative and sleep-inducing effects
of apomorphine were prevented by haloperidol, pimozide and
by sulpiride (Corsini, Del Zompo, Manconi, Piccardi, Onali
and Mangoni, 1977). A relationship between the
dopaminergic system and sleep was also suggested by Bassi,
Albizzati, Frattola, Passerini & Trabucchi (1979), who
induced sleep in healthy volunteers after the administration
of apomorphine, but failed to show significant effect on a
group of Parkinsonism patients who had received long term
treatment with L-dopa.

vi) Gastric Emptying
In man, dopamine reduces gastric motility and consequently
delays gastric emptying. The dopamine antagonists
domperidone and metoclopramide stimulate gastric phasic
activity, increase pyloric dilatation and promote gastric
emptying (Weihrauch, Förster & Kriegstein, 1979).
2.6.3 Other Pharmacological Actions

i) Muscarinic Block

Klawans (1973) found two main classes of drugs to be effective in the treatment of movement disorders, and this was considered to illustrate the antagonistic effect of the dopaminergic and cholinergic influences in the extra-pyramidal system (Miller & Hiley, 1975). The relationship between muscarinic and dopaminergic activity was investigated by Kelly & Miller (1975), who tested the effects of muscarinic and antipsychotic drugs on the turning behaviour induced by methylamphetamine and apomorphine in rats with unilateral lesions of the substantia nigra. Turning towards the side of the lesion induced by methylamphetamine was inhibited by α-flupenthixol and α-clopenthixol, but not by high doses of their β-enantiomers. Turning was also inhibited by chlorpromazine and pimozide. These findings correlate well with the dopamine receptor-blocking potencies of these agents in vitro (Miller, Horn & Iversen, 1974) and support the view that the rat-turning model is a measure of dopaminergic-blocking activity. The antimuscarinic potencies of various antipsychotic drugs were measured by Miller and Hiley (1975) and they found an inverse correlation between the antimuscarinic potencies of the drugs and their ability to produce drug-induced Parkinsonism. Thioridazine and clozapine, which give the lowest incidence of drug-induced Parkinsonism, were found to be the most powerful antimuscarinics, whereas flupenthixol and spiroperidol, which produce the highest incidence of drug-induced Parkinsonism, were found to have poor antimuscarinic activity.
ii) **Alpha-adrenoceptor Block**

Symptoms of autonomic blockade, such as orthostatic hypotension and tachycardia, are side effects often associated with antipsychotic treatment, and compounds with a low norepinephrine antagonism to amphetamine antagonism ratio have the highest adrenergic blocking potential (Janssen & Van Bever, 1978). In summarising the receptor-blocking properties of antipsychotic drugs, Carlsson (1976) observed that chlorpromazine, thioridazine and chlorprothixene blocked central $\alpha$-adrenergic receptors as well as dopamine receptors.

iii) **Antihistaminic Action**

Antipsychotic drugs also possess antihistaminic properties, and because those with histamine-$H_1$ receptor blocking action cause drowsiness they are frequently used clinically as sedatives and hypnotics (Richelson, 1980). Additionally, the histamine-$H_1$ receptor blockade by antipsychotics may play a role in the appetite stimulating effect of these drugs (Richelson, 1979).

Antipsychotic drug antagonism of histamine-$H_2$ receptors has been studied with the use of histamine-stimulated adenylate cyclase activity (Kanof & Greengard, 1978). In the assay system they employed thioridazine was found to be more potent than cimetidine as an $H_2$-receptor antagonist.

iv) **Serotonin Antagonism**

A number of dopamine-related and serotonin-related drugs were compared for their ability to displace spiroperidol binding from rat striatum and frontal cortex (Quik, Iversen, Larder & Mackay, 1978). Spiroperidol was found to bind with
high affinity not only to dopamine- related sites in the striatum, but also with an almost equal affinity to serotonin sites in the frontal cortex. It was concluded that dopamine-related drugs are more potent in displacing spiroperidol binding from the striatum than from the cortex, whereas serotonin-related drugs are more potent in displacing from the medial frontal cortex than from the striatum. Iversen (1978) observed that some neuroleptics, including \( \alpha \)-flupenthixol, are remarkably potent not only as dopamine blockers but also as serotonin antagonists.

Using a mouse climbing model Costall and Naylor (1977) found that dopamine agonistic effects of clozapine, thioridazine and sulpiride were reduced by the serotonin antagonist methysergide, and they suggested that the use of the mouse climbing model with methysergide may aid the search for antipsychotic drugs lacking undesirable side effects.

2.7 TARDIVE DYSKINESIA

2.7.1 History

In the late 1950s clinical reports described an involuntary movement disorder in psychiatric patients undergoing treatment with antipsychotic drugs. The persistence of involuntary movements of the lower part of the face 6 months after stopping medication with chlorpromazine was reported by Ey, Faure & Rappard (1956). In this case the dyskinesia disappeared 2 years after cessation of antipsychotic therapy. In the same year,
neurotoxic reactions resulting from antipsychotic medication were also described (Hall, Jackson & Swain, 1956) and in their group of 90 patients who received chlorpromazine for about 2 months, 6 patients showed persisting neurological signs 60 days or more after administration of the drug was completed.

Schonecker (1957) reported three cases of dyskinetic movements as a complication of long term phenothiazine therapy, and this was followed by similar observations by Sigwald, Bouttier, Raymond & Piot (1959) who reported four cases of dyskinesia and introduced the descriptive term "facial bucco-linguo-masticatory dyskinesia". The condition was described in detail in a review of neurological complications of antipsychotic drugs (Sigwald, Bouttier & Courvoisier, 1959). The term "tardive dyskinesia" was first used by workers in Sct. Hans Hospital, Roskilde, Denmark, who referred initially to the fact that the syndrome occurred more frequently in elderly persons and in patients with organic brain diseases (Uhrbrand & Faurbye, 1960). In a later publication they stated that tardive dyskinesia occurred only after treatment for a long time, and that it was seldom observed during the first 6 months and it may occur even after several years of symptom-free treatment (Faurbye, Rasch, Peterson, Brandborg & Pakkenberg, 1964).

The early reported tardive dyskinesias are listed in Table 2.1 together with a number of further reports of persistent dyskinesias resulting from antipsychotic medication.

The tardive dyskinesia syndrome has been the subject of reviews and a number are shown in Table 2.2.
<table>
<thead>
<tr>
<th>TABLE 2.1</th>
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<td><strong>CLINICAL REPORTS OF TARDIVE DYSKINESIA</strong></td>
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<tr>
<th>Ey, Faure &amp; Rappard, 1956.</th>
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<td>Hall, Jackson &amp; Swain, 1956.</td>
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<td>Schonecker, 1956.</td>
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<td>Uhrbrand &amp; Faurbye, 1960.</td>
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<td>Druckman, Seelinger &amp; Thulin, 1962.</td>
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<td>Faurbye, Rasch, Peterson, Branborg &amp; Pakkenberg, 1964.</td>
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<td>Hunter, Earl &amp; Thornicroft, 1964.</td>
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<td>Evans, 1965.</td>
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<td>Morphew &amp; Barber, 1965.</td>
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<td>Heathfield, 1965.</td>
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<td>Rosin &amp; Exton-Smith, 1965.</td>
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<td>Degkwitz, 1967.</td>
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<td>Fann, Davis &amp; Janowsky, 1972.</td>
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<td>Crane &amp; Smeets, 1974.</td>
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<td>Merriett, 1975.</td>
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<td>Mehta, Mehta &amp; Mathew, 1977.</td>
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**TABLE 2.2**

<table>
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<tr>
<th>Review Articles on Tardive Dyskinesia</th>
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<tr>
<td>Faurbye, Rasch, Peterson, Brandborg &amp; Pakkenberg, 1964.</td>
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<td>Ayd, 1967.</td>
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<td>Marsden, Tarsy &amp; Baldessarini, 1975.</td>
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<td>Tarsy &amp; Baldessarini, 1976.</td>
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<tr>
<td>Klawans, Goetz &amp; Perlik, 1980.</td>
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Tardive dyskinesia is a well defined clinical entity, although occasionally it is confused with acute drug reactions (Parkes, 1976). The most conspicuous and frequent disorder is in the oral region and may be sufficiently severe to affect the function of speech and deglutition (Crane, 1968a) and even life-threatening by respiratory and gastro-intestinal complications (Casey & Rabins, 1978). The first sign of tardive dyskinesia to appear is often a vermicular movement of the tongue, followed by repetitive movements of the lip, jaw and cheeks, which result in constant sucking, licking, chewing, blowing and tonguing. There is little or no regular rhythm to these movements which almost always affect the lower face more than the upper, although the periorbital muscles may be involved. Many patients also have choreic movements of the extremities and swaying or rocking of the trunk, torsion of the axial skeleton and particularly the head and neck, legs and disturbances of respiratory rhythms. When extreme, the appearance is characteristic and bizarre. As with most involuntary movements, those of tardive dyskinesia are increased with physical stress and disappear during sleep (Parkes, 1976).

Generally, patients are unaware or only slightly emotionally disturbed by their tardive dyskinesia, but the movements are particularly striking to those around them, and can therefore become a considerable problem on discharge from hospital (Gerlach, 1979).

Tardive dyskinesia in its pure hyperkinetic, hypotonic or normotonic form, may become clinically evident after antipsychotic treatment for several months, sometimes following the reduction or withdrawal of the drug, or during supplementary anticholinergic
treatment. If tardive dyskinesia develops after the termination of
the antipsychotic treatment, it appears in the course of a few days
up to 2 to 3 weeks. In young subjects the movements then usually
disappear, while in older subjects they often either persist
(irreversible tardive dyskinesia) or disappear only slowly in the
course of some months to a year (Gerlach, 1979).

2.7.3 Prevalence

The reported prevalence of tardive dyskinesia varies between 0.5
per cent and 50 per cent (Lancet, 1979), although a number of
individual studies show higher rates.

In a sample of 332 patients, tardive dyskinesia was present in 186
(56 per cent), and when the patients were distributed into 3 age
groups, the prevalence in those over 70 was 75.6 per cent (Jus,
Pineau, Lachance, Pelchat, Jus, Pires & Villeneuve, 1976). The
prevalence of tardive dyskinesia in 65 chronic schizophrenic
inpatients was 55 per cent (Barnes & Kidger, 1979a), and in a
group of 41 female mentally handicapped patients, with a mean
period of hospitalisation of 31.6 years, the prevalence was 84 per
cent in the 50 to 69 years age group, and 86.7 per cent in the 70
years and above group (Blowers & Bicknell, 1980).

Estimates have in fact a very limited value, as they depend on
various factors such as the age of the subjects examined, the
psychopharmacological treatment and the validity and sensitivity
of the assessment employed (Gerlach, 1979).

2.7.4 Aetiology

The permanent nature of tardive dyskinesia may be due to drug-
induced structural changes in the central nervous system although
these have not been convincingly demonstrated in man (Parkes, 1976). As stated in the History (see 2.7.1.) there is considerable evidence that antipsychotic drugs can induce tardive dyskinesia. Both the dosage (Crane, 1970 & 1974; Gibson, 1978b), and the duration of treatment (Faurbye, Rasch, Peterson, Brandborg & Pakkenberg, 1964; Crane, 1974; Allen & Stimmel, 1977), appear to play a role.

Prospective clinical studies cannot be carried out, however, as dosage and duration of treatment must be adjusted to the mental state of the patient. Furthermore, the various predisposing factors are just as important as the antipsychotic treatment. It is thus impossible to establish fixed risk boundaries for dosage and duration of treatment (Gerlach, 1979). It should be mentioned that in one report, one patient developed a crippling tardive dyskinesia, having received no more than 10 mg of trifluoperazine daily for less than one year, which did not remit on withdrawal of medication. A further 2 patients treated with small dosages of antipsychotic medication were unable to dress themselves or function in the outside world because of their dyskinesias. All 3 patients were female and of Eastern European Jewish background, which raises the question of increased susceptibility to this syndrome (Simpson, 1973).

Brain Damage

Some reports show a correlation between tardive dyskinesia and brain damage (Uhrbrand & Faurbye, 1960; Faurbye, Rasch, Peterson, Brandborg & Pakkenberg, 1964; Edwards, 1970; Blowers & Bicknell, 1980), but others have been unable to repeat this finding (Brandon, McClelland & Protheroe, 1971; Fann, Davis & Janowsky, 1972). Specific lesions in the basal ganglia could probably promote the development of tardive dyskinesia, but with
the methods of investigation available it would hardly be possible to identify such a lesion in the living subject (Gerlach, 1979). It may be that brain damaged patients have higher doses of antipsychotics, although in a small survey of tardive dyskinesia in a group of mentally handicapped patients, 9 who were treated with antipsychotic drugs had received dosages well below the manufacturer's recommended maximum (Bicknell & Blowers, 1980b).

Age

Uhrbrand & Faurbye (1960) were the first to observe that tardive dyskinesia is more frequent in the elderly, and Kruse (1960) suggested that in patients of 50 years and above the presence of vascular changes in the extrapyramidal system might predispose towards the development of the syndrome. It has also been postulated the sensitivity to drugs in aged patients varied from that in young adults (Paulson, 1968). It could be that most older patients will have received more drugs. The positive relationship between age and tardive dyskinesia has been further supported (Crane, 1971; Tarsy & Baldessarini, 1976; Mehta, Mehta & Mathew, 1977; Simpson, Varga, Lee & Zoubok, 1978).

Sex

Female patients have been considered more prone to the syndrome than males (Hunter, Earl & Thornicroft, 1964; Simpson, Varga, Lee & Zoubok, 1978), and in particular chorea was more common in women than in men (Kennedy, Hershon & McGuire, 1971). Whilst this observation has not always been consistent in published work (Crane, 1970; Fann, Davis & Janowsky, 1972; Jus, Pineau, Lachance, Pelchat, Jus, Pires & Villeneuve, 1976), there have not been any reports of a higher incidence in males.
2.7.5 Drugs Causing Tardive Dyskinesia

i) Antipsychotics

All effective antipsychotic drugs in common use have been implicated as causing tardive dyskinesia (Schiele, Gallant, Simpson, Gardner, Cole, Crane, Chase, Ayd, Levine & Ochota, 1973) and although this is most commonly due to long-term phenothiazine or butyrophenone treatment, it is extremely rare with reserpine (Parkes, 1976). The dopamine depleting antipsychotic oxypertine has not been associated with causing tardive dyskinesia, and has been used in its treatment (Kazamatsuri, 1980; Freeman, Soni & Carpenter, 1980) (See 2.7.7).

Piperazine derivatives may be especially liable to cause tardive dyskinesia (Uhrbrand & Faurbye, 1960), but many different phenothiazine compounds, including chlorpromazine and trifluoperazine, the thioxanthenes, thiothixene and chlorprothixene, and haloperidol and droperidol may be responsible (Parkes, 1976). The depot antipsychotics have also been implicated, and seem more likely than oral medication to be associated with tardive dyskinesia (Drug and Therap. Bull., 1979). In 374 chronic schizophrenics receiving depot antipsychotics the syndrome appeared with steadily increasing frequency and had affected about a quarter of them in 3 years (Gibson, 1978b). In this latter study 6 out of 167 patients developed generalised chorea within months of starting flupenthixol, and a national survey was then undertaken. The proportion of cases reported as developing chorea were, depot flupenthixol, 1 in 230, depot fluphenazine, 1 in 400, and oral antipsychotics, 1 in 1800 (Gibson, 1979). The severity of tardive dyskinesia correlated significantly
with both total dose and average daily dose of fluphenazine decanoate in the examination of a group of 22 psychiatric outpatients (Csernansky, Grabowski, Cervantes, Kaplan & Yesavage, 1981).

ii) **Anticholinergics**

Cases of tardive dyskinesia have been associated with treatment with a variety of anticholinergic drugs (Committee on Safety of Medicines, 1979). Anticholinergic treatment can uncover latent tardive dyskinesia and accentuate existing tardive dyskinesia (Klawans, 1973a; Gerlach, Reisby & Randrup, 1974; Klawans & Rubovits, 1974). In milder cases this response may be delayed, while in severe cases there may be a momentary fluctuation in condition from hypokinesia to hyperkinesia, e.g. following intravenous injection of physostigmine and scopolamine (Gerlach, Reisby & Randrup, 1974). It has been suggested that patients in a study who developed tardive dyskinesia were erroneously treated with anticholinergic drugs which impaired their condition and accounted for the finding of a significant relationship between severity of tardive dyskinesia and the amount of anticholinergic drug. (Perris, Dimitrijevic, Jacobsson, Paulsson, Rapp & Froberg, 1979).

iii) **Other Drugs**

Although tardive dyskinesia is generally regarded as a complication of antipsychotic drug therapy, the condition has been reported as a complication of treatment with other drugs.
Lavy, Melamed & Penchas (1978) reported a case of severe involuntary movements after chronic use of high doses of metoclopramide which were identical to the syndrome of tardive dyskinesia. The drug had been prescribed for persistent nausea without vomiting or other gastrointestinal symptoms. Metoclopramide has been reported to cause extrapyramidal reactions in man (Casteels-Van Daele, Jaeken & Van Der Schueren 1970), and has been shown to induce catalepsy and increase striatal homovanillic acid content in mice (Ahtee & Buncombe, 1974). This latter property has been shown to occur with antipsychotics (O'Keefe, Sharman & Vogt, 1970).

Fann, Sullivan & Richman (1976) described two cases of the dyskinetic syndrome occurring during the administration of amitriptyline therapy. Whilst it is recognised that amitriptyline is structurally similar to the phenothiazines, it should be mentioned that both patients did receive some phenothiazine medication during their treatment period. In describing a case of oral-buccal dyskinesia following low dose diazepam and flurazepam over a period of 13 months, it was noted that the patient had been treated earlier with amitriptyline (Kaplan & Murkofsky, 1978), and whilst Rosenbaum and De La Fuente (1979) referred to a clear temporal association between the use of benzodiazepines and tardive dyskinesia in six patients only two of these received diazepam alone, the other four had their benzodiazepine therapy complicated by earlier treatment with either antipsychotic or antidepressant drugs.

The occurrence of oral facial dyskinesia associated with prolonged use of antihistamine decongestants was reported by
Thach, Chase & Bosma (1975), and also by Davis (1976), who observed a progressive left-sided facial dyskinesia in a patient who had received chlorpheniramine for 10 years. A further case of tardive dyskinesia was reported in a patient who had taken a variety of antihistamine preparations intermittently for 30 years and continuously for 10 years (Hale & Heins, 1978). Tardive as well as permanent dyskinesias have been described in three young drug addicts taking narcotics and marihuana (Marshall, 1972), although it is notoriously difficult to obtain full drug histories from many subjects and these patients may conceivably have taken many different drugs (Parkes, 1976). A case of dyskinesia in which body rocking and fly-catching movement of the tongue were featured occurred following the discontinuation of a compound analgesic containing oxycodone (Gardos, 1977).

Dyskinesias have also been reported following the administration of methylphenidate (Fann, Davis & Wilson, 1973; Platatucci, 1974), dextroamphetamine (Mattson & Calverley, 1968), anti-convulsants (Chadwick, Reynolds & Marsden, 1976), and levodopa (Williams & Calne, 1981; Le Witt & Calne, 1981).

2.7.6 Spontaneous Dyskinesia

Whilst it is generally accepted that tardive dyskinesia occurs as a result of long-term antipsychotic medication there is evidence to suggest that the disorder can appear in persons who have never received these compounds. Brandon, McClelland & Protheroe (1971), in a study of the total population of a psychiatric hospital observed that 20 men (5 per cent) and 36 women (7 per cent) who
showed facial dyskinesia had never been exposed to phenothiazines.

Crane & Smeets (1974) were of the opinion that naturally occurring involuntary movements might be diagnosed as tardive dyskinesia and offered this as an explanation for the unusually high prevalence of the disorder in some studies of drug and non-drug treated patients. In a study in a retirement home 38 (18 per cent) of 211 residents who had never been treated with an antipsychotic drug showed dyskinetic movements (Bourgeois, Bouilk, Tignol & Yesavage, 1980).

2.7.7 Treatment of Tardive Dyskinesia

1) Withdrawal of Medication

If possible, the antipsychotic drug should be discontinued at the first sign of tardive dyskinesia. The syndrome will then become temporarily intensified, but after a few weeks it will diminish. In young patients it will usually disappear completely, while in elderly patients it may persist, possibly in a weakened form. In view of present possibilities of treatment, and as long as the patient has no subjective discomfort, there is no indication for any antihyperkinetic treatment (which would merely accentuate the syndrome on the longer view). If psychotic symptoms recur or become intensified, it may be necessary to reinstitute the anti-psychotic treatment, possibly employing an antipsychotic with a weak striatal dopamine receptor-blocking effect (Gerlach, 1979).
**Dopamine blocking drugs**

Paradoxically the most effective treatment for suppressing tardive dyskinesia is the administration of antipsychotics (Jeste & Wyatt, 1979). Increasing of the dosage of an antipsychotic drug whenever signs of tardive dyskinesia appeared provided additional dopamine receptor-blockade and there was an alleviation of dyskinetic symptoms (Kazamatsuri, Chien & Cole, 1972a; Crane, 1973; Klawans, 1976). However dyskinetic symptoms reappear, and on repeating the process, the patient becomes subjected to an escalating dosage of antipsychotic drug with ultimately an increasing level of dyskinesia (Klawans, 1976; Lader, 1978).

In double-blind interrupted cross-over trial in two established cases of oral dyskinesia, thiopropazate was found to be highly effective (Roxburgh, 1970). It was suggested that the use of the compound required caution and justification. Thiopropazate was also used by Singer & Cheng (1971) who found it to be significantly more effective than a placebo in relieving dyskinesia in 23 patients. Eighteen patients improved and further research was advised to determine the long-term effectiveness of the drug.

In 10 hospitalised psychiatric patients who had shown persistent dyskinesia for a minimum of 4 years, one patient improved following a 12 week placebo controlled, cross-over study with thiopropazate (Ananth, Ban & Lehmann, 1977). Haloperidol was used in the treatment of tardive dyskinesia which had been exacerbated by levodopa, and although a
decrease in dyskinesia was obtained, doubt was expressed as to whether the improvement would be permanent (Klawans & McKendall, 1971). In treating a group of 10 patients who showed typical signs of tardive dyskinesia, Frangos & Christodoulides (1975) obtained improvement using increasing doses of haloperidol, and were prepared to recommend its further use. Kazamatsuri, Chien & Cole (1972b) reported improvement with both haloperidol and thiopropazate, and were of the opinion that partial reblockage of hypersensitive dopamine receptors should suppress dyskinesia.

Widroe and Heisler (1976) in addition to using deanol in the treatment of tardive dyskinesia recommended the continuation of, and if necessary, the increasing of phenothiazine medication. This approach was however considered unwise and potentially harmful if it led to a further increase in dopamine receptor sensitivity (Curzon, 1976).

A double-blind study of the antipsychotic pimozide was undertaken in 24 patients with tardive dyskinesia (Calne, Claveria, Teychenne, Haskayne & Lodge-Patch, 1974). Results indicated that pimozide achieved a significant therapeutic action on dyskinesia, although pimozide dosage required limitation due to the development of parkinsonism. In a study of 374 outpatients receiving antipsychotic depot injections, tardive dyskinesia developed in 84. Of these 84 patients 33 were selected for pimozide administration, and over a period of 6-18 months 29 patients showed dramatic improvement in their dyskinesia. A follow up 12 months later showed that of the group of 29 patients who had improved, 19
had the condition in a mild form with constant, though slight movements of the lower face and tongue. In 9 of the remaining 10 who had received pimozide, dyskinesia was found to be still apparent after the pimozide had been discontinued for a period of 5 weeks (Gibson, 1977).

Sulpiride, a selective type-2 dopamine receptor antagonist, was evaluated in a blind, placebo-controlled trial in 11 patients with tardive dyskinesia (Casey, Gerlach & Simmelsgaard, 1979). There was a significant suppression of tardive dyskinesia, although scores returned to their baseline level during the final placebo phase. Similar results were obtained in a group of six chronic schizophrenics with pronounced tardive dyskinesia. Dyskinetic signs were diminished unrelated to dosage, but returned to the starting level, two weeks after the discontinuation of sulpiride (Haggström, 1980).

The dibenzodiazepine derivative clozapine has been shown to be effective in the treatment of tardive dyskinesia. In a study to evaluate its effect as an antipsychotic agent in 9 chronic schizophrenics, it was observed that two patients who showed tardive dyskinesia during the placebo phase lost these symptoms when the active clozapine was administered (Simpson & Varga, 1974). In a further study clozapine was used to treat 12 chronic schizophrenic patients with tardive dyskinesia. Seven patients completed the study and all showed a steady improvement in their dyskinesia after 18 weeks on clozapine. When they were then given placebo medication the dyskinetic symptoms returned. Problems
encountered during the study included neutropenia in two patients (Simpson, Lee & Shrivastava, 1978). Clozapine differs from the classic antipsychotics in that it is able to antagonise dopamine-receptor hypersensitivity by a mechanism other than blockade of the dopamine receptors themselves (Sayers, Burk, Ruch & Asper, 1978), and it is suggested that clozapine has an antihyperkinetic effect without increasing the risk of a recurrence of tardive dyskinesia after the withdrawal of the treatment (Gerlach & Simmelsgaard, 1978). However the occurrence of agranulocytosis as a side effect with clozapine (Lancet, 1975), has led to this compound being no longer available in the United Kingdom. The worldwide incidence of this side effect was reviewed by Griffiths & Saameli (1975).

Jeste & Wyatt (1979) suggested that the use of antipsychotics to treat antipsychotic-induced tardive dyskinesia may be compared to the use of opiates in the treatment of opiate dependence. Increasing the dose of antipsychotics generally abates the abnormal movements, but can aggravate the pathogenesis by further denervation and subsequent hypersensitivity, and is clearly contraindicated (Klawans, Goetz & Perlik, 1980).

Papaverine, a smooth-muscle relaxant used in the treatment of cerebral arteriosclerosis has been found to antagonise dopamine in the caudate nucleus of the rat (Gonzalez-Vegas, 1974). Dopamine blocking properties of papaverine were also suggested by Duvoisin (1975) who showed that papaverine
administration produced relapse in levodopa-treated patients with Parkinson's disease. In a pilot study 3 chronic female hospitalised patients with moderately severe dyskinesia were treated with papaverine in doses of 300-600 mg for 3 weeks. Orofacial dyskinesia improved in all three patients (Gardos & Cole, 1975). A further study in 9 patients showed a modest 20 to 25 per cent improvement in oral dyskinesia (Gardos, Cole & Sniffin, 1976).

In a larger sample of 23 psychogeriatric patients and 18 chronic schizophrenic patients, a single blind study which included a 6 week no drug period was undertaken. Whilst orofacial dyskinesia was significantly reduced by papaverine in the psychogeriatric group during the first 6 weeks, only a few patients reached a 50 per cent improvement of dyskinesia scores. The authors concluded that overall the drug effects were modest (Gardos, Granacher, Cole & Sniffin, 1979).

Oxiperomide, a new dopamine-receptor antagonist, in dosage of 5 to 10 mg daily, decreased drug-induced dyskinesias without increasing Parkinsonian symptoms of akinesia and rigidity in 6 patients with idiopathic Parkinson's disease (Bedard, Parkes & Marsden, 1978). The same compound was evaluated in a blind, placebo-controlled trial in 10 patients with tardive dyskinesia. Significant results in reducing dyskinetic movements were obtained in 8 patients during the oxiperomide treatment phase, and the dyskinesia returned to the pretreatment level during the placebo phase (Casey & Gerlach, 1980).
Alpha-methyl-para-tyrosine (AMPT) reduces the formation of dopamine by inhibiting the rate-limiting enzyme tyrosine hydroxylase (Gerlach, Reisby & Randrup, 1974), and was shown to be effective in reducing dyskinesia in all 8 patients in a 3 day study. A further 3 day study showed improvement in dyskinetic signs in 10 patients of 24 treated with AMPT (Gerlach & Thorsen, 1976).

iii) **Dopamine depleting drugs and dopamine synthesis blockers**

Reserpine, a dopamine blocking agent, and methyldopa, a blocker of catecholamine synthesis, were used in treating 37 patients with tardive dyskinesia (Villeneuve & Bőszörményi, 1970). Within the limitations of an open study, improvement was seen in approximately half of the patients in each group. In a double-blind, placebo-controlled study in 3 groups of 10 patients, receiving reserpine, alpha-methyldopa and placebo respectively, statistically significant improvement of the tardive dyskinesia symptomatology with the two active preparations was noted when compared with the results obtained with the placebo (Huang, Wang, Hasegawa & Alverno, 1980). Methyldopa was found to be more effective than a placebo in relieving tremor, rigidity and orofacial dyskinesia in 15 chronic psychogeriatric patients who were studied during a 4 week double-blind experiment (Viukari & Linnoila, 1975). The dopamine-depleting agent tetrabenazine, an analogue of reserpine, was used in an open study to treat 4 cases of drug-induced tardive dyskinesia (Brandrup, 1961). The dyskinetic movements disappeared in all 4 patients and recurred when the tetrabenazine was experimentally discontinued for a period of 8 days during the
study. In a small double-blind study with 6 dyskinetic patients treated with tetrabenazine, abnormal movements were abolished in 3 patients and there was some improvement in 2 others (Godwin-Austen & Clark, 1971). A longer-term open study in 6 patients treated with tetrabenazine at a dose-level of 100 mg a day gave promising results initially but required a doubling of dosage after 15 weeks. The effect of dosage increase was transient as by the 18th week an increase in oral dyskinesia was observed (Kazamatsuri, Chien & Cole, 1973). A further single case open study in which tetrabenazine was successful when combined with choline has also been reported (Snell, Cleary & Sambrook, 1980).

Oxypertine, an indole derivative dopamine depleter, was used to treat tardive dyskinesia in 10 chronic hospitalised patients. Seven patients improved but it was necessary to continue antipsychotic medication to prevent the worsening of psychotic symptoms (Kazamatsuri, 1980). In a double-blind, placebo-controlled study involving 28 patients from whom previous medication was withdrawn, more of the 14 patients receiving oxypertine improved than those receiving placebo, though the difference did not reach statistical significance (Freeman, Soni & Carpenter, 1980).

iv) Cholinergic agents

Among the hypotheses advanced to explain tardive dyskinesia, the suggestion of dopaminergic/cholinergic imbalance in the extrapyramidal system, has gained considerable acceptance (Baldessarini & Tarsy, 1976). A
number of studies have been undertaken with the objective of restoring the balance between the dopaminergic and cholinergic systems, and attempts have been made to increase cholinergic activity with drugs such as deanol, physostigmine, choline and lecithin. Miller (1974a) reported the complete disappearance of levodopa-induced dyskinesia in 8 of 11 patients treated with deanol, 500 to 900 mg daily for 4 weeks. When the patients were transferred to placebo, dyskinetic signs returned within 3 to 8 days. In the same year he reported the successful treatment of 2 cases of tardive dyskinesia with deanol at doses up to 600 mg daily (Miller, 1974b).

Deanol, the 2-dimethylamino-ethanol salt of para-acetamidobenzoic acid, is thought to be a precursor of acetylcholine and once it crosses the blood-brain barrier it is probably converted to acetylcholine (Klawans, Topel & Bergen, 1975). In their own study in 18 cases of levodopa-induced dyskinesias, these authors failed to confirm the observations of Miller (1974a), and observed improvement in only 4 patients, and in none were the dyskinesias completely eliminated. Other studies under open conditions also failed to confirm Miller's results (Escobar & Kemp, 1975; Crane, 1975; Laterre & Fortemps, 1975). Positive results however were obtained in all 10 deanol treated cases of tardive dyskinesia (Fann, Sullivan, Miller & McKenzie, 1975) and in all 4 treated cases (De Silva & Huang, 1975). In a detailed single case study, severe orofacial dyskinesia was completely relieved although within a week of stopping deanol because of occipital headaches, dyskinetic movements returned (Casey &
Denney, 1975). In a review article (Re, 1975), reference was made to the conflict and controversy as to the effects of deanol in the management of dyskinesias, and the conclusion was drawn that different results seemed to be related to the integrity of receptor sites in the striatum and to proper diagnostic selection.

This theme was supported by Granacher, Baldessarini & Cole (1975), who advocated that until it was possible to distinguish cases of tardive dyskinesia that would respond to deanol, the drug should be used empirically. Ayd (1975) urged the setting up of studies involving large numbers of dyskinetic patients treated with deanol for many months to determine that the antidyskinetic efficacy of the drug does not diminish with time or interfere with the efficacy of antipsychotic therapy. In a subsequent double-blind study some therapeutic effect in oral hyperkinesia was seen in 5 of a group of 20 patients treated with deanol (Bockenheimer & Lucius, 1976). However 3 placebo controlled, double-blind studies in 10 patients, 25 patients and 14 patients respectively showed no statistical differences in dyskinetic scores between the deanol therapy period and that when placebo medication was administered (Simpson, Voitashevsky, Young & Lee, 1977; Jus, Villeneuve, Gautier, Jus, Villeneuve, Pires & Villeneuve, 1978; Penovich, Morgan, Kerzner, Karch & Goldblatt, 1978).

An antihyperkinetic effect was obtained by intravenous administration of the cholinergic drug physostigmine (Klawans & Rubovits, 1974), but its duration of action is short, and it can produce nausea, vomiting and impaired
cognitive functioning (Davis, Berger, Hollister & Simonton, 1977). Choline chloride administration has been shown to increase blood choline, brain choline, and brain acetylcholine levels in rats (Cohen & Wurtman, 1975 & 1976). On this basis choline chloride was administered to 4 patients with tardive dyskinesia. All 4 patients had significantly less abnormal movements during the choline treatment (Davis, Berger, Hollister & Simonton, 1977). In a double-blind, placebo-controlled, crossover study, choline was administered to 20 patients with tardive dyskinesia. Blood choline levels rose during the period of choline therapy in all patients and 9 were significantly improved (Growdon, Hirsch, Wurtman & Wiener, 1977).

Adverse reactions to choline included a "fishy" body odour and gastrointestinal irritation (Gelenberg, 1979), and double-blind trials with choline chloride are made difficult because the fishy odour indicates which patients are receiving choline chloride (Davis, Hollister, Vento & Simonton, 1978).

Lecithin, another precursor of acetylcholine, and a major source of dietary choline, has been shown to be more effective in raising serum choline levels than choline chloride, and this increase is more prolonged (Wurtman, Hirsch & Growdon, 1977). In a double-blind, placebo controlled study in 8 chronic schizophrenic patients with moderate to severe tardive dyskinesia, Branchey, Branchey, Bark & Richardson (1979) were unable to confirm earlier promising results of others, and found no difference between the severity of tardive dyskinesia observed during lecithin
treatment and that observed during placebo administration. Using double the dose of lecithin than that employed in the previous study, significant improvement was seen in the dyskinesia of 6 long-term patients with moderate or severe tardive dyskinesia, who participated in a double-blind, placebo controlled trial (Jackson, Nuttall, Ibe & Perez-Cruet, 1979).

v) **GABA minergic agents**

Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, has been linked with nigrostriatal dopaminergic functions in both electrophysiological and behavioural studies (Stevens, Wilson & Foote, 1974). On this basis it was hypothesised that GABAminergic agents such as sodium valproate might be useful for treating tardive dyskinesia through their inhibition of the dopamine neuronal supersensitivity in the nigrostriatum (Linnoila, Viukari & Hietala, 1976). In their double-blind crossover study in 32 chronic psychiatric patients, orofacial dyskinesias were totally or significantly relieved in 17 cases. These results were not confirmed in an open study in which 25 schizophrenic patients with tardive dyskinesia were given sodium valproate for 1 month. Films for each patient taken before and after treatment were screened side by side as a randomly allocated pair and viewed by a multidisciplinary audience of 9, who tried to identify the 'after' film. A majority made the correct adjudication in only 8 cases, and it was concluded that the treatment was unsuccessful (Gibson, 1978c). In the former trial sodium valproate was administered at a level of 300mg thrice daily and in the latter the dosage was 200mg.
thrice daily. Muscimol (3-hydroxy-5-amino-methylisoxazole), thought to be a GABA agonist was administered to 7 chronic schizophrenics with symptoms of tardive dyskinesia. Whilst dyskinetic movements were improved, the psychotomimetic properties of the drug limited its value as a treatment agent in tardive dyskinesia (Tamminga, Crayton & Chase, 1979).

The benzodiazepines are thought to have central GABA minergic action, and clinically they exert sedative and muscle relaxant effects. It is however uncertain whether these drugs act specifically or merely as sedatives in controlling the symptoms of tardive dyskinesia (Jeste & Wyatt, 1979). O'Flanagan (1973) described the use of diazepam in controlling dyskinesia. Diazepam in doses of 10 mg 3 times a day was effective, but patients became drowsy and dull. In a later report, (O'Flanagan 1975), clonazepam was used in place of diazepam to control dyskinesia, and in 42 patients who had been given clonazepam in doses of 0.5 mg twice daily to 1 mg 3 times a day, there had been a distinct improvement, without drowsiness in all cases. These results were not repeated in an open study with 18 chronic psychiatric patients with tardive dyskinesia. Only 2 showed noticeable improvement, and side effects included drowsiness, behavioural changes, confusion and ataxia (Sedman, 1976).

The parachlorophenyl analogue of GABA, baclofen, induces biochemical changes similar to GABA agonists (Fuxe, Hökfelt, Ljungdahl, Agnati, Johansson & de la Mora, 1975). In a double-blind crossover trial in 20 female patients
suffering from antipsychotic-induced tardive dyskinesia, 15 patients showed improvement on baclofen (Korsgaard, 1976). Side effects observed included sedation, muscular hypotonia, dizziness, vomiting and muscular rigidity. Similar results were obtained in a further double-blind crossover study, but the authors considered that side effects limited the practical usefulness of baclofen in the treatment of tardive dyskinesia (Gerlach, Rye & Kristjansen, 1978). Whilst no statistically significant changes were found between baseline scores and those at the end of baclofen and placebo periods, in a double-blind study in 10 chronic schizophrenic patients (Nair, Yassa, Ruiz-Navarro & Schwartz, 1978), the results cannot be compared with the 2 previously mentioned studies as in this trial all antipsychotic medications were withdrawn for at least 3 months prior to entry.

vi) **Dopamine agonists**

If the hypothesis that tardive dyskinesia is related to an abnormal hypersensitivity of dopaminergic receptors to normal or relatively normal levels of brain dopamine (Klawans, Ilahi & Shenker, 1970; Klawans, 1970) it might be expected that dopamine agonists would markedly exacerbate these abnormal movements. This was confirmed in a short-term trial in which levodopa (L-3, 4-dihydroxyphenylalanine) was given for 2 weeks to a patient who had developed tardive dyskinesia following chlorpromazine and haloperidol therapy (Klawans & McKendall, 1971). The dyskinesia worsened strikingly and after discontinuation of the levodopa, the
condition was only improved by the administration of haloperidol, and whilst the authors observed that it was unclear at that time whether the reinstitution of an antipsychotic drug would bring about permanent improvement in the dyskinesia, the procedure was subsequently condemned (Klawans, Goetz & Perlik, 1980).

Confirmation of a worsening of dyskinetic symptoms following levodopa treatment in a 36 year old female patient was reported by Carroll, Curtis & Kokmen (1977); however on a reduced dosage, improvement was observed. The authors postulated that this paradoxical and unexpected improvement may have been due to a stimulation of presynaptic dopamine receptors. Improvement was also reported using apomorphine, a directly acting dopamine agonist in the treatment of tardive dyskinesia in an undisclosed number of patients, although in the same study, d-amphetamine, an indirectly acting dopamine agonist, increased dyskinetic movements (Smith, Tamminga, Haraszti, Pandey and Davis, 1977).

In a single-blind study comparing the effects of 2 dopamine agonists, levodopa and bromocriptine and an anticholinergic (trihexyphenidyl), on antipsychotic induced tardive dyskinesia in 3 groups of 16 patients, bromocriptine was effective in 50 to 70 per cent of those treated and schizophrenia was not exacerbated. Levodopa was found to be unsuitable as, although it had a slight effect on kinetic disorders, side effects such as hallucinations and excitation were observed. With trihexyphenidyl improvement was noted in 10 of the 16 patients treated (Ringwald, 1978).
Iivanainen, Kaste, Juntunen, Kruus, Ranta & Seppälä (1978) investigated the effect of bromocriptine in a double-blind, placebo controlled crossover study in 10 mentally retarded patients. No beneficial effect on dyskinesia was observed. Bromocriptine and another dopamine agonist (CF 25-397) were administered to 8 schizophrenic patients with tardive dyskinesia. Neither agent significantly improved the dyskinesia (Tamminga & Chase, 1980). Earlier studies with bromocriptine were carried out with a relatively high daily dosage. A mean daily dosage of 32mg (range 20-50mg) was used by Ringwald (1978) and in the study above (Iivanainen et al, 1978) up to 50mg a day was given. It has been postulated that a low dose of bromocriptine may lead to predominant stimulation of the presynaptic inhibitory dopaminergic receptor thus reducing pre-synaptic dopamine release (Barnes, Kidger & Taylor, 1978), but 7 patients in the Tamminga and Chase study referred to above failed to improve after 3 weeks treatment with bromocriptine with a maximum daily dosage of 10mg. This study had the disadvantage that antipsychotic medication was discontinued prior to patients entry into the trial.

An alternative viewpoint on dosage of dopamine agonists was put forward by List & Seeman (1979) who suggested that short term high dose therapy with dopamine agonists might be of some value in alleviating antipsychotic-induced tardive dyskinesia clinically. They had shown that dopamine agonists could reverse antipsychotic-induced elevation of brain anti-
psychotic drug binding, by a 5 day administration of bromocriptine or levodopa + carbidopa to rats who had previously been subjected to chronic administration of large doses of haloperidol for 21 days.

vii) **Lithium**

Gerlach, Thorsen & Munkvad (1975) demonstrated an antihyperkinetic effect with lithium in antipsychotic induced tardive dyskinesia. In a double-blind, placebo controlled, crossover study in 20 patients they found a slight, but significant reduction in the dyskinesia. Eleven patients showed improvement, 3 patients were excluded from the study because of toxic reactions to lithium, and a further 2 refused to continue medication. Some improvement in dyskinesia was also reported in an open study in 6 patients (Reda, Escobar & Scanlan, 1975) but in a single-blind pilot study, followed by a placebo controlled double-blind trial with lithium, no improvement in dyskinesia was observed (Simpson, Branchey, Lee, Voitashevsky & Zoubok, 1976). This result was confirmed in 23 patients with tardive dyskinesia who were given lithium for an 8 week period. No significant improvement in dyskinetic movement was obtained, and in 2 patients there was an aggravation of the dyskinesia (Jus, Villeneuve, Gautier, Jus, Villeneuve, Pires & Villeneuve, 1978). This latter observation was also made by Beitman (1978) who treated a 56 year old female patient, who had previously shown signs of tardive dyskinesia, with lithium for depression. Within a few weeks of lithium therapy dyskinesia reappeared.
viii) **Pyridoxine**

Pyridoxine (Vitamin B₆) was used in treating 11 patients with tardive dyskinesia, because it had been observed earlier to diminish the effects of L-dopa in parkinsonian patients, but only 1 patient showed any improvement (Crane, Turek & Kurland, 1970). However, in an open study in 5 patients with tardive dyskinesia, oral doses of pyridoxine ranging from 1000 to 1400mg daily, was found to reduce the frequency and the severity of the dyskinesia (DeVeagh-Geiss & Manion, 1978).

ix) **Cyproheptadine**

Conflicting results have been obtained using the serotonin antagonist cyproheptadine in tardive dyskinesia. In open studies Goldman (1976) reported good results in all 3 patients treated; Kurata, Hosokawa & Koshino (1977) observed marked amelioration of dyskinesia in 4 of 11 patients treated, with lesser degrees of improvement in 4 others, but Gardos & Cole (1978) were unable to demonstrate any lasting effects in 5 patients treated with cyproheptadine.

x) **Oestrogens**

Raymond, Beaulieu, Labrie & Boissier (1978) demonstrated that chemical synaptic transmission can be influenced by hormones, namely oestrogens. In an open pilot study in 20 male patients with tardive dyskinesia, 16 patients showed varying degrees of improvement in dyskinetic scores (Villeneuve, Cazejust & Côté, 1980). The authors were, however, cautious in drawing definite conclusions, as in some instances the improvement was very slight.
xi) **Clonidine**

In an open study in 2 patients showing tardive dyskinesia, clonidine was observed to have a beneficial effect on both the psychotic condition and the dyskinesia (Freedman, Bell & Kirch, 1980). The authors noted that the hypotensive effect of clonidine was a particular disadvantage.

xii) **Propranolol**

Low-dose (20 to 40 mg per day) of the beta-adrenoceptor blocking agent, propranolol, was added to current anti-psychotic medication to treat tardive dyskinesia in a group of 10 chronic, psychiatric male patients. Seven showed significant improvement in their dyskinetic movements, which reappeared in 2 patients when propranolol therapy was stopped. These results were supported by a further study in which 3 psychotic patients with tardive dyskinesia, showed improvement in both dyskinetic movements and extrapyramidal side effects, when treated with propranolol in doses of 30 to 60 mg per day (Kulik & Wilbur, 1980).

xiii) **Manganese chelate**

Postulating that tardive dyskinesia was associated with a deficiency of manganese, doses of manganese chelate were administered to 15 patients with the syndrome. Four patients responded dramatically, and a further 9 patients showed a definite improvement in 2 to 5 days (Kunin, 1976). Similar responses were reported "in a smaller number of cases" (Hoffer, 1977) and in 6 cases (Norris & Sams, 1977).
xiv) **Fusaric acid**

Fusaric acid, a selective and potent dopamine-ß-hydroxylase inhibitor, has been shown to decrease noradrenaline and increase serotonin, but not to alter dopamine concentrations in the brain (Hidaka, 1971). The effect of fusaric acid on tardive dyskinesia and mental state was studied in 15 chronic psychogeriatric patients. Fusaric acid significantly relieved oro-facial dyskinesia, tremor and rigidity, and it improved the mental state of patients (Viukari & Linnoila, 1977).

xv) **Co-dergocrine**

It has been suggested that co-dergocrine is a dopamine agonist, a serotonin agonist and a noradrenaline antagonist (Loew, Vigouret & Jaton, 1979). In an uncontrolled study, 7 out of 10 schizophrenic patients showed improvement in their dyskinetic movements (Gomez, 1977).

This observation was supported in a further open study in which all 6 patients with tardive dyskinesia, treated with co-dergocrine improved (Hajioff, 1978). In a group of 9 psychotic patients with tardive dyskinesia treated with a placebo for 1 week, followed by active co-dergocrine for 7 weeks and then placebo for a final 2 weeks, all 9 patients showed highly significant improvement during the period of active medication (Arranz, Múñecas, Ganoza García & Forcadell Puyo, 1979). These findings were not confirmed in a small open study in 5 patients, as although 2 patients showed some improvement, 3 worsened (Mohamed, Kazarian, Merskey & Thompson, 1980). In a preliminary report on a double-blind study in 8 patients, superiority of co-dergocrine
over placebo was noted (Chien, Marder, Van Putten & Escobar, 1980). Work with co-dergocrine is reported in greater detail in Chapter 6.

xvi) Electroconvulsive Therapy

Although the effects of ECT on the dyskinetic process are unclear, and 1 report suggested that tardive dyskinesia had resulted from ECT (Uhrbrand & Faurbye, 1960), reports on the benefits of ECT in Parkinson's disease (Lebensohn & Jenkins, 1975; Asnis, 1977) suggested that tardive dyskinesia might improve following ECT treatment. However only 1 of 4 patients treated with ECT showed any improvement in dyskinetic scores, and the authors concluded that ECT had a negligible effect on the dyskinetic process (Asnis & Leopold, 1978). An improvement in a single patient was seen following 7 sessions of ECT with a concomitant improvement in depressive symptoms (Price & Levin, 1978).

2.7.8 Conclusions

In reviewing methods that have so far been used in the treatment of tardive dyskinesia, Jeste & Wyatt (1979) observed that it is interesting to note that most of these investigations have been based on some theoretical rationale about the mechanism of action of the treatments being tested, and yet the neuropathology underlying tardive dyskinesia, as well as the mode of action of the treatments used to combat it, so far has eluded understanding.

Most of the treatment methods reviewed in this chapter have yielded inconclusive results. Early enthusiasm produced by
apparent improvement in open studies has been tempered by disappointing results under double-blind, placebo controlled conditions. Numbers of patients in most of the studies have been small, and the period of treatment has been short. Improvements reported have not been maintained when the treatment has been stopped. Results are also difficult to interpret when in many instances antipsychotic medication has been stopped whilst the tardive dyskinesia is being treated. Factors influencing poor results also include age, chronicity of psychotic illness, length of hospitalisation and the variety and duration of antipsychotic medication.

2.8 IMPLICATIONS FOR PSYCHIATRY

In considering issues in tardive dyskinesia, Gardos & Cole (1980), stated that public health concern over tardive dyskinesia has been rising, but the magnitude of the problem has been undetermined. Incidence (as distinct from prevalence) refers to the number of new cases emerging in a well-defined population during a given time period, and in respect of tardive dyskinesia the true incidence is unknown. Prevalence rates yield conflicting and misleading estimates, and Gardos & Cole (1980) stated that it is premature to draw alarming conclusions from high and seemingly increasing prevalence rates. The major public health concern is the real possibility that with each passing year of widespread antipsychotic drug use, increasing numbers will develop tardive dyskinesia. Gathering reliable incidence figures from a wide-range of populations at risk over a long time period appears to be the only direct method of clarifying this issue.
In the Task Force report of the American Psychiatric Association (1980), on late neurological effects of antipsychotic drugs, the observation is made that while the problem is serious, an alarmist view is not warranted, especially since many cases are detected early and improve spontaneously. The best approach currently is to use antipsychotic drugs thoughtfully for clear indications, the best supported of which, scientifically, is chronic schizophrenia.

The subject is considered in greater detail in Chapter 7.

2.9 SUMMARY

The historical background to the treatment of mental illness, which has been characterised by the imposition of much physical suffering on the patient, is traced. The transformation that occurred following the discovery and introduction of antipsychotic drugs is then described, followed by consideration of the chemistry and animal pharmacology of these drugs. Clinical use, side effects and pharmacology of the antipsychotic drugs is outlined.

Tardive dyskinesia is then reviewed following its first observation in 1956, including a description of its clinical manifestations, its prevalence and the aetiology of the condition. The various agents, including antipsychotics as well as other drugs which have been implicated in the syndrome are listed, and attention is drawn to the occurrence of spontaneous dyskinesias.

The many methods so far used in the treatment of tardive dyskinesia, including their rationale, are reviewed, and reasons suggested for the many disappointing results obtained. Preliminary comments are made on the implications for psychiatry of tardive dyskinesia.
## CHAPTER 3

**METHODS OF ASSESSING TARDIVE DYSKINESIA**

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<td>3.6.4</td>
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<td>112</td>
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</tbody>
</table>
Much of the current confusion about the prevalence, incidence and seriousness of tardive dyskinesia grows out of confusion as to how to diagnose the condition and how to measure its intensity (Cole, 1975). He was of the opinion that the descriptive statement contained in the special report of the Task Force of the American College of Neuropsychopharmacology and the Food and Drug Administration (Schiele, Gallant, Simpson, Gardner, Cole, Crane, Chase, Ayd, Levine & Ochota, 1973) made the situation even more complicated. This descriptive statement which was recommended as a definition of the condition is here given in full:

'Tardive dyskinesia as usually seen in older, more chronic patients is characterised by stereotyped, repetitive, involuntary movements of the mouth, lips and tongue and sometimes accompanied by choreiform movements of the limbs or trunk.'

'The most widely described symptoms make up the 'bucco-linguomasticatory' (BLM) triad; this consists of sucking and smacking movements of the lips, lateral jaw movements, and the tongue will thrust, roll, or have fly catching movements. This movement may be carried out with the mouth closed, in which case the tongue will hit the inside of the cheek and a chewing-the-cud type of movement will be seen. While the BLM syndrome is the most frequently described and seen, it is by no means the only mode of onset. Sometimes tic-like movements involving the lips and eyes may antedate these symptoms and other parts of syndrome to be described later may also appear first. The oral movements usually worsen under emotional tension; they disappear during sleep.'
The extremities may show choreiform movements which are variable, purposeless, involuntary quick movements. They sometimes intensify on attention but are irregular in occurrence. Frequently associated with these symptoms are athetoid movements which are continuous arrhythmic worm-like slow movements in the distal parts of the limbs. The choreo-athetoid movements particularly affecting the arms and fingers are to be differentiated from schizophrenic stereotyped movements.

Another feature of the syndrome may be axial hyperkinesis, i.e. a to-and-fro clonic movement of the spine in the antero-posterior direction, a rare symptom, but one that has been seen as the only manifestation of the syndrome. Ballistic movements can also occur, as can rhythmical swaying movements of the body from one side to the other which can take on a rocking quality if the patient sits down. All of these features are seldom present at the same time, but the BLM signs, plus choreo-athetoid movements of the limbs with an inability to stand or sit still, are a frequent grouping of signs in severe cases. All involuntary movements disappear during sleep.

'Parkinsonian symptoms can coexist with tardive dyskinesia'.

Tarsy and Baldessarini (1976) suggested that the diagnosis of tardive dyskinesia should be considered in any patient displaying chorea, athetosis, dystonia, orofacial dyskinesia, facial grimacing, or tic-like disturbances, who have been taking phenothiazines or butyrophenones for a period of at least several months. Differential diagnosis between tardive dyskinesia
and other syndromes induced by antipsychotic drugs is discussed in Chapter 2, and recently attention has been drawn to the existence of 'subsyndromes' of tardive dyskinesia (Milavic & Gaind, 1980). Jus, Pineau, Lachance, Pelchat, Jus, Pires and Villeneuve (1976) distinguished four subgroups on a phenomenological basis, and Jeste, Potkin, Sinha, Feder & Wyatt (1979) differentiated two clinical categories of reversible and persistent tardive dyskinesia, and attributed different discriminant variables to each category. Barnes & Kidger (1979b) observed that on the basis of a factor analysis of abnormal movements in a population of chronic schizophrenics, tardive dyskinesia is not a single syndrome. They proposed that orofacial movements would constitute a central component, and the dyskinetic trunk and limb movements would constitute peripheral tardive dyskinesia. It appears that different subtypes of tardive dyskinesia may exist which are phenomenologically and neurochemically distinct (Barnes & Kidger, 1979b; Mackay & Sheppard, 1979).

The Task Force (1980) drew particular attention to the wide range of abnormal movements that are encountered clinically and may be called tardive dyskinesia. These abnormalities include minor movements that may be difficult to distinguish from habit spasms, other tics of unknown cause, psychotic mannerisms, manifestation of senescence, or even normal movements with ill-fitting dentures. Factors to be considered in differential diagnosis include schizophrenic reversible neuroleptic syndromes, and dyskinesias induced by other drugs (Table 3.1). It is nearly impossible to specify precise prevalence rates of tardive dyskinesia since there is no currently accepted standard for diagnosis (Task Force, 1980).
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Neuroleptic withdrawal-emergent dyskinesias or other transient acute dyskinesias associated with neuroleptics.</td>
</tr>
<tr>
<td>2.</td>
<td>Late and persistent &quot;classical&quot; tardive dyskinesia itself. *</td>
</tr>
<tr>
<td>3.</td>
<td>Stereotyped movements of schizophrenia. *</td>
</tr>
<tr>
<td>4.</td>
<td>Spontaneous oral dyskinesias of advanced age or senility. *</td>
</tr>
<tr>
<td>5.</td>
<td>Oral dyskinesias related to dental conditions or prostheses.</td>
</tr>
<tr>
<td>6.</td>
<td>Idiopathic torsion dystonia.</td>
</tr>
<tr>
<td>7.</td>
<td>Focal dystonia (oromandibular dystonia, blepharospasm, spasmodic torticollis) and habit spasms (tics).</td>
</tr>
<tr>
<td>8.</td>
<td>Huntington's disease. *</td>
</tr>
<tr>
<td>10.</td>
<td>Wilson's disease (hepato-cerebral-lenticular degeneration due to abnormal copper metabolism), manganism, and other disorders due to heavy metal poisoning. *</td>
</tr>
<tr>
<td>11.</td>
<td>Fahr's syndrome and other disorders with calcification of the basal ganglia.</td>
</tr>
<tr>
<td>12.</td>
<td>Postanoxic, postencephalitic and encephalitic extrapyramidal syndromes. *</td>
</tr>
<tr>
<td>13.</td>
<td>Rheumatic chorea (Sydenham's chorea, St Vitus' dance).</td>
</tr>
<tr>
<td>14.</td>
<td>Drug intoxications involving L-dopa and amphetamines and, less commonly, anticholinergics, antidepressants, lithium and phenytoin. *</td>
</tr>
<tr>
<td>15.</td>
<td>CNS complications of systemic metabolic disorders, such as hepatic or renal failure, hyperthyroidism, hypoparathyroidism, hypoglycemia and vasculitides. *</td>
</tr>
<tr>
<td>16.</td>
<td>Brain neoplasm (thalamic, basal ganglia).</td>
</tr>
</tbody>
</table>

* both psychiatric disorder and dyskinesia may be present.

Granacher (1981) whilst suggesting that research studies on the incidence or prevalence of tardive dyskinesia have included patients with movements completely unrelated to that disorder, was of the opinion that most cases of dyskinesia in chronic psychiatric patients who have been exposed to antipsychotic drugs will, in fact, be true tardive dyskinesia.

The methodological problems inherent in survey research are formidable (Gardos & Cole, 1980), and include the following:

1. Arbitrary definitions of tardive dyskinesia.
2. Measurement problems (particularly questionable reliability of rating scales).
3. Generalisability (study populations often consist of elderly, hospitalised patients, and the findings do not apply to drug-treated schizophrenic patients in the community).
4. The confounding effect of concurrent antipsychotic treatment, which may influence the level of observed dyskinesia.

3.2 **SUBJECTIVE ASSESSMENT**

The severity of dyskinesias may be expressed in very simple terms, such as mild, moderate or severe, or may be defined by more extensive and complex rating scales. The latter can take into account not only the severity of the abnormal movements at a given site, but can also document the movements at various sites throughout the body. Both approaches have been used to rate a number of dyskinesias, but there is no general agreement as to whether complex rating scales are more efficient or sensitive than simpler techniques (Marsden & Schachter, 1981). These two
authors have found that rating dyskinesias at different body sites (face, neck, trunk, each arm and each leg) on a simple 0 - 3 scale (nil, mild, moderate and severe) is the most satisfactory way of approaching the problem. This simple subjective rating scale, however, does not take into account the fact that dyskinesias may occur intermittently. Marsden & Schachter (1981) suggested the rating of dyskinesias at each body site not only for their severity, but also for the frequency (occasional, frequent or continuous). The severity factor is then multiplied by the frequency factor to give an overall dyskinesia score for each body site.


Videotaping has been used as a method of recording examination for abnormal movements in a number of studies (Gerlach & Thorsen, 1976; Itoh, Miura & Yagi, 1976; Gerlach, 1979). Whilst videotaping can record and sometimes reveal movements not observed at the time the examination is conducted (Gerlach, 1979), it does reduce three-dimensional movements to two dimensions, making movements such as undulations of the tongue harder to see (Gardos, Cole & La Brie, 1977). The merits and demerits of videotaping or filming are shown in Table 3.2. Techniques of measuring abnormal involuntary movements are described in the following section.
Table 3.2

**AUDIOVISUAL RECORDINGS IN THE ASSESSMENT OF DYSKINESIAS**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent record</td>
<td>Cost of apparatus</td>
</tr>
<tr>
<td>Opportunity for repeated assessment by several observers</td>
<td>Time needed to set up apparatus and record</td>
</tr>
<tr>
<td>Observers can be truly ignorant of treatment and side-effects</td>
<td>Difficulty in distinguishing normal from abnormal movements or speech</td>
</tr>
<tr>
<td>Sequences can be randomised to ensure blind rating</td>
<td>Impossible to prolong observation period in case of doubt.</td>
</tr>
<tr>
<td>Sequences can be used to train raters and validate rating scales</td>
<td>Impossible to ask patient to undertake tasks which may resolve ambiguities or provoke dyskinesias.</td>
</tr>
<tr>
<td></td>
<td>Visual recording in two dimensions only.</td>
</tr>
</tbody>
</table>

Source: Marsden & Schachter, 1981.
3.3 OBJECTIVE ASSESSMENT

A number of techniques for measuring the severity of tardive dyskinesia have been described. Electro-myography, in which muscular activity is recorded by the use of electrodes, has been successfully employed. Villeneuve, Jus & Jus (1973) placed electrodes on the right and left sides of the upper and lower lip, and used an electroencephalograph to record changes. The same authors were able to differentiate tardive dyskinesia which disappeared during sleep from the rabbit syndrome which persisted (Jus, Jus & Villeneuve, 1973). A modification of this technique in which a pneumatic transducer was connected to a small inflatable balloon placed inside the patient's mouth, whilst sensitive to changes was, nevertheless, stressful to patients (Casey & Denney, 1975). Similar findings were recorded by Chien, Jung, Ross-Townsend & Stearno (1977) who showed high correlations with clinical ratings but experienced difficulties in patient co-operation.

An ultrasound system for measuring patients' activity and disorders of movement was reported by Haines & Sainsbury (1972), and the authors were able to differentiate categories of depression and mania in terms of movements. The apparatus has been subsequently adapted to record and quantify disorders of facial movement with particular reference to tardive dyskinesia (Resek, Haines & Sainsbury, 1981). Serial measurements of tardive dyskinesia over five months revealed striking individual consistency.

Chorea of the upper extremities was measured photographically using small pocket torches attached to each hand, with the patient being required to hold his arms out in front of himself (Klawans, 1973; Klawans & Rubovits, 1974). A quantitative acceleration profile using triaxial vector
accelerometry providing a graphic display of the motion characteristics of a particular anatomical site has been described by Fann, Stafford, Malone, Frost & Richman (1977). The technique was evaluated in a group of normal subjects and the authors hypothesised that characteristic differences would be apparent in the motion profiles of patients developing drug-induced movement disorders and that the findings would be useful in diagnosing emerging symptoms and monitoring treatment-related changes.

A technique for the differential diagnosis of tremors, in which a jugular pressure recorder is reversed and strapped to the back of the patient's hand, has been described by Griffiths & Good (1981). An adapted phonocardiograph machine produced traces after amplification of the signal produced. The pattern and frequency of tremor and the ratio of postural to resting tremor frequency provided a positive diagnosis in most cases.

The unpredictability of most dyskinesias and most of their considerable variability from moment to moment have not encouraged extensive use of objective methods. Technical advances in the future may improve the reliability and sensitivity of objective methods of recording abnormal involuntary movements, but at the present clinical pharmacologists rely upon subjective assessment, perhaps coupled with very simple timing tests (Marsden & Schachter, 1981).

3.4 SELECTION OF RATING PROCEDURE

3.4.1 Objectives

A major section of this thesis involves a study of abnormal movements in 500 elderly subjects. It was necessary therefore to
decide upon an assessment procedure that would give a high probability of observing the majority of involuntary movements and their degree of severity in each subject within a limited period of examination.

3.4.2 Examination Procedure

The standardised examination procedure devised at the U S National Institute of Mental Health (AIMS, 1976) has gained universal acceptance (Smith, Kucharski, Oswald & Waterman, 1979a & 1979b; Kane & Schooler, 1980; Smith, Burke & Moon, 1981; Rey, Hunt & Johnson, 1981; Marsden & Schachter, 1981). This procedure has been varied slightly by Gaind & Kidger (1977), who commenced the examination by placing a text on a lectern and asking the subject to study the text. This distracting manoeuvre helped in unmasking dyskinetic movements.

In view of the wide acceptance of the AIMS examination, this procedure was adopted with minor modifications, the most important of these being the use of a composite picture of a series of animals that had been cut from Christmas cards, instead of the text described above. This was found to be very popular with elderly subjects, and their immediate attention was focussed on to the picture and abnormal movements, particularly in the orofacial region were quickly unmasked. The examination procedure is described in detail in Appendix 1 and the position of the subject is shown in Figure 3.1.
FIGURE 3.1

EXAMINATION OF SUBJECT FOR ABNORMAL MOVEMENTS
3.4.3 Rating Procedure

Several rating scales are currently available (Chapter 3, para 3.2) and the one developed at the Rockland State Hospital (Simpson, Zoubok & Lee, 1976) and subsequently revised (Simpson, Lee, Zoubok & Gardos, 1979) appears to be one of the most popular (Mackay & Sheppard, 1979).

The original Rockland Scale consisted of 33 items of movement abnormalities, and in order to simplify the rating it was decided to use the Abbreviated Rockland Dyskinesia Scales (Simpson, Lee, Zoubok & Gardos, 1979) which covered 13 items of abnormal movements. A further modification to this Abbreviated Scale was made by reducing the range of severity from 1 to 6 down to 0 to 4, omitting the one point on the Scale which fell between 1 (absent) and 3 (mild). The reason for this further modification was that the Abbreviated Rockland Dyskinesia scale gives a score of 1 where no movements are observed under each item listed on the scale. Thus, a patient with no abnormal movements under each of the 13 items listed would have a total score of 13 and yet have no dyskinesia. The Abnormal Involuntary Movement Scale (AIMS) (Task Force, 1980) uses a score of 0 denoting no movements under each item listed on the scale, and it was decided to follow a similar pattern. The Abbreviated Rockland score of 2 under each item denoting a questionable movement was also omitted with the aim of being more precise in observation. Thus, mild movements were rated 1, moderate movements 2, moderately severe movements 3 and severe movements 4. The total score for each patient consisted of the addition of all of the scores for each individual item. The modified scale is shown in Appendix 2. Definitions of the various items of abnormal movements are set out in Appendix 3.
3.5 ASSESSMENT OF ABNORMAL MOVEMENTS BY USE OF VIDEO TAPES

3.5.1 Materials and Methods

A preliminary study was undertaken in which three psychiatric patients from the Abraham Cowley Unit at St Peter's Hospital, Chertsey, and 4 patients from Horton Hospital, Epsom, were selected for examination. All 7 patients had been observed by ward staff to have exhibited abnormal involuntary movements over a period of several months, including the week prior to examination.

3.5.2 Ethical Consent

Approval for the study was obtained from the Consultant responsible for each patient. Individual patients were invited to participate in the procedure after it had been explained to them in detail. An assurance was given that the videotapes were to be used only for research purposes.

3.5.3 Recording of Abnormal Movements

In order that manifest movements could be observed under standard conditions, patients were seated on a firm, straight-backed, armless chair with feet placed firmly on the floor and slightly apart. The hands were rested unsupported on the knees in order that manifest movements could be observed.

The patients were taken through the procedure described in Appendix 1 and the entire examination was recorded using a videocamera which had been set up previously. The operator had been instructed to record any observed movements, with particular attention being given to the orofacial region.
3.5.4 **Assessment of Abnormal Movements**

Two raters, AJB and CMB, simultaneously observed the playback of the videotape and independently recorded their interpretation of the type and severity of abnormal movements of each patient, using the abnormal involuntary movements rating scale (Appendix 2).

3.5.5 **Results**

Due to the small sample of patients and the number of zero movement scores, it was impossible to calculate the Intraclass Coefficient (ICC) (Bartko & Carpenter, 1976) for each individual item of the AIMS examination. The overall ICC was calculated and indicated a reliability between the 2 raters of 0.90 (p<0.001). An ICC of 1 indicates perfect agreement, and thus that obtained between the two raters would be classified as good (Bartko & Carpenter, 1976).

In comparing the intra-rater reliability of rater AJB, an ICC of 0.93 (p<0.001) was achieved, showing that agreement between successive ratings by the same rater was good (Bartko & Carpenter, 1976).

3.5.6 **Discussion**

Within the limitation of a small sample of patients it has been possible, using a standard method, to show that there is 'good' consistency in both inter and intra-rater assessments of abnormal involuntary movements using the AIMS rating procedure, and recording movements on the Rockland Research Institute Scale.

The high number of zero movements scores, 286 out of 364, reduced the amount of data available for subsequent analysis.
3.6 ASSESSMENT OF ABNORMAL MOVEMENTS IN A SMALL GROUP OF ELDERLY SUBJECTS

3.6.1 Materials and Methods

Fifty five residents, the total population of one home for the elderly in Surrey, were included in the study. These were 13 males and 42 females with ages ranging from 67 to 100 years (mean 85.5 years).

3.6.2 Ethical Consent

Approval for the study was obtained from both the Social Services Department of Surrey County Council and the General Practitioners responsible for the medical care of the subjects (See chapter 5, para 5.2.2).

3.6.3 Recording of Abnormal Movements

Residents were examined individually under standard conditions. They were seated on a firm, straight-backed, armless chair with feet placed firmly on the floor and slightly apart. The hands were rested on the knees in order that manifest movements could be observed. The residents were taken through the procedure in Appendix 1.

3.6.4 Assessment of Abnormal Movements

Two raters, AJB and CMB, simultaneously observed the residents and independently recorded their interpretation of the type and severity of abnormal movements of each resident using the abnormal involuntary movements rating scale (Appendix 2). The
scores were subsequently analysed to test for inter-rater reliability.

3.6.5 Results

Thirty eight of the 55 residents examined had no observed abnormal involuntary movements.

Forty one of the 46 readings (89.1 per cent) excluding zeros agreed. Of these, 43.9 per cent would be expected due to chance, hence the difference between observed and chance agreement is 45.2 per cent. The very high chance agreement is due to the fact that most of the scores are either 1 or 2 here, compared with a larger spread of readings in the previous group (para 3.5.5).

The Intraclass Correlation Coefficient (ICC) for this data is 0.88 (p<0.001) which is very close to the corresponding results from the previous work para (3.5.5). The ICC for the individual items of the AIMS examination is shown in Table 3.3

3.6.6 Discussion

As in the previous work (para 3.5), within the limitations of a small sample of subjects it has been possible, using a standard method, to show 'good' consistency in inter-rater assessments of abnormal involuntary movements using the AIMS rating procedure and recording movements on the modified Rockland Research Institute Scale. A high number of zero movements scores, 1338 out of 1430, reduced the amount of data available for subsequent analysis. The high correlations in both of these reliability studies may be
TABLE 3.3
INTER-RATER RELIABILITIES FOR THE ABNORMAL INVOLUNTARY
MOVEMENTS RATING SCALE - TWO RATER SCORES

<table>
<thead>
<tr>
<th>ITEM</th>
<th>I.C.C.</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial and oral movements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Periocular area (blinking of eyes, tremor of eyelids)</td>
<td>(1.00)</td>
<td>2</td>
</tr>
<tr>
<td>2. Movements of the lips (pouting, puckering and smacking)</td>
<td>1.00</td>
<td>7</td>
</tr>
<tr>
<td>3. Chewing movements</td>
<td>.71</td>
<td>8</td>
</tr>
<tr>
<td>4. Sweet in mouth sign</td>
<td>(1.00)</td>
<td>2</td>
</tr>
<tr>
<td>5. Tongue protrusion</td>
<td>1.00</td>
<td>6</td>
</tr>
<tr>
<td>6. Tremor and/or choreoathetoid movements of the tongue.</td>
<td>.58</td>
<td>12</td>
</tr>
</tbody>
</table>

| Neck and Trunk | | |
| 7. Axial hyperkinesis (patient standing) | - | 0 |
| 8. Rocking movements | - | 0 |
| 9. Torsion movements | (1.00) | 2 |

| Extremities | | |
| 10. Movements of fingers and wrists | (1.00) | 4 |
| 11. Movements of ankles and toes | - | 1 |
| 12. Stamping movements | - | 0 |

| Entire body | | |
| 13. Akathisia | (1.00) | 2 |

I.C.C. = Intraclass Correlation Coefficient
- = Movement absent
N = The correlations were based on 17 subjects; the numbers in this column indicate the number of subjects in which the movement was present.
0 = Numbers too small to draw conclusions
partially due to the fact that the two raters had worked together on a number of occasions and had carried out training sessions with films and videotapes of dyskinetic patients.

Other authors have reported good consistency in inter-rater reliability using the AIMS rating procedure. Using 4 raters, Smith, Oswald, Kucharski & Waterman (1978) achieved inter-rater reliability on the total score ranging from 0.84 to 0.93. Where 2 raters were employed, reliabilities of 0.77 and 0.78 were obtained by Gardos, Cole & La Brie (1977), 0.92 by Moore & Bowers (1980) and 0.80 by Smith, Burke & Moon (1981). Problems can occur on rater bias, and Smith, Kucharski, Oswald & Waterman (1979b) noted that even with well-trained raters consistent differences can occur, and whilst 3 of their raters were in fairly good agreement, the 4th rater rated significantly higher on several scale items.

In this study it has not been possible to investigate further the effect of stress, food intake, circadian rhythm, time of day, time in relation to administration of drugs and other factors, on the severity of movement disorder. It is strongly recommended that where within patient ratings are undertaken on successive occasions, the examination procedure should be conducted at the same hour of day each time. Location of the examination should also be constant.

3.7 SUMMARY

The differentiation of tardive dyskinesia from other movement disorders is outlined and both subjective and objective assessment techniques discussed. A simple examination and rating procedure aimed to give a high probability of observing the majority of involuntary movements and their degree of
severity is described. This method was then validated for inter, and intra-rater reliability both from videotaped examination of patients and during actual examination sessions. Good consistency in inter-rater and intra-rater assessments of abnormal involuntary movements were obtained.
CHAPTER 4

PILOT STUDY TO TEST RATING TECHNIQUE

4.1 INTRODUCTION 115

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  4.2.1 Clinical Population 116
  4.2.2 Ethical Consent 116
  4.2.3 Assessment of Abnormal Movements 117
  4.2.4 Drop-outs 117

4.3 RESULTS 117

4.4 DISCUSSION 121

4.5 SUMMARY 124
4.1 INTRODUCTION

Uhrbrand & Faurbye (1960) were the first to observe that tardive dyskinesia is more frequent in the elderly and in patients with organic brain diseases. Many mentally handicapped patients have congenital or long-standing brain damage and, because of the increasing life span, the geriatric population of mentally handicapped individuals is increasing so that between 10 per cent and 24 per cent of patients in most long-stay hospitals are over 65 years. Thus, surveys for abnormal movements in these patients should therefore yield fruitful results, although such surveys will challenge diagnostic skills, as by no means will all the movement disorders be tardive dyskinesia; the involuntary movements of the cerebral palsies must be distinguished (Bicknell & Blowers, 1980b).

Having selected an examination procedure to assess abnormal movements, a pilot study was undertaken to establish the prevalence of tardive dyskinesia in a small population of elderly female patients in a hospital for the mentally handicapped because there would be many movements to observe, and to establish whether there were any differences between those who had received antipsychotic medication during the past seven years and those who had not.
4.2 MATERIALS AND METHODS

4.2.1 Clinical Population

Forty-one female patients, the total population available from one ward at Botleys Park Hospital, Chertsey, were included in the study. Ages ranged from 42 to 87 years with a mean age of 65.49 years. Time spent in the present hospital ranged from 2 to 50 years with a mean of 31.6 years. Most of the patients had spent a lifetime in institutions, including periods of time in other than the present hospital. Examination of past records revealed that some had been certified as moral defectives of dull intelligence but with no clear history of brain damage. Their current intellectual status ranged from a mental age of less than 5 years in 8 patients, to normal intelligence (IQ above 75) in 5 patients. Many patients had probably functioned at a higher level in the past, but their present rating had been affected by years of living in hospital, increasing age and the handicaps of progressive visual and hearing loss associated with the older age groups.

4.2.2 Ethical Consent

Approval for the study was given by the consultant responsible for the ward, who was herself one of the raters (DJB). The 2 ward sisters explained the procedure to each patient as far as was possible, bearing in mind levels of impaired mental function, and patients were given the opportunity to decline to participate, should they so wish.
4.2.3 Assessment of Abnormal Movements

The patients were examined individually under standard conditions using the examination technique described in Chapter 3 (para 3.4.2). Rater 1 (AJB) took the patients through the procedure with appropriate sympathetic encouragement and Rater 2 (DJB) recorded details of abnormal involuntary movements on the abbreviated dyskinesia rating scale of the Rockland Research Institute (Appendix 2).

4.2.4 Drop-outs

One patient aged 70 years who had a dyskinetic movement score of 30 was excluded from the study as her medical records showed that when she was admitted to the hospital in 1936 she was observed to have "tremor of the head". Other abnormal movements were noted in her records before antipsychotic drugs were available as therapeutic agents.

4.3 RESULTS

Abnormal movements indistinguishable from tardive dyskinesia were seen in 34 (85 per cent) of the 40 patients remaining in the study. Severity was considered to be mild (Abbreviated Rockland scores of 2 or less) in 15 patients (37.5 per cent) and moderate or greater (Abbreviated Rockland scores of 3 or more) in 19 patients (47.5 per cent).

Patients were then assigned to 1 of the 2 groups - group A which included those who had no antipsychotic medication in the past 7 years and group B which included those who had received antipsychotic medication.
during the past 7 years. In the 31 patients who had not received antipsychotic medication, 25 had abnormal movements noted, and in the 9 patients who had received antipsychotic medication, all patients had some abnormal movements.

Each group was subdivided into those below 65 years and those above 65 years, the mean dyskinetic scores were calculated and the standard errors obtained. The results are shown in Tables 4.1 & 4.2.

The age distribution is similar for the 2 groups (mean age of 65.3 for Group A and 65.7 for Group B). Differences between the 4 mean scores are not statistically significant at the 5 per cent level, but there is a trend for the scores to be greater in Group B, than in Group A, and a trend for the score to increase with age, but neither trend was very pronounced.

A variety of abnormal movements were seen in patients in both groups (Table 4.3). Most of the abnormalities seen were in the orofacial region. Of the 31 patients with abnormal movements all had 1 or more movement in the orofacial region. Tremor and/or choreoathetoid tongue movements were most frequently seen (15 patients) closely followed by movements of the lips (14 patients). Two patients had symptoms more typical of a cerebellar disorder and they had received no medication in the last 7 years. Two patients had Parkinson's disease, one was arteriosclerotic and the other post encephalitic, the latter improving with L-dopa. Two patients were epileptic and were on anti-convulsants. Three were receiving treatment for depression or anxiety and 2 maintained euthyroid with thyroxine therapy. Four patients received iron for anaemia, and 2 received analgesics for osteoarthritis.
### TABLE 4.1

**MEAN DYSKINETIC SCORES IN 31 PATIENTS NEVER EXPOSED TO ANTIPSYCHOTIC MEDICATION (GROUP A)**

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Patients</th>
<th>Mean Dyskinetic Score</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>13</td>
<td>2.69</td>
<td>0.59</td>
</tr>
<tr>
<td>&gt;65</td>
<td>18</td>
<td>3.78</td>
<td>0.86</td>
</tr>
<tr>
<td>All ages</td>
<td>31</td>
<td>3.32</td>
<td>0.56</td>
</tr>
</tbody>
</table>

### TABLE 4.2

**MEAN DYSKINETIC SCORES IN 9 PATIENTS WITH HISTORY OF ANTIPSYCHOTIC MEDICATION (GROUP B)**

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Patients</th>
<th>Mean Dyskinetic Score</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>4</td>
<td>5.25</td>
<td>1.65</td>
</tr>
<tr>
<td>&gt;65</td>
<td>5</td>
<td>5.20</td>
<td>1.56</td>
</tr>
<tr>
<td>All ages</td>
<td>9</td>
<td>5.22</td>
<td>1.06</td>
</tr>
</tbody>
</table>
# Table 4.3

<table>
<thead>
<tr>
<th>MOVEMENT</th>
<th>With anti-psychotic medication (n = 9)</th>
<th>Without anti-psychotic medication (n = 31)</th>
<th>All patients (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periocular area</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Movement of lips</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Chewing movements</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Bonbon sign</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tongue protrusion</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Tremor and/or choreoathetoid</td>
<td>3</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Tongue movements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial hyperkinesis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rocking movements</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Torsion movements</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Movement of fingers and wrists</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Movements of ankles and toes</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stamping movements</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Body akathisia</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Eight patients were mildly hypertensive and obese, and were controlled by diuretics and anti-hypertensives. The average dyskinetic score in this group receiving treatment for hypertension was 2.3, which was lower than for any of the defined groups. The reason for this was not apparent.

Of the 9 patients who had received antipsychotic preparations during the past 7 years, 5 had received thioridazine alone, one haloperidol followed by the addition of thioridazine and flupenthixol, and one haloperidol followed by thioridazine. In addition, these 9 patients had received antidepressants (5 prescriptions), antiparkinsonian drugs (5 prescriptions), minor tranquillisers (5 prescriptions) and barbiturates (2 prescriptions).

4.4 DISCUSSION

The examination to observe dyskinetic movements was brief, easy to conduct, and hearing, visual or intellectual impairment in the patient sample proved no major obstacle. The patients appeared to enjoy the procedure and co-operation was easy to obtain. The possibility of anxiety, provoked by the examination, masking abnormal movements was reduced by the fact that both raters were known to the patients.

Whilst it is generally accepted that tardive dyskinesia occurs as a result of long-term antipsychotic medication, there is evidence to suggest that the disorder can occur in persons who have never received these compounds (Brandon, McClelland & Protheroe, 1971; Crane, 1973; Crane & Smeets, 1974). This aspect is dealt with in greater detail in Chapter 2 (para 2.7.6).
Whilst the results in this pilot study point to a high prevalence rate of abnormal movements in a selected group of elderly, long-stay, female, mentally handicapped patients, they are similar to those obtained by Jus, Pineau, Lachance, Pelchat, Jus, Pires & Villeneuve, (1976) who, with careful screening, eliminated abnormal movements found in other neurological disorders, and showed a prevalence rate of 60 per cent in the 50 to 69 years age group, and in those of 70 years and above the rate had risen to 75.6 per cent. The prevalence rate in this study was 84 per cent in those up to 69 years of age, and 86.7 per cent in the 70 years and above age group. These findings may possibly be related to the sex of the patients, their increasing age and the frequency of brain damage. The failure to establish a significant link with antipsychotic medication may be due to the overall high frequency of abnormal movements.

Of the 9 patients who had received antipsychotic medication, the 2 showing the highest dyskinetic movements were receiving haloperidol, whereas those receiving thioridazine produced lower scores. In fact in the treated group the 2 patients showing the least dyskinetic movements (score of 2 and 1) were from patients who had received thioridazine for 7 years (total intake 255gm) and 17 years (total intake 679gm) respectively. The possibility of thioridazine causing less dyskinetic movements is considered further in Chapter 5 (para 5.3.2).
4.5 **SUMMARY**

Forty-one female patients in a hospital for the mentally handicapped were examined for abnormal movements characteristic of tardive dyskinesia. Whilst mild abnormal movements of the tongue, lips, jaws and hands were found in 37.5 per cent and more obvious movements in a further 47.5 per cent, there was no significant relationship to intake of antipsychotic medication during the last 7 years nor to chronological age. The trend, however, was for increased prevalence of movements with a history of antipsychotic medication and increasing age. The examination protocol was found to be easy to administer and patient co-operation quickly obtained despite limited cognitive abilities.
CHAPTER 5

PREVALENCE OF TARDIVE DYSKINESIA IN THE ELDERLY

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5.5 SUMMARY 151
5.1 **INTRODUCTION**

By definition the term "tardive dyskinesia" implies an iatrogenic disease caused by chronic antipsychotic drug therapy (Klawans, Goetz & Perlik, 1980). A number of epidemiological studies have been conducted to establish the frequency of the disorder and the significance of such factors as age, sex, and type of underlying psychiatric disease (Villeneuve, Lavallee & Lemieux, 1969; Brandon, McClelland & Protheroe, 1971; Crane 1973). Other factors additional to age and sex have been studied including length of hospitalisation, history of antipsychotic drug-induced extrapyramidal syndromes and type of schizophrenia (Jus, Pineau, Lachance, Pelchat, Jus, Pires & Villeneuve, 1976). No established patterns have emerged to clarify these epidemiological issues, and it appears that these are not significant factors in the development of tardive dyskinesia.

The occurrence of involuntary movements similar to tardive dyskinesia in elderly subjects who have never been exposed to antipsychotic medication has also been reported (Marsden & Parkes, 1973; Crane & Smeets, 1974; Bourgeois, Bouilh, Tignol & Yesavage, 1980; Blowers & Bicknell, 1980.)

In discussing the aetiology of tardive dyskinesia and advocating an open-minded attitude, Tarsy & Baldessarini (1976) suggested that more work should be done to study the possible relationships of drug effects and the tardive dyskinesia syndrome. They also suggested that more epidemiological studies in countries where drugs are still not generally available would be helpful.
The availability of a large population of elderly subjects in the care of a local authority presented an opportunity of conducting a detailed study to determine the presence of abnormal involuntary movements with a view to establishing prevalence rates of antipsychotic drug-induced tardive dyskinesia and spontaneous dyskinesia. As drugs other than antipsychotic agents have been reported to have caused tardive dyskinesia, additional objectives would be to examine individual drug histories with a view to ascertaining which drugs and what other physical factors may contribute to the presence of dyskinetic movements.

5.2 MATERIALS AND METHODS

5.2.1 Clinical Population

Five hundred elderly subjects, 138 males and 362 females, who were resident or receiving short term or day care in 12 local authority residential homes for the elderly were included in the study. Ages ranged from 59 - 102 years with a mean age of 82.6 years (male mean age 81.4 years, female mean age 83.1 years). Five subjects had been admitted as short-stay holiday residents, 14 subjects were attending the homes on a continuing day-care basis, and the remaining 481 subjects had been resident in this type of accommodation for a period of between 2 months and 17 years (mean 3.3 years). Additionally, 49 of these subjects had spent periods of their lives in other institutional care in psychiatric or mental handicap hospitals for periods of between 3 months and 38 years (mean 10.4 years). The total period of institutional care for the entire sample ranged from 2 months to 39 years (mean 4.3 years). During their period of care 122 (24.4 per cent) of the total
population in the study had been treated with antipsychotic drugs. There were no significant age differences between the group who had received antipsychotic drugs and the group who had never been exposed to this class of drugs (Table 5.1).

5.2.2 Ethical Consent

Approval for the study was first sought through the Social Services Department of Surrey County Council. At a joint meeting with the Area Specialist in Community Medicine and the Deputy Director of Social Services the project was outlined and formal approval obtained. Letters and a study protocol were then sent to the General Practitioners who were responsible for the provision of medical services for residents of Homes for the Elderly in Surrey, informing them of approval given to the project. The General Practitioners' consent was sought and obtained in writing in order that medical records and drug histories could be searched subsequent to the examination for abnormal movements (Appendix 4).

A protocol of the proposed study was submitted to the Secretary of the Surrey Local Medical Committee and subsequent questions answered. In view of the widespread involvement of General Practitioners in the care of the elderly, 500 copies of the letter (Appendix 4) were sent to all GPs who were practising within the area covered by the Surrey Family Practitioner Committee. Letters were then sent to Officers in Charge of the Homes for the Elderly within the County of Surrey giving them details of the study and informing them of a planned presentation on how the work would be carried out in their respective Homes (Appendix 5).
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Male &amp; Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Population</strong></td>
<td>138</td>
<td>362</td>
<td>500</td>
</tr>
<tr>
<td><strong>Mean Age (yrs)</strong></td>
<td>81.4</td>
<td>83.1</td>
<td>82.6</td>
</tr>
<tr>
<td><strong>Antipsychotic Treated Group</strong></td>
<td>30</td>
<td>92</td>
<td>122</td>
</tr>
<tr>
<td><strong>Mean Age (yrs)</strong></td>
<td>81.0</td>
<td>82.8</td>
<td>82.4</td>
</tr>
<tr>
<td><strong>NonAntipsychotic Group</strong></td>
<td>108</td>
<td>270</td>
<td>378</td>
</tr>
<tr>
<td><strong>Mean Age (yrs)</strong></td>
<td>82.9</td>
<td>83.2</td>
<td>82.6</td>
</tr>
</tbody>
</table>
Individual residents were invited by care staff to participate in the examination procedure, without creating an anxiety situation as far as that was possible. Where any patient expressed reluctance they were not included in the study. In all 12 establishments involved in the project a total of 8 residents declined to take part.

5.2.3 Assessment of Abnormal Movements

The residents were examined individually under standard conditions described in Appendix 1. Rater 1 (AJB) took the residents through the procedure with appropriate sympathetic encouragement. The composite picture of the animals was a source of immediate interest and the resident was reassured by being told that this was a very simple memory test. The finger to thumb exercise was introduced by indicating that it was a simple check for arthritis, and whilst this often brought forth a history of arthritic development, the widespread acceptance of the manoeuvre was justified.

Rater 2 (CMB) recorded details of abnormal movements on the abnormal involuntary movements rating scale (Appendix 2). Dyskinetic movements were considered in two categories for determination of prevalence rates. Global AIMS scores of 1 and above were all categorised as having abnormal involuntary movements, and those with an AIMS global score of 3 and above were considered to have tardive dyskinesia, or where there was no recorded history of antipsychotic medication, to have dyskinesia indistinguishable from tardive dyskinesia. The AIMS score of 3 is considered indicative of true tardive dyskinesia (Smith, Kucharski, Oswald & Waterman, 1979b; Borison, 1981).
5.3 RESULTS

5.3.1 Association of Tardive Dyskinesia with Antipsychotic Drugs

Abnormal involuntary movements (AIMS score of 1 or more) were observed in 180 (36 per cent) of the 500 subjects who were examined. Orofacial involvement was present in 140 of the 180 subjects with abnormal movements.

In the 122 subjects (24.4 per cent) who had received antipsychotic drugs for a minimum period of 3 months, abnormal involuntary movements were present in 58 (47 per cent), and in the 378 subjects (75.6 per cent) who had no recorded history of antipsychotic medication, abnormal movements were present in 122 (32 per cent). The Chi Square test (Kirkwood, 1981) indicated that the difference in the prevalence of abnormal movements between subjects who had received antipsychotics and those who had never been exposed to these compounds was statistically significant ($p < 0.001$), thus confirming the association of dyskinetic movements with antipsychotic medication.

The prevalence figures using an AIMS score of 3 and above were lower, and a total of 77 (15 per cent) of the 500 residents showed dyskinetic movements. In the 122 residents who had a history of antipsychotic medication, dyskinesias were present in 27 (22 per cent) as compared with 50 (13 per cent) in the 378 residents who had never received antipsychotics. This difference between the 2 groups was statistically significant ($p < 0.001$) (Table 5.2).
TABLE 5.2

ASSOCIATION OF TARDIVE DYSKINESIA WITH ANTIPSYCHOTIC MEDICATION

<table>
<thead>
<tr>
<th></th>
<th>1 or more</th>
<th>3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Population</strong></td>
<td>500</td>
<td>180 (36%)</td>
</tr>
<tr>
<td><strong>Antipsychotic Treated Group</strong></td>
<td>122</td>
<td>58 (47%)</td>
</tr>
<tr>
<td><strong>NonAntipsychotic Group</strong></td>
<td>378</td>
<td>122 (32%)</td>
</tr>
</tbody>
</table>
Twelve residents in the antipsychotic-treated group had AIMS scores of between 5 and 9 inclusive, and a further 3 residents had scores of 11, 15 and 15 respectively. In the non-antipsychotic-treated group, 7 residents had scores of between 5 and 9 inclusive, and a further 3 residents had scores of 11, 11 and 18 respectively. The resident with a score of 18, which was the highest score in the total study, was an 85 year old lady who had been admitted from the community 6 months previously. She had been living on her own and was deemed to be in need of care following a period of self neglect. She had never been exposed to antipsychotic medication during her lifetime.

5.3.2 Association of Tardive Dyskinesia with the use of Multiple Antipsychotics

The prevalence of tardive dyskinesia increased in residents who had a history of medication with more than one antipsychotic drug. In the 91 patients who had received one antipsychotic drug, 13 (14 per cent) had tardive dyskinesia. Where 2 antipsychotic drugs had been administered, 10 of 20 residents (50 per cent) had dyskinesia, and in the 11 residents who had received 3 antipsychotics, 5 (45 per cent) had dyskinesia (Table 5.3). The difference between the prevalence rate of dyskinesia in the 13 residents (14 per cent) who had received only 1 antipsychotic drug and the 15 (49 per cent) who had received 2 or more antipsychotics was statistically significant (p < 0.001). Boll & Smith (1978), in a large scale study, showed that in a group of 576 patients those on 2 or more antipsychotic drugs had higher dyskinetic scores than those on 1 antipsychotic drug.
# TABLE 5.3

## ASSOCIATION OF TARDIVE DYSKINESIA WITH THE USE OF MULTIPLE ANTIPSYCHOTICS

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of Patients</th>
<th>Patients with Tardive Dyskinesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Antipsychotics</td>
<td>378</td>
<td>50 (13%)</td>
</tr>
<tr>
<td>One Antipsychotic</td>
<td>91</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>Two Antipsychotics</td>
<td>20</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Three Antipsychotics</td>
<td>11</td>
<td>5 (45%)</td>
</tr>
</tbody>
</table>
5.3.3 Association of Tardive Dyskinesia with Specific Antipsychotics

In examining the effect of individual antipsychotics, data are presented where 4 or more residents were on a particular compound. Table 5.4 shows that of the 4 most popular phenothiazines prescribed in these nursing homes, 3 of the 17 residents (18 per cent) who received promazine had tardive dyskinesia, 2 (11 per cent) of the 18 who had received prochlorperazine were affected, 3 (11 per cent) of the 27 who received chlorpromazine were affected, but none of the 13 who received thioridazine had tardive dyskinesia. Table 5.5 indicates the range of dosage, the treatment period and the range of total intake of each of these 4 compounds, and it is of interest to note that thioridazine, the compound used for the longest period and with the highest daily range and total intake, is the drug which is free from the complications of tardive dyskinesia.

In the multiple use of antipsychotics, the highest prevalence of tardive dyskinesia occurred where haloperidol was used, and of the 9 residents receiving haloperidol in their drug regimen, 5 (56 per cent) had tardive dyskinesia. In the 6 residents who received haloperidol in the multiple drug regimen plus an antiparkinsonian drug, 4 (67 per cent) had tardive dyskinesia.

5.3.4 Association of Tardive Dyskinesia with Antiparkinsonian Drugs

Analysis of data from drug histories of the 500 residents in the study showed that 48 (9.6 per cent) had received one or more antiparkinsonian drug during the previous 7 years. In this group of 48, dyskinesias were observed in 17 (35 per cent) whereas in the
<table>
<thead>
<tr>
<th>DRUG</th>
<th>No of Patients</th>
<th>Patients with Tardive Dyskinesia</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promazine</td>
<td>17</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>18</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>27</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRUG</td>
<td>No. of Patients</td>
<td>Daily Dosage Range</td>
<td>Total Intake Range</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Promazine</td>
<td>17</td>
<td>25 - 150 mg</td>
<td>4.5 - 216 gm</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>18</td>
<td>10 - 50 mg</td>
<td>1.3 - 27 gm</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>27</td>
<td>10 - 300 mg</td>
<td>2.7 - 401 gm</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>13</td>
<td>30 - 450 mg</td>
<td>6 - 1751 gm</td>
</tr>
</tbody>
</table>
group of 452 who had never received antiparkinsonian drugs dyskinesias were present in 60 (13 per cent) indicating that the use of antiparkinsonian drugs was associated with more dyskinesias ($p<0.001$). The prevalence of tardive dyskinesia in those who had received antiparkinsonian drugs was higher in the group of 37 females, where 15 (41 per cent) had AIMS scores of 3 and above, compared with that seen in the 11 males where 2 (18 per cent) had dyskinesias ($p<0.001$). However, in the group of 452 residents who had not received antiparkinsonian drugs the reverse was observed. In females 33 (10 per cent) had dyskinetic movements compared with 27 (21 per cent) in males ($p<0.001$) (Table 5.6).

In the 32 residents receiving antiparkinsonian drugs in combination with antipsychotic drugs, 13 (41 per cent) had dyskinesias, whereas in the 16 who received antiparkinsonian drugs without antipsychotic medication 4 (25 per cent) had dyskinetic movements ($p<0.001$) (Table 5.6).

It has been shown (see para 5.3.2) that the use of multiple antipsychotic agents produced more dyskinesias than the use of any single agent. Similarly, the prevalence of tardive dyskinesia resulting from the combination of antiparkinsonian drugs with antipsychotic drugs also increased with the number of antipsychotic drugs taken. This rose from 4 of 16 (25 per cent) where one antipsychotic drug was taken to 4 of 5 (80 per cent) who had received 3 or more antipsychotic agents.

5.3.5 Association of Tardive Dyskinesia with Benzodiazepine Drugs

One hundred and thirty of the 500 residents (26 per cent) had received one or more benzodiazepine during the previous 7 years.
### TABLE 5.6

ASSOCIATION OF TARDIVE DYSKINESIA WITH ANTIPARKINSONIAN MEDICATION

<table>
<thead>
<tr>
<th>DRUG</th>
<th>POPULATION</th>
<th>T D PRESENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Antiparkinsonian</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>No Antiparkinsonian</td>
<td>126</td>
<td>326</td>
</tr>
<tr>
<td>Antiparkinsonian with Antipsychotic</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Antiparkinsonian with No Antipsychotic</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>No Antiparkinsonian No Antipsychotic</td>
<td>102</td>
<td>260</td>
</tr>
<tr>
<td>No Antiparkinsonian with Antipsychotic</td>
<td>24</td>
<td>66</td>
</tr>
</tbody>
</table>
tardive dyskinesia was present in 24 (18 per cent) in those who had taken benzodiazepines compared with 53 (14 per cent) of the 370 who had never received benzodiazepine therapy (Table 5.7). The fact that this difference did not reach a level of statistical significance is interesting in view of reports on the use of benzodiazepines to control tardive dyskinesia (O'Flanagan 1973; O'Flanagan 1975; Jeste & Wyatt, 1979).

The combination of benzodiazepines with antipsychotics was associated with the presence of tardive dyskinesia in 12 of the 34 residents (35 per cent) who had been treated with both drugs. In the 96 residents where benzodiazepines had been administered without antipsychotic drugs, tardive dyskinesia was present in 12 (13 per cent), whereas in the 88 who were receiving antipsychotics without concomitant benzodiazepines 15 (17 per cent) showed dyskinesia (Table 5.7).

In the 280 residents who did not receive benzodiazepines or antipsychotics, 38 (13 per cent) had dyskinesia which is significantly less (0.25> p> 0.01) than in the 34 who received both compounds, where dyskinesia was present in 12 (35 per cent) (Table 5.7).

5.3.6 Association of Tardive Dyskinesia with Antidepressant Drugs

Seventy four residents in the total population studied received antidepressant compounds and in this group tardive dyskinesia was present in 12 (16 per cent). In the group of 426 who did not receive antidepressants, 65 (15 per cent) had dyskinesia, indicating that these compounds did not significantly affect the presence of tardive dyskinesia (Table 5.8).
### TABLE 5.7

**ASSOCIATION OF TARDIVE DYSKINESIA WITH BENZODIAZEPINES**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>POPULATION</th>
<th>T D PRESENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>29</td>
<td>101</td>
</tr>
<tr>
<td>No Benzodiazepine</td>
<td>108</td>
<td>262</td>
</tr>
<tr>
<td>Benzodiazepine with Antipsychotic</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>No Benzodiazepine with Antipsychotic</td>
<td>22</td>
<td>74</td>
</tr>
<tr>
<td>No Benzodiazepine w/ No Antipsychotic</td>
<td>84</td>
<td>196</td>
</tr>
<tr>
<td>No Benzodiazepine w/ Antipsychotic</td>
<td>24</td>
<td>64</td>
</tr>
</tbody>
</table>
# Table 5.8

## Association of Tardive Dyskinesia with Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population</th>
<th>T D Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>16</td>
<td>58</td>
</tr>
<tr>
<td>No Antidepressant</td>
<td>121</td>
<td>305</td>
</tr>
<tr>
<td>Antidepressant with Antipsychotic</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Antidepressant with No Antipsychotic</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>No Antidepressant with Antipsychotic</td>
<td>96</td>
<td>239</td>
</tr>
<tr>
<td>No Antidepressant with No Antipsychotic</td>
<td>25</td>
<td>66</td>
</tr>
</tbody>
</table>
The combination of antidepressants with antipsychotics in 31 residents was associated with dyskinesia in 9 (29 per cent), whereas in the group of 335 residents where neither drug had been prescribed dyskinesia was present in 47 (14 per cent) (Table 5.8). This was not statistically significant.

In the 31 residents who received antidepressants without antipsychotic drugs, 3 (20 per cent) showed dyskinesia, compared with 18 (20 per cent) of the 91 who received antipsychotic drugs without antidepressants (Table 5.8).

5.3.7 Association of Tardive Dyskinesia with Hypnotic/Sedative Drugs

One hundred and twenty nine residents in the total population in the study were receiving hypnotics or sedatives for night-time sedation, and of these 27 (21 per cent) had dyskinesia. In the 371 residents who were not treated with hypnotics or sedatives dyskinesia was present in 50 (13 per cent) (Table 5.9). This did not reach a level of statistical significance (0.1 > p > 0.05).

5.3.8 Association of Tardive Dyskinesia with Age and Sex

The subjects were grouped by decades and 9 (32 per cent) of the 28 residents in the 60 to 70 years decade had dyskinesia. In the 70 to 80 decade, 25 (19 per cent) had dyskinesia and in the 80 to 90 decade, 23 (9 per cent) were affected (Table 5.10). No consistent trend of increasing dyskinesias with age was observed in either males or females, or in the total population over the age of 70, but the prevalence rate of dyskinesias in the 30 subjects under the age of 70 years was 30 per cent (9 subjects) and in the 470 over 70
### TABLE 5.9

**ASSOCIATION OF TARDIVE DYSKINESIA WITH HYPNOTICS/SEDATIVES**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>POPULATION</th>
<th>T D PRESENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Hypnotic/Sedative</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td>No Hypnotic/Sedative</td>
<td>108</td>
<td>263</td>
</tr>
</tbody>
</table>
### TABLE 5.10

**ASSOCIATION OF TARDIVE DYSKINESIA WITH AGE AND SEX**

<table>
<thead>
<tr>
<th>Population</th>
<th>&gt;50</th>
<th>&gt;60</th>
<th>&gt;70</th>
<th>&gt;80</th>
<th>&gt;90</th>
<th>&gt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M &amp; F</strong></td>
<td>500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS 3 or over</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>138</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS 3 or over</td>
<td>29</td>
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<td></td>
</tr>
<tr>
<td>Percentage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>362</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS 3 or over</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
years the prevalence rate was 14 per cent (67 subjects). However, this was not statistically significant (0.1 > p > 0.05).

Twenty nine of the 138 males (21 per cent) in the study had dyskinesias (AIMS score of 3 and above) compared with 48 (13 per cent) of the 362 females. The difference between these two groups was not statistically different (0.1 > p > 0.05) (Table 5.10).

There was no significant difference in the frequency of dyskinesias in the 31 males who had received antipsychotic drugs, where 9 (29 per cent) had AIMS scores of 3 and above compared with 20 of the 107 (19 per cent) who had never been exposed to antipsychotic medication. However, in the 91 females who had received antipsychotics, 18 (20 per cent) had dyskinesias, which was statistically significant (p < 0.001), compared with the presence of dyskinesias in 30 (11 per cent) of the 271 who had never received antipsychotic drugs (Table 5.11).

5.4 DISCUSSION

Whilst Evans (1965) observed that the causal relationship between treatment with antipsychotic drugs and oral dyskinesia is presumptive, but is likelier than other possibilities, epidemiologic studies strongly support an association between the use of antipsychotic drugs and the development of persistent, as well as relatively transient, forms of tardive dyskinesia (Baldessarini, 1974).

One criticism of the concept of tardive dyskinesia is that dyskinesia frequently occurs spontaneously among chronic psychiatric patients, especially the elderly (Jeste & Wyatt, 1981).
TABLE 5.11

SEX DIFFERENCES IN THE PREVALENCE OF DYSKINESIAS

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of Subjects</th>
<th>AIMS Score 3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotic Treated Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>31</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>F</td>
<td>91</td>
<td>18 (20%)</td>
</tr>
<tr>
<td>M &amp; F</td>
<td>122</td>
<td>27 (22%)</td>
</tr>
<tr>
<td><strong>Non Antipsychotic Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>107</td>
<td>20 (19%)</td>
</tr>
<tr>
<td>F</td>
<td>271</td>
<td>30 (11%)</td>
</tr>
<tr>
<td>M &amp; F</td>
<td>378</td>
<td>50 (13%)</td>
</tr>
</tbody>
</table>
Marsden & Parkes (1973) estimated that some 2 per cent of the inmates of chronic geriatric homes exhibit some spontaneous orofacial dyskinesia and the same prevalence rate was noted by Greenblatt, Dominick, Stotsky & DiMascio (1968) who examined a group of 270 patients in 2 large nursing homes. Pakkenberg & Fog (1974) suggested that spontaneous dyskinesia was treatable with drugs such as tetrabenazine and pimozide that have been used in the treatment of tardive dyskinesia. In a review, Jeste & Wyatt (1981) found 12 major studies comparing the prevalence of dyskinesia among antipsychotic-treated and non-antipsychotic-treated patients. Ten of these 12 studies found a significantly higher prevalence of dyskinesia among antipsychotic-treated patients. Taking all 12 studies together, the overall weighted mean prevalence of dyskinesia for chronically institutionalised individuals was 3.25 greater in the antipsychotic group than in the non-antipsychotic-treated group.

In the present study, abnormal involuntary movements (AIMS score 1 or greater) were present in 58 of 122 residents (47 per cent) who had a history of antipsychotic medication, and in the non-antipsychotic-treated group 122 of 378 residents (32 per cent) had abnormal movements. The difference between the 2 groups was statistically significant ($p < 0.001$). Using an AIMS score of 3 or greater as being indicative of true tardive dyskinesia (Borison, 1981), the prevalence figures were 22 per cent in the antipsychotic treated group and 13 per cent in the non-antipsychotic-treated group. The difference was again statistically significant ($p < 0.001$). From these results it seems clear that there is a level of idiopathic or spontaneous dyskinesia and that the administration of antipsychotic drugs increases the prevalence of dyskinesias.
The wide variation in prevalence rates of tardive dyskinesia is referred to earlier (see 2.7.3). Smith, Kucharski, Oswald & Waterman (1979a) showed prevalence rates ranging from 62.1 per cent using a criterion level of an AIMS score of 2, to 6.8 per cent using an AIMS score of 4, in a group of 377 psychiatric inpatients. They suggested an AIMS score of 3 as being an acceptable criterion. In this study the prevalence rate of tardive dyskinesia ranges from 47 per cent with an AIMS score of 1, down to 22 per cent with an AIMS score of 3, in the group receiving antipsychotic medication.

In other studies age has been reported a significant factor. Marsden & Parkes (1973) were of the opinion that orofacial dyskinesia rarely appeared below the age of 40. Kane, Wegner, Stenzler & Ramsey (1980) felt that their relatively low prevalence rate of tardive dyskinesia of 4.6 per cent might in a large part have been due to the relatively young age of their population. Crane (1974), in a survey of 699 chronic hospitalised patients, showed that age is a major contributing factor, in that the prevalence of tardive dyskinesia increased sharply after 55 years of age.

The present study shows that after age 70 there were no significant differences found in the prevalence of dyskinesias among the various age groups defined by decades. However, prevalence was higher in the under 70 years age group as compared with those over 70, although this did not quite reach a level of statistical significance.

The Task Force (1980) referred to the ageing brain having an increased likelihood of antipsychotic-related tardive dyskinesias, especially in the oral region. Whilst Ezrin-Waters, Seeman & Seeman (1981) reported that tardive dyskinesia increased directly with age, their study population of 94 ranged in age from 19 to 65, and only 3 patients were over 60 years of age.
Sex differences are frequently referred to in published reports and although Crane (1974) showed that sex did not appear to play a significant role in the prevalence of dyskinesia, Smith, Oswald, Kucharski & Waterman (1978) found a significant linear trend with age for their female sample and a significant quadratic trend for the male sample. Smith & Dunn (1979) were of the opinion that female/male prevalence ratios are difficult to interpret without consideration of the age and sex distribution of the sample. Whilst Smith, Kucharski, Oswald & Waterman (1979a) felt that the often quoted 2:1 female/male prevalence rate is true of only the 2 oldest age groups, Perényi & Arato (1980) found tardive dyskinesia in a significantly higher number of men than women. Ezrin-Waters, Seeman & Seeman (1981) found no sex differences in the overall prevalence rate.

In the current study, whilst there was no significant difference in the frequency of dyskinesias in males receiving antipsychotics and those who were not, the position with females was significantly different, with those receiving antipsychotic drugs having almost twice the frequency of dyskinesias than their non-antipsychotic treated counterparts.

The chronic use of anticholinergic (antiparkinsonian) drugs is to be avoided (Klawans, Goetz & Perlik, 1980; Task Force, 1980). Since anticholinergic agents clearly exacerbate already present tardive dyskinesia, it is possible that with chronic administration these drugs may alter the striatal neurochemical balance and potentiate the development of abnormal movements de novo (Klawans, 1973). Chouinard, De Montigny & Annable (1979) also showed that the central anticholinergic agent procyclidine exacerbated tardive dyskinesia, and they suggested that tardive dyskinesia might be uncovered by short-term administration of an anti-parkinsonian drug, and this might aid early detection and help to prevent the subsequent
development of incapacitating forms of the disorder. Bell & Smith (1978) reported that the administration of concomitant antiparkinsonian medication together with antipsychotics was only weakly related (p < 0.1) to patients' dyskinesia scores, and patients with higher than standard dose of antiparkinsonian medication did not have significantly higher dyskinesia scores.

In this study the total use of antiparkinsonian drugs in the population was associated with more dyskinesias (35 per cent) than residents not receiving these drugs (13 per cent) (p < 0.001). Residents receiving antiparkinsonian drugs in combination with antipsychotic drugs had a significantly higher rate of dyskinesias (41 per cent) than patients receiving antiparkinsonian drugs alone (25 per cent) (p < 0.001). The 2 residents with the most severe dyskinesia (AIMS scores of 15) in the antipsychotic-treated group had been receiving orphenadrine and amantadine respectively. The use of antiparkinsonian drugs and "high potency" antipsychotic agents dramatically increased the frequency of dyskinesias.

Whilst benzodiazepines have been used to treat tardive dyskinesia (O'Flanagan, 1973 & 1975), and may ameliorate the condition a little (Cole & Gardos, 1980), this study has shown that tardive dyskinesia appears more likely to occur in subjects receiving a combination of benzodiazepines and antipsychotics than those on either of these 2 drugs administered on their own. Rosenbaum & De La Fuente (1979) did report an association between the benzodiazepines and tardive dyskinesia.

Antidepressant drugs have only rarely been reported in connection with tardive dyskinesia (see 2.7.5) and where they had been used in the present study they did not significantly affect the presence of tardive dyskinesia.
The use of night-time hypnotics and sedatives in combination with antipsychotics produced a trend towards more dyskinesia.

5.5 SUMMARY

In a study of 500 residents in residential homes for the elderly, abnormal involuntary movements, indistinguishable from tardive dyskinesia, were found in 15 per cent. In those subjects who had received antipsychotic medication 22 per cent had dyskinesia, and in those who had never received antipsychotic medication 13 per cent had dyskinetic movements. The difference in prevalence of movements was statistically significant.

A trend which did not reach a level of statistically significant difference was observed in more dyskinesias occurring in residents under the age of 70 than in those over 70. No significant differences were found in dyskinesias among the various age groups defined by decades over the age of 70.

There was no significant difference in the frequency of dyskinesias between males receiving antipsychotic drugs and those who had not. However, women receiving antipsychotic drugs had almost twice the frequency of dyskinesias in comparison with those who had never been exposed to antipsychotics.

Dyskinesia was more prevalent where residents received more than one antipsychotic drug, and the use of antiparkinsonian medication in conjunction with antipsychotics also increased the frequencies of dyskinesias.
Benzodiazepines combined with antipsychotic drugs also increased the rate of dyskinesias to a level of statistical significance. The use of hypnotics and sedatives in combination with antipsychotics increased the frequency of dyskinesias but this did not reach significance levels. Antidepressants did not significantly affect the presence of tardive dyskinesia.

Analysis of the data relating to the use of individual antipsychotic drugs for a minimum period of 3 months suggested that those who had received thioridazine were least likely to develop tardive dyskinesia.
CHAPTER 6

EVALUATION OF CO-DERGOCRINE IN THE TREATMENT
OF TARDIVE DYSKINESIA

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<th>Section</th>
<th>Page</th>
</tr>
</thead>
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<td>6.4 DISCUSSION</td>
<td>160</td>
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<tr>
<td>6.5 SUMMARY</td>
<td>164</td>
</tr>
</tbody>
</table>
In reviewing all of the studies on antipsychotic drug-induced tardive dyskinesia published in the English literature up until August 1978, Jeste & Wyatt (1979) observed that there was as yet no single satisfactory method of treating the disorder, and that until recently most of the treatment studies were carried out on a small number of patients and were uncontrolled. This view has been subsequently supported (Committee on Safety of Medicines, 1979; Lancet, 1979; Mackay, Sheppard, Saha, Motley, Johnson & Marsden, 1980; British Medical Journal, 1979 & 1981).

Gardos & Cole (1980) stated that from a public health view, the treatment of tardive dyskinesia was unsatisfactory. Safe, effective and specific treatment methods were lacking and therefore the search for newer and better therapeutic agents needed to be pursued relentlessly. In a treatment review, Paulson (1981) did not confirm one ideal treatment among the dozens of therapeutic approaches that have been suggested. The many suggested treatment methods have been reviewed earlier (Chapter 2, para 2.2.7).

In 1977 Smith, Tamminga, Haraszti, Pandey & Davis investigated the effects of dopamine agonists on tardive dyskinesia. They showed that apomorphine actually reduced dyskinetic movements - a finding contrary to predictions based on animal models. Subsequently it was suggested that apomorphine may have stimulated the presynaptic dopamine receptor to produce this improvement (Barnes, Kidger & Taylor, 1978).
The ergot derivative co-dergocrine appears to play a role in cerebral synaptic transmission and has been shown in vitro to displace dopamine and haloperidol from their specific binding sites in the caudate nucleus (Goldstein, Lew, Hata & Lieberman, 1978) and in vivo to produce an acceleration of noradrenaline turnover and a slowing of dopamine and serotonin brain turnover, suggesting noradrenaline antagonism, dopamine agonism and serotonin agonism (Loew, Vigouret & Jaton, 1979).

Co-dergocrine contains equal proportions of the mesylates of dihydroergocornine, dihydroergocristine and dihydroergokryptine. It has been in clinical use since 1951 and its principal indication has been in the treatment of the wide range of symptoms associated with mild to moderate impairment of mental function in the elderly (Ditch, Kelly & Resnick, 1971; Rao & Norris, 1972; Rehman, 1973; McConnachie, 1973 & Nelson, 1975).

In an open study in 10 patients suffering from schizophrenia of long standing and, additionally, cerebral arteriosclerosis and tardive dyskinesia, Gomez, (1977) administered co-dergocrine in dosages ranging from 2 to 3 mg a day. Dyskinetic movements in 7 patients disappeared after 2 to 4 weeks, and a follow-up of these patients for up to 8 months showed them to be free from tardive dyskinesia. The study is limited by the fact that all 7 patients had their antipsychotic therapy discontinued or altered, and it would be impossible to determine how much this affected the improvement in dyskinetic symptoms.

A pilot study was subsequently undertaken by Hajoiff (1978) in which 6 patients who had been on long-term phenothiazone medication were given 4.5 mg co-dergocrine daily for 6 weeks, and there was no alteration to
their phenothiazine therapy. All 6 patients responded within 2 to 4 weeks, and by 6 weeks one had lost all symptoms of tardive dyskinesia and the others had mild symptoms only. Work is continuing with a placebo phase, and after 6 months dyskinetic movements remain abated (Hajioff, 1979). The author suggested that co-dergocrine may work either by correcting disturbed dopamine activity in the striatum or by improving the metabolism of cells in the area by increased oxidation.

In a group of 9 patients with tardive dyskinesia treated with a placebo for 1 week, followed by active co-dergocrine for 7 weeks and then by placebo for a final 2 weeks, all 9 patients showed highly significant improvement during the period of active medication. Doses were increased from 4.5 mg to 7.5 mg daily during the study, and there were no variations made in existing antipsychotic medication (Arranz Munecas, Ganoza Garcia & Forcadell Puyo, 1979).

The promising results obtained in these open, uncontrolled studies indicated the need for an evaluation of co-dergocrine under double-blind conditions.

6.2 MATERIALS AND METHODS

6.2.1 Clinical Population

Forty-three chronic psychiatric in-patients (18 male and 25 female) from the Herrison Hospital, Dorchester, were included in the study. The following criteria for admission were established:

1) The presence of persistent involuntary movements predominately in the orofacial region.
2) The movements had been present for at least 1 year and were considered to have resulted from antipsychotic drug administration.

3) Antipsychotic drug treatment had been for a period of at least 18 months.

The following exclusion criteria were applied:

1. Patients with marked natural physical disabilities which would prevent accurate assessment of tardive dyskinetic signs.

2. Patients taking vasodilators, central nervous system stimulants, antihypertensive drugs like reserpine or any other drug with reserpine as a component.

3. Patients with a past history or current symptoms of brady-cardia. (Pulse rate < 60).

Of the forty-three patients selected, case note diagnoses were schizophrenia (30), dementia (7), depressive psychosis (3), oligophrenia (2), bipolar affective psychosis (1). Median age was 70.44 years (range 40 to 92; S.D. 10.85; S.E. 1.65) and the median period of psychiatric hospitalisation was 25.8 years (range 1.5 to 55 years). All patients had been treated with a variety of antipsychotic drugs (mean 3.8 compounds: range 1 to 9) during their psychiatric care. Background antipsychotic and antiparkinsonian medication was held constant throughout the study period.
6.2.2 Ethical Consent

Approval was given by the Ethical Committee of Herrison Hospital, and informed consent was obtained from patients participating in the study and approved by individual patients' psychiatric consultant.

6.2.3 Study Design

A double-blind placebo controlled, parallel group procedure was used. The randomisation preparation of drug supplies was carried out in the Research and Development Laboratories of Sandoz Products Limited, at Horsforth, and the randomisation code was held at the laboratories. A sealed envelope containing a copy of the randomisation code was sent to the Chief Pharmacist at Herrison Hospital with the instructions "To be opened only in emergency". The two raters, ward staff, pharmacy staff and patients were blind to the treatment procedure. Patients were randomly allocated to two groups according to their trial number, and received either co-dergocrine 4.5 mg tablets once daily for 6 weeks or an identical placebo tablet for the same period.

6.2.4 Rating Procedures

Patients were examined individually under standard conditions, using the examination technique described in Chapter 3 (para 3.4.2), at approximately the same time of day on each occasion, by two raters (SCR and AJB). The AIMS examination (Appendix 1) was employed and abnormal movements were assessed using the abbreviated Rockland Research Institute Rating Scale (Appendix 2). Rating procedures were carried out prior to entry into the
study, at the conclusion of the 6 week drug/placebo treatment period and again at 6 weeks after the drug/placebo treatment period to observe any possible carry over effect.

6.2.5 Drop Outs

Patient number 12 was omitted from the study as she was missing from the hospital on the day on which her second rating procedure was due to be carried out. Patient numbers 40 and 41 both died during the study period. Their ages were 92 and 81 respectively and death in both cases was considered due to pneumonia secondary to senile dementia, and in no way to drugs administered during the study.

6.2.6 Statistical Analysis

Due to limitations on availability of patients and the subsequent random allocation of patients to the two groups it was necessary to ascertain the importance of sex ratio, mean age and pre-treatment scores between the 2 groups. This was obtained by using 'Generalised Linear Models' (Nelder & Wedderburn, 1972), to carry out the analysis on score decreases over the study period.

6.3 RESULTS

Decrease in the scores of dyskinetic movements were obtained after the 6 week medication period in both the group receiving active medication and the placebo group. The improvement in the active treatment group was reflected in a mean reduction of 3.79 from the pre-treatment mean score
of 10.1 (± 1.1). In the placebo group the mean reduction was 2.48 from a pre-treatment mean score of 8.7 (± 0.7). At the end of the further 6 week period following the drug/placebo treatment phase, a small additional improvement in mean scores was seen in the co-dergocrine group of 0.58 and in the placebo group of 0.66.

The comparability of the groups is set out in Table 6.1 and the comparison of treatments is shown in Table 6.2. Both results indicated there were no sex differences present in the data. However the use of the pre-drug score as a covariate indicates that it has a significant effect in both cases; thus, the higher the pre-drug score, the greater the improvement in scores between:

1) Pre-drug and after week 6.
2) Pre-drug and after week 12.

A significant effect was also noted when age was used as a second covariate (p<0.01 for pre-drug and after week 6, and p<0.05 for pre-drug and after week 12), indicating that the improvement (i.e. reduction) in scores is less as age increases. The reduction in scores in the active group was higher than the placebo group for both periods, but this did not reach a level of statistical significance.

6.4 DISCUSSION

This study has shown that under double-blind conditions improvement in tardive dyskinesia did not reach a level of statistical significance between co-dergocrine and placebo, and thus fails to confirm earlier promising uncontrolled open studies. A further double-blind evaluation reported after the conclusion of this study demonstrated superiority of co-dergocrine over
### TABLE 6.1

**COMPARABILITY OF THE GROUPS**

(*Co-dergocrine v placebo*)

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Placebo</th>
<th>Overall Means</th>
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<tbody>
<tr>
<td>Mean Age (± Se)</td>
<td>69.7 (± 2.1)</td>
<td>70.0 (± 2.6)</td>
<td>69.9</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/12</td>
<td>11/10</td>
<td>18/22</td>
</tr>
<tr>
<td>Mean Predrug score (± Se)</td>
<td>10.1 (± 1.1)</td>
<td>8.7 (± 0.7)</td>
<td>9.4</td>
</tr>
<tr>
<td>Number in group</td>
<td>19</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 6.2

**COMPARABILITY OF TREATMENTS**

*(Co-d ergocrine v placebo)*

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of scores pre→first 6 weeks</td>
<td>3.79</td>
<td>2.48</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.92</td>
<td>0.95</td>
</tr>
<tr>
<td>Reduction of scores pre→second 6 weeks</td>
<td>4.37</td>
<td>3.14</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.95</td>
<td>0.82</td>
</tr>
</tbody>
</table>
placebo (Chien, Marder, Van Putten & Escobar, 1980). Their report, however, is only based on 8 patients, but it is of interest that they commenced their co-dergocrine dosage at 3 mg daily and increased this at weekly intervals to 6 mg daily. It may well be that the standard 4.5 mg daily dosage of co-dergocrine employed in this study was insufficient. Insufficient dosage could possibly have accounted for the disappointing results experienced with deanol under controlled conditions (Simpson, Voltashevskey, Young & Lee, 1977; Jus, Villeneuve, Gautier, Jus, Villeneuve, Pires & Villeneuve, 1978), as a recent study under double-blind controlled conditions showed significant reduction in mean rating of dyskinetic movements in a group of 11 patients using a daily dosage of 2000 mg deanol whereas the 11 receiving 1000 mg deanol and the 11 in the placebo group failed to improve (George, Pridmore & Aldous, 1981).

A problem frequently encountered in the conduct of drug studies is that the patient sample includes those who have been previously treated for the indication under study. In this evaluation 5 patients had been previously treated unsuccessfully with tetrabenazine for their tardive dyskinesia, 3 had been treated unsuccessfully with sodium valproate for the condition, and 1 had received both of these compounds and failed to show improvement. The separation of this previously treated group into a subgroup did not show any significant differences from the pattern of results in the total population in the study.

The patient sample in this study included a high proportion of chronic schizophrenics, who had been in institutional care for many years. Of the 43 patients in the study, 35 had been in psychiatric hospitals for more than 10 years, and of those, 24 had been in for more than 20 years. Thirty-four
patients had been treated with 3 or more antipsychotic agents during their illness and 39 had been prescribed one or more antiparkinsonian drug for earlier extrapyramidal side effects. In addition 27 patients were over the age of 70 and it would seem unlikely that any drug would produce improvement in a group where tardive dyskinesia was probably irreversible.

Further studies with a longer treatment period and at a higher dosage level in a younger patient sample should be undertaken.

6.5 SUMMARY

In a double-blind placebo controlled study with co-dergocrine in the treatment of tardive dyskinesia in a group of 43 elderly chronic psychiatric in-patients, the reduction in dyskinetic scores in the group receiving active medication was slightly greater than in the placebo group, but this did not reach a level of statistical significance. It is suggested that further work could be undertaken with a longer period of treatment, and at a higher dosage of co-dergocrine in a younger patient sample.
CHAPTER 7

GENERAL DISCUSSION AND RECOMMENDATIONS

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7.7 SUMMARY 186
7.1 RESULTS OF THESE STUDIES

This research project has provided information on the prevalence of dyskinesia in a group of mentally handicapped patients. The high prevalence rate of 47.5 per cent observed is suggested as being related to the sex of patients, their increasing age and the frequency of brain damage.

The major undertaking has been a detailed prevalence study in 500 residents in residential homes for the elderly. Prevalence rates of dyskinesia in those with a history of antipsychotic medication were, statistically, significantly greater than those in the group who had never received antipsychotic drugs.

It is suggested that dyskinesias are more likely to occur in females receiving antipsychotic drugs than in males, and that the use of more than one antipsychotic drug in the same subject is likely to produce more dyskinesias than where a single agent is administered.

The association of an increase in prevalence of tardive dyskinesia where antiparkinsonian agents are used in conjunction with antipsychotic drugs is identified, and there was also an increase in dyskinesias where benzodiazepines were given in conjunction with antipsychotic drugs.

In view of the fact that none of the 13 residents who had received thioridazine had tardive dyskinesia, it might be appropriate to suggest the use of this compound in the elderly, where agitation, anxiety and disturbed behaviour are manifested.
A double-blind evaluation of co-dergocrine, a drug which had given promising results in open studies, was also undertaken. Results were inconclusive but there was a trend in favour of the active drug, and further work is suggested in a younger, less chronic group of patients. A higher dosage and longer periods of treatment are also recommended.

Additional studies that could be undertaken in the 500 residents of the residential homes for the elderly might centre on the following:-

1. The withdrawal of antipsychotic medication to observe whether or not tardive dyskinesia appears in subjects who do not have dyskinesia at the present. This would have ethical considerations in that the possibility of disturbed behaviour might result from the removal of antipsychotic medication.

2. A subsequent follow-up rating to observe whether the dyskinesias observed have shown signs of progression or not.

Further work could be carried out in respect of rating procedures. There is a need for standardisation of techniques and the effect of variables such as stress, circadian rhythms and food intake should be examined. Drug intake and time of administration might also be explored as, unless a steady state exists, the peaks and troughs of antipsychotic and sedative drugs may affect the severity of dyskinesias.

7.2 IMPLICATIONS FOR PSYCHIATRY OF TARDIVE DYSKINESIA

In a University Lecture to the University of Surrey entitled "Man, Health and Technology, the next 100 years?", Davis (1977) considered 2 models in
the projections of future population. With a 1.63 children per family breeding rate, mental illness rates would remain the same but there would be a rise in geriatric illness in the next 30 years. A 2 children per family breeding rate would produce a growth in mental illness of 16 per cent, and an increase in geriatric illness of 38.4 per cent. He drew attention to the reduction in the working population and the consequent problems of staffing hospitals and clinics, and stressed the need for better preventive and social medicine. Unless positive action is taken in respect of tardive dyskinesia the problem will increase with the rise in mental and geriatric illness.

Jeste & Wyatt (1981) drew attention to the fact that the rising prevalence of tardive dyskinesia has obvious implications for the use of antipsychotic drugs. They pointed out that the development of tardive dyskinesia is only one aspect of antipsychotic drug treatment, and that antipsychotic drugs have had a far greater impact than any other treatment on the management of schizophrenic patients. Nearly 3 decades after the discovery of chlorpromazine as an antipsychotic agent, there is still no single substitute for antipsychotics for control of symptoms and prevention of relapse in the majority of chronic schizophrenic patients (Davis & Cole, 1973).

For many years psychiatrists were reluctant to accept that tardive dyskinesia was a side effect of the antipsychotic drugs (British Medical Journal, 1979). There followed a period of intense concern as exampled in the popular press and in the law-review literature (DuBose, 1976) following an editorial on the risks versus the benefits of antipsychotic drugs (Baldessarini & Lipinski, 1973). In an article entitled "Maintenance antipsychotic therapy; is the cure worse than the disease?", Gardos & Cole (1976) stated that tardive dyskinesia in particular was becoming recognised as a major therapeutic challenge.
By the late 1970's the problem of tardive dyskinesia had produced considerable reaction in the USA. Some 30 law suits in which patients and/or their relatives sued their physicians were in process and in those that had been settled, patients had all been successful (Borison, 1980).

Gardos & Cole (1976) stressed that every chronic schizophrenic outpatient maintained on antipsychotic medication should have the benefits of an adequate trial without drugs. They listed a suggested programme of withdrawal of antipsychotic medication. By 1980, the same authors referred to the fact that the response of the profession had shifted from curiosity and mild concern to panic (Gardos & Cole, 1980). They drew attention to the likelihood of increasing litigation but accepted the fact that with no suitable alternatives to antipsychotic medication on the horizon, tardive dyskinesia was not likely to diminish but might, in fact, become more widespread.

More recently, attitudes have shifted from the panic situation to one of balancing benefits against risks. In making the point that in drug therapy one cannot have benefits without risks, Teeling-Smith (1981) expressed the view that disproportionate emphasis on the risks of medicines can itself be extremely harmful. This is further emphasised by Baldessarini & Lipinski (1981), who were concerned that excessive and unbalanced criticism may lead physicians, patients and their families or the courts to avoid a treatment with established efficacy and reasonable safety in patients with psychoses.

Ananth (1980), in discussing the advisability of warning patients of side effects of antipsychotic medication, could not imagine himself fully
explaining the side effects of antipsychotics to a highly paranoid schizophrenic patient and obtaining full consent for treatment. Additionally, he felt that because it was not possible to predict who will develop tardive dyskinesia, explaining this side effect to patients such as acute schizophrenics was not warranted. Where patients had insight, and long-term maintenance was necessary, they should be made aware of the risks and benefits of antipsychotic therapy.

Gelenberg (1980) felt that psychiatrists could not and should not practice every moment with a lawyer at the elbow, but they could and should remember that a doctor-patient relationship requires mutual respect and ongoing dialogue - and that, after all, was the best way to avoid a legal morass. Cole (1976) was of the opinion that the first duty was to treat the patients and then to go into the more remote, possible consequences of therapy at a later date.

One of the biggest problems has been the potential harm of overdiagnosis in what is a complex area, against a background of major public health, legal and ethical implications (Kane, Wegner, Stenzler & Ramsey, 1980). They felt that because investigators are all eager to identify important risk variables, there has been a tendency to perform rather dramatic statistical overkill on limited data.

In considering the current situation in regard to implications for psychiatry of tardive dyskinesia, the consensus viewpoint seems to be reflected in the comment of the Drug and Therapeutics Bulletin (1978) that the balance between control of psychotic symptoms and avoidance of tardive dyskinesia is one of the most difficult in psychiatric therapy.
7.3 DRUG TREATMENT OF TARDIVE DYSKINESIA

The treatment of established tardive dyskinesia has been considered in detail earlier (See 2.7.7). Attempts to treat tardive dyskinesia with specific agents have not been encouraging, and no single drug has emerged as the agent of choice (Kobayashi, 1977a). This view is supported by many authors (Mackay & Sheppard, 1979; Deveaugh-Geiss, 1979). Gardos & Cole (1980) stated that from a public health view the treatment of tardive dyskinesia is unsatisfactory. Safe, effective and specific treatment methods are lacking. This is supported by the Task Force (1980) report which observed that although many therapies for tardive dyskinesia have been evaluated, none has been either thoroughly studied or proven safe and effective. The same report postulates that it is possible that tardive dyskinesia is a heterogenous group of disorders with a variety of anatomical, neuropathological and pathophysiological bases, corresponding to the varieties of natural history and responses to treatment. No treatment to date uniformly benefits dyskinesias in all patients. Kobayashi (1977a) suggested an appropriate approach might be to challenge dyskinetic patients with several different categories of drugs with relatively rapid actions. The existence of pharmacological subtypes and the employment of a strategy of acute drug challenge as suggested by Kobayashi (1977a) is supported by Casey & Denney (1977) and Mackay & Sheppard (1979).

7.4 ADJUSTMENT OF ANTIPSYCHOTIC DOSAGE

7.4.1. Drug Holidays

The concept of drug holidays was suggested by Ayd (1970) and Crane (1973). These can be the subject of considerable variation
such as the administration of antipsychotic drugs for 5 days during the week and the weekend left free from medication. An alternative is to stop antipsychotic medication for a period of several weeks after continuous administration of drugs for several months.

Casey (1978) suggested that the drug-free interval might also uncover mild tardive dyskinesia symptoms which were previously masked by the drug. Thus, early detection could lead to early treatment and prevention of advanced symptoms. A further advantage would be the fact that with periodic termination of antipsychotic medication the patient might be able to go for a long period of time without drug therapy. Caution is advocated in that some patients cannot tolerate drug holidays and begin to relapse shortly after discontinuing their drug (Casey, 1978).

One controlled study to establish the effects of drug holidays has shown that after a 6 week period without antipsychotic medication there was no significant development or reduction of tardive dyskinesia, and no clinical worsening in the global severity of illness (Goldberg, Shenoy, Sadler, Hamer & Ross, 1981). The authors did draw attention to the low level of tardive dyskinesia at baseline in their study. Others have produced evidence that interrupted courses of antipsychotic medication are worse than continuous treatment (Jeste, Potkin, Sinha, Feder & Wyatt, 1979). It is suggested that repeated drug challenges may have a kindling effect on the development of hypersensitivity in dopamine receptors (Kennedy, 1980). Caution in the use of drug holidays is also advanced by La Bruzza (1981).
7.4.2 Discontinuation of Antipsychotic Medication

In a controlled study in 34 psychiatric patients the effects of total withdrawal of medication for a 10 week period were observed. Dyskinesia persisted throughout this period and there was a slight worsening in behavioural effects in 9 patients, and 6 patients were much worse. Whilst the results were disappointing from the aspect of improving dyskinesia, the authors strongly recommended that drugs should be kept to a minimum in patients exhibiting tardive dyskinesia (Crane, Ruiz, Kernohan, Wilson & Royalty, 1969).

Lehmann (1975) suggested that the withdrawal of antipsychotic medication should be by means of gradual decrease to a lowest effective dosage level. In a double-blind study in 21 patients, medication was decreased in successive steps of 4 weeks duration to one-half, one-fourth and finally one-eighth of its initial level, and was then followed by a 6 month placebo medication period. Sixteen of the patients (76 per cent) relapsed, one during the period of progressive drug reduction and 15 between the 2nd and 14th week after medication had been discontinued. In a control group of 11 patients who were maintained on the same dose of antipsychotic drug, 2 patients (18 per cent) showed signs of deterioration. In the experimental group there was a non-significant increase in dyskinesia during the period of gradual drug reduction, and a greater increase after complete drug withdrawal (Branchey, Branchey & Richardson, 1981).
7.4.3 Reduction of Antipsychotic Medication

The current consensus viewpoint suggests that antipsychotic drugs should be used only when clearly indicated and that they be restricted to the lowest effective dosage. This aspect is considered in detail later (see 7.6).

7.5 RESEARCH STRATEGIES

7.5.1 Diagnosis of Tardive Dyskinesia

Granacher (1981) observed that for the psychiatrist, all that moves in patients receiving antipsychotics may not be tardive dyskinesia, even though in the large majority of cases that diagnosis is correct. Attention must be paid to other causes of abnormal involuntary movements. Emphasis on the basics of medical description and classification may add to knowledge of the tardive dyskinesia syndrome. In this respect, the description of the disorder by Parkes (1976) is concise and less complicated than the Task Force description (Schiele, Gallant, Simpson, Gardner, Cole, Crane, Chase, Ayd, Levine & Ochota, 1973) (see 3.1). A standardisation on diagnostic criterion in respect of an AIMS total score will prevent the wide variations in studies of prevalence rates, and should put the syndrome in true perspective.
7.5.2 Animal Models

After repeated administration of classical antipsychotics to the rat, supersensitivity of striatal dopamine (DA) receptors towards DA-receptor agonists can be demonstrated. This effect can be quantified (a) by measuring the turning response to apomorphine in rats with unilateral striatal lesions or (b) by measuring the changes induced by neuroleptics in the DA metabolism in the striatum of intact rats (Sayers, Bürki, Ruch & Asper, 1977). Using the rat model Clow, Jenner, Theodorou & Marsden (1979) showed that the initial behavioural and biochemical evidence for striatal-DA-receptor blockade by trifluoperazine disappeared within a few weeks of starting therapy to be replaced by supersensitivity after 6 months of drug administration despite continued drug intake. They suggested this might explain why drug-induced parkinsonism may disappear and why tardive dyskinesias may appear during chronic antipsychotic therapy. It was also suggested that this type of experiment may provide a realistic animal model for testing drugs for their capacity to induce dyskinesias. In the test system used by Sayers, Bürki, Ruch & Asper (1977) thioridazine was shown to induce an increase in DA-receptor sensitivity which is significantly less intense and of shorter duration than that induced by haloperidol. They postulated that the tendency of a drug to increase DA-receptor sensitivity has been related to its propensity to induce tardive dyskinesia in man, and on this basis it may be expected that tardive dyskinesias following treatment with thioridazine will be rare and less intense than those seen after classical neuroleptics. This has been supported by clinical evidence (Blowers & Bicknell, 1980). Davidson (1981) observed
that the chronic cebus monkey model appears to be homologous to tardive dyskinesia in all respects, and the same author with colleagues, in unpublished work, has produced early dyskinetic symptoms in squirrel monkeys after 8 to 12 weeks of treatment with haloperidol. Two other models have been identified but not studied extensively, they are Fisher rats (Smith & Leelavathi, 1978) and frontally lesioned rats (Glassman & Glassman, 1979). In these latter two models, spontaneous mouth movements that may be related to tardive dyskinesia appeared in some rats after approximately 2 months of chronic antipsychotic therapy. In a further study the potential of a drug to cause tardive dyskinesia was assessed by measuring adaptive changes in the striatal dopamine metabolism. Homovanillic-acid concentration in the striatum was measured after a high dose of haloperidol had been administered to rats pre-treated with test drugs (Bürki, 1979).

Experimental work was conducted with guinea-pigs who were given chronic high dosage amphetamine treatment for several weeks to elicit stereotyped behaviour. They were then subjected to testing with low doses of D-amphetamine to determine whether the chronic high-dosage pre-treatment altered the response to low doses. Data obtained suggested that chronically increased activity of dopamine at dopamine receptors (caused by chronic amphetamine administration) could alter the function of the striatum in such a way as to predispose the animal to stereotyped behaviour. This predisposition may reflect an increase in dopaminergic receptor sensitivity since the behavioural sensitivity to apomorphine was altered (Klawans, Crosset & Dana, 1974). This may have some implications in tardive dyskinesia. If tardive
dyskinesias are a manifestation of dopamine acting at dopamine receptors, they must represent altered or increased activity of dopamine at the involved receptors. The chronic persistence of tardive dyskinesia must then represent chronic increased dopaminergic activity at specific receptors. If this is analogous to the chronic amphetamine exposure described above, then allowing the clinical manifestations of tardive dyskinesia to persist may further predispose to the perpetuation of the movement abnormality (Klawans & Rubovits, 1975).

Further research with animal models is necessary, not only to clarify early impressions that there are fundamental differences in the propensity of existing antipsychotics to produce tardive dyskinesia, but also to screen newly developed antipsychotic preparations before they are subjected to volunteer studies in humans as part of the testing programme prior to the issue of a Clinical Trials Certificate.

7.5.3 Human Studies

Reference has already been made to the proposition that uncovering tardive dyskinesia by short-term administration of an antiparkinsonian drug may aid in early detection and help to prevent the subsequent development of incapacitating forms of the disorder (Chouinard, De Montigny & Annable, 1979). The use of pharmacologic probes was suggested by Moore & Bowers (1980), who observed that some patients with tardive dyskinesia fit the cholinergic-dopaminergic imbalance theory, but some do not. To study this heterogeneity further, they measured the responses of 10 patients with tardive dyskinesia to intravenous challenge doses
of drugs that facilitate or inhibit acetylcholine transmission (physostigmine or benzotropine, respectively). They then measured the response of these patients to an open outpatients deanol trial. They found that the responses of half the patients followed the classic theory, 2 responded paradoxically and 3 responded inconsistently. The authors suggested that there is a subgroup of tardive dyskinesia patients who fit the theory but that more research is needed to identify the subgroups who do not. Mackay & Sheppard (1979) suggested that the definition of a pharmacological signature for each patient in an acute dose-response design seems to offer the most sensible and economical therapeutic approach to tardive dyskinesia at the present time. Correlation of pharmacological response with careful clinical classification may lead to the identification of clinical predictors and even to a better understanding of the underlying neurological disorder(s).

Rosenbaum, Maruta, Jiang, Auger, de la Fuente & Duane (1979) hypothesised that primary affective disorders are a major predisposing factor for the development of tardive dyskinesia and that patients with tardive dyskinesia have neuroendocrine abnormalities similar to those of patients with primary affective disorders. To test this hypothesis, they measured the levels of 24 hour urinary free cortisol (UFC) and blood thyroid-stimulating hormone (TSH) in consecutive patients with tardive dyskinesia and compared these levels with those found in controls. In an earlier reported study, in patients with primary affective disorders, 24 hour UFC levels were elevated (Carroll, Curtis, Davies, Mendels & Sugerman, 1976) but this did not occur in schizophrenia. In the first mentioned study, Rosenbaum and his colleagues
showed that 13 of the 18 patients (72 per cent) had elevated UFC levels, which supported their hypothesis that the endocrine dysfunction in these patients was similar to that in patients with primary affective disorders. Further, patients with low TSH levels tended to have elevated UFC levels, which suggested an inverse relationship. None of these patients fulfilled research diagnostic criteria for schizophrenia at the time of the authors evaluation. Instead, all of the patients with elevated UFC levels, except the manic and paranoid patients, fulfilled 4 to 6 of the 8 research diagnostic criteria depressive symptoms, although many denied a dysphoric mood. The authors suggested that their findings indicate that a subgroup of patients with tardive dyskinesia have endocrine dysfunction similar to that seen in primary affective disorders. They advocated further testing using dexamethasone suppression and thyrotropin-releasing hormone (TRH) stimulation, along with determination of UFC levels.

Kane, Struve, Weinhold & Woerner (1980) defined a high risk patient as anyone who developed presumptive tardive dyskinesia after less than 1 year cumulative lifetime exposure to antipsychotics. A small group of "high-risk" patients were selected. EEG evaluations were made and 5 of 7 patients examined showed an abnormal reading. Four of the 7 had the B-mitten dysrhythmia. The authors suggested that EEG abnormalities may indicate an increased risk factor for tardive dyskinesia, and are in process of collecting further data.

In a study to determine the value of a tongue protrusion test in the early detection of tardive dyskinesia (Pi & Simpson, 1981), the test was positive in 5 of 11 possible cases of tardive dyskinesia and in 1 of 11 doubtful subjects. The recommendation is made for
a controlled prospective study of the evolution of tardive dyskinesia in subjects with an initial mild abnormal tongue movement.

There is clearly an area of research in which "risk" patients for tardive dyskinesia can be identified, either by the use of biochemical methods or EEG examination. Additionally, the selective use of drugs in the treatment of the disorder, particularly if specific sub-groups can be identified, has considerable possibilities, and may overcome the disappointing results obtained so far. A study in which a group of patients with tardive dyskinesia could be treated firstly, for example, with deanol, the non-responders then treated with tetrabenazine, and the non-responders treated with co-dergocrine, and so on, or a permutation on these and other drugs, might be worthy of initiation.

One study by Casey & Denney (1977) evaluated the effects of challenge doses of dopamine and acetylcholine agonists and antagonists on dyskinetic symptoms and found that drug responses formed sub-groups which divided into pharmacological mirror images. Dopaminergic antagonists or acetylcholinergic agonists reduced symptoms in group 1 but increased symptoms in group 2, whilst dopamine agonists or acetylcholinergic antagonists increased symptoms in group 1 but reduced them in group 2. These seemingly paradoxical results suggest that inhibitory and excitatory dopamine receptors might play differential roles in the pathophysiology of the tardive dyskinesia syndrome.
A low dosage study with the dopamine agonist bromocriptine might also be undertaken to investigate the long-term effect in treating tardive dyskinesia. An initial worsening of dyskinesia might well occur but subsequently a beneficial effect might be obtained. A Clinical Trials Certificate for the use of bromocriptine in tardive dyskinesia is currently in existence.

7.5.4 New Antipsychotic Compounds

In a leading article (British Medical Journal, 1979) the observation was made that in the long term the answer must lie in the development of a new class of antipsychotic drugs that will control schizophrenia without producing tardive dyskinesia. Marsden (1976a) refers to the current hypothesis that antipsychotic drugs possess their antipsychotic activity because they block cerebral dopamine receptors, not only in the striatum but also in areas of the mesolimbic system, brainstem and hypothalamus. The unwanted extrapyramidal effects of antipsychotic activity are attributed to striatal dopamine receptor blockade, but it is generally accepted that they are not necessary for antipsychotic activity. The latter may depend on the effects of the drugs on dopamine receptors elsewhere, for example, the mesolimbic system. He suggested that if this assumption was correct, it may be possible to create antipsychotics devoid of striatal dopamine antagonism, and hence of extrapyramidal unwanted actions.

The Task Force (1980) stressed the urgent need for the development of effective antipsychotics that do not have the risk of inducing tardive dyskinesia, and pointed to the requirement to
develop better drug screening tests. They suggested that clozapine and sulpiride are examples of experimental drugs that seem to be effective antipsychotic agents with little or late extrapyramidal effect. Whilst they refer to the discontinuation of trials with clozapine due to its association with agranulocytosis (see 2.7.7) it is understood that following clinical use of clozapine in a number of countries, including South Africa, its association with agranulocytosis is no greater than that with other antipsychotics.

It is planned to introduce clozapine into the United States in the near future. Marsden (1976b) described clozapine as a fascinating drug, that does not appear to cause much parkinsonism, acute dystonias or akathisia, and whilst most of the evidence is based on short-term trials, tardive dyskinesia has not been described. He felt that if tardive dyskinesia was not produced following long-term administration then this crucial question may be answered.

Both clozapine and thioridazine have been shown to have a site specificity for blocking dopamine receptors in the limbic rather than the extrapyramidal system (Borison, Bauer, Havdala & Diamond, 1980; Borison, Fields & Diamond, 1981; Borison, Blowers & Diamond, 1982) and this may account for their low incidence of extrapyramidal side effects.

Further research on analogues of clozapine at the Sandoz/Wander Research Institute in Berne have produced a new compound, NB 106-689, which has an antipsychotic profile similar to clozapine, but has successfully completed an agranulocytosis animal model screening programme. This compound is in the early stages of clinical trials in the United Kingdom.
7.6 RECOMMENDATIONS

7.6.1 Continuation of Antipsychotic Medication

As the search for more selective treatments for acute and chronic schizophrenia free of neurological side effects progresses, the use of available antipsychotic agents continues to be the cornerstone of management of these serious and disabling mental illnesses (Baldessarini, 1980). Cole & Gardos (1980) pointed to the dilemma faced by the psychiatrist, with dyskinesia in an ambulatory, socially adjusted schizophrenic with a history of overt, severe psychosis, doing well on maintenance antipsychotic therapy. Stopping the antipsychotic medication has to be seriously considered but may lead rapidly to relapse and rehospitalisation. A clinical decision has to made that takes into account the patient's history of drug response and relapse. In a patient who clearly relapses rapidly when taken off drugs, continued drug therapy at the lowest possible dose seems to be the best therapy of the total problem. Obviously, the undesirability of the dyskinesia must be weighed against the hazards of psychotic relapse.

7.6.2 Guidelines for Antipsychotic Therapy

The following recommendations are made to effectively use antipsychotic drugs and, at the same time, decrease the incidence of tardive dyskinesia:

1. Limit the use of antipsychotic drugs to those indications where they are absolutely necessary, e.g. acute and chronic schizophrenia, manic phase of manic-depressive psychosis.

2. Continue medication only when efficacy is clear, and use lowest effective daily dosage.

3. Use lower doses with elderly patients and children, and aim to achieve minimum effective dose.

4. Avoid multiple antipsychotic drug prescriptions.

5. Avoid long-term use of antiparkinsonian drugs, and only use when clearly indicated.

6. Advise patients (if appropriate) and families of risks and benefits of antipsychotic drug therapy.

7. Aim to detect tardive dyskinesia as early as possible, and urge nursing staff to be alert to the possible appearance of the syndrome.

8. Re-assess the patient on a regular basis and attempt to reduce dosage.

9. At the earliest signs of tardive dyskinesia, lower antipsychotic drug dosage, withdraw medication if possible, or switch to a less potent agent (e.g. thioridazine).

10. Treat dyskinesias with benign agents initially (e.g. deanol, choline, lecithin). Reinstitute antipsychotics if relapse occurs using minimum effective dosage.
7.6.3 The Role of Thioridazine

Klawans, Goetz & Perlik (1980) stated that where antipsychotics were absolutely required, they tended to switch to thioridazine. They indicated that their practice is based on several considerations. Firstly, there appears to be some relationship between drug-induced parkinsonism and tardive dyskinesia, and thioridazine has the lowest incidence of drug-induced parkinsonism of available antipsychotics. Evidence from animal experiments also suggests that some agents may be less likely to induce receptor hypersensitivity than others. In animals it has been shown that thioridazine produces a short-lived sensitisation of striatal dopamine receptors, whereas haloperidol and fluphenazine produced much more marked and longer-lived receptor sensitisation (Borison, Blowers & Diamond, 1982). In their laboratories Klawans, Goetz & Perlik (1980) have been unable to produce receptor-site hypersensitivity measured either biochemically or behaviourally with chronic thioridazine, but can easily produce this state with other phenothiazines and haloperidol in equivalent doses. They stated that there was no human data to establish a lower incidence of tardive dyskinesia with thioridazine, but, because of the above consideration, they felt it reasonable to substitute thioridazine in this situation. The present study has produced some evidence to support the use of thioridazine in that it has been shown to produce less tardive dyskinesia than haloperidol (see 4.4.) and where pure culture groups of antipsychotic-treated subjects could be identified, those on thioridazine did not have tardive dyskinesia (see 5.3.3).
Further support for the use of thioridazine in patients where tardive dyskinesia has occurred following treatment with other antipsychotics is reported by Kobayashi (1977), Tarsy & Baldessarini (1980), Dominguez (1980) and Richelson (1980).

Gerlach & Simmelsgaard (1978) suggested that strong dopamine-receptor blocking antipsychotics (e.g. haloperidol) induce the pathological basis for tardive dyskinesia to a greater degree than weak dopamine-receptor blocking antipsychotics (e.g. thioridazine) and Klawans, Goetz & Perl (1980), whilst accepting that thioridazine can cause tardive dyskinesia, stated that they feel safer using it when antipsychotic treatment is necessary.

7.7 SUMMARY

The main findings of this research are outlined, including the presentation of data from prevalence studies of tardive dyskinesia in 40 mentally handicapped patients and 500 subjects in residential homes for the elderly. Association of tardive dyskinesia with antipsychotic drugs, antiparkinsonian agents and benzodiazepines is summarised. Results of a double-blind evaluation of co-dergocrine in the treatment of tardive dyskinesia are briefly discussed.

Suggestions are made for future research in the group of 500 subjects who were included in the prevalence study, as well as identifying areas where further work is necessary in rating procedures.
Implications for psychiatry of tardive dyskinesia are discussed and the current practices for treating the syndrome are considered. Research strategies are reviewed, and finally recommendations are made for both the attempts to limit the incidence of tardive dyskinesia and to manage the problem if it presents.
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Acknowledgements invariably conclude with references to one's wife and I suggest that this reflects the position that without total support from one's partner the whole project would be impossible. I gratefully record my thanks to my wife, Yvonne, who has seen our leisure time together completely eroded and yet has given me every encouragement.
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APPENDICES

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ABNORMAL INVOLUNTARY MOVEMENT EXAMINATION

Observation begins when the patient enters the room and the whole body movements, with particular attention to the lower limbs, are noted.

The patient is asked to sit on a firm straight-backed, armless chair, with feet placed firmly on the floor and slightly apart.

The hands are rested unsupported on the knees so that manifest movements can be observed.

The patient is invited to examine the large composite picture placed on a music stand in front of him, and told that he should look at the picture for a few minutes and then he will be asked to tell the rater what different animals were seen in the picture.

This distracting manoeuvre will enable the rater to make an overall assessment of the patient for visible abnormal involuntary movements.

At the end of 2 minutes, the patient is asked to name the species of animals seen. No specific importance will be attached to the answers given.

If abnormal movements are observed the patient is asked if he is aware of them and if the movements cause him concern.

The patient is asked if has anything in his mouth, e.g. a sweet or chewing gum.
The patient is asked if he is wearing dentures and, if so, do they fit properly or cause any discomfort.

The patient is asked to open his mouth as wide as he can, and the tongue is observed as it rests in the buccal cavity. Differentiation is made between normal fine tremor and the choreoathetoid movement of tardive dyskinesia.

The patient is then asked to close the mouth and then open it again as widely as possible. The tongue is again observed. Sovner (1978) stated that tongue movement that may not be present when the mouth is first opened can occur after the mouth is opened on the 2nd occasion.

The patient is then asked to close the mouth, and then to open it and stick out the tongue as far as possible. This manoeuvre can activate previously undetected tongue movements or increase the severity of movements already present (Sovner, 1978).

The patient is then asked to close the mouth and again open it and stick out the tongue as far as possible. Observations are again noted.

The patient is then invited to participate in an activating task in which, firstly, the right hand is slightly extended, and each of the fingers in turn is touched by the thumb. This thumb touching manoeuvre is repeated three more times.

The procedure is then carried out with the left hand and the patient is urged to speed the movement up.

During this activating task which is designed as an unmasking technique, the patient is observed for tongue and eye movements and involuntary mouth movements.
The patient is then asked to put his hands down on his lap and to let them go loose. Muscle tone flexibility is then checked by shaking wrists and forearm in order to differentiate from drug induced Parkinsonian tremor.

The patient is asked to stand and put his arms out in front, and in this activating manoeuvre observation is made for choreoathetoid hand movements.

The arms are then returned to the patient's side and he is asked to turn to his side (90°) and again put out his arms in front of himself. The arms are again returned to the side and the patient asked to walk across the room, turn around, and then come back to the chair and sit down. During this activating test, close watch is kept on hand movements.

A minimum of 10 minutes is spent with each patient, and any subsequent examination should be carried out to the exact pattern of that described above.

Details of abnormal involuntary movements are recorded on the relevant sheet and in accordance with the Abbreviated Dyskinesia Rating Scale of the Rockland Research Institute (Appendix 2).
ABNORMAL INVOLUNTARY MOVEMENT EXAMINATION

Check List for Rating Procedure

1. Observe patient as he enters room.

2. After patient is correctly seated, invite him to examine picture. Observe for 2 minutes.

3. Check mouth for sweets, chewing gum, ill-fitting dentures.

4. Open wide and close mouth twice - observing tongue.

5. Open mouth and extend tongue fully and observe tongue - close mouth - then repeat.

6. Slightly extend right hand and touch each finger with thumb - repeat 4 times.

7. Repeat with left hand urging patient to speed up - observe tongue, eyes and mouth.

8. Relax hands - flex arms - observe for Parkinsonian tremor.

9. Stand - extend arms - and return to side.

10. Rotate patient 90° and repeat arm extension - observe for choreoathetoid hand movements.

11. Ask patient to walk across room and return observe hand movements.
## APPENDIX 2

### ABNORMAL INVOLUNTARY MOVEMENT RATING SCALE

<table>
<thead>
<tr>
<th>Hospital/Home</th>
<th>Ward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's Initials</td>
<td>Age:</td>
</tr>
<tr>
<td>Date of Exam:</td>
<td>Time:</td>
</tr>
</tbody>
</table>

**Facial and Oral Movements:**

1. Periocular area (blinking of eyes, tremor of eyelids) 0 1 2 3 4
2. Movements of the lips (pouting, puckering and smacking). 0 1 2 3 4
3. Chewing movements 0 1 2 3 4
4. Sweet in mouth sign 0 1 2 3 4
5. Tongue protrusion 0 1 2 3 4
6. Tremor and/or choreoathetoid movements of the tongue. 0 1 2 3 4
   OTHER (describe) 0 1 2 3 4

**Neck and Trunk**

7. Axial hyperkinesis (patient standing) 0 1 2 3 4
8. Rocking movements 0 1 2 3 4
9. Torsion movements 0 1 2 3 4
   OTHER (describe) 0 1 2 3 4

**Extremities**

10. Movements of fingers and wrists 0 1 2 3 4
11. Movements of ankles and toes 0 1 2 3 4
12. Stamping movements 0 1 2 3 4
   OTHER (describe) 0 1 2 3 4

**Entire body**

13. Akathisia 0 1 2 3 4
   OTHER (describe) 0 1 2 3 4

**Rating**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>absent</td>
</tr>
<tr>
<td>1</td>
<td>mild</td>
</tr>
<tr>
<td>2</td>
<td>moderate</td>
</tr>
<tr>
<td>3</td>
<td>moderately severe</td>
</tr>
<tr>
<td>4</td>
<td>severe</td>
</tr>
</tbody>
</table>

**Source:** Adapted from Rockland Research Institute Abbreviated Dyskinesia Rating Scale.
## PATIENT'S MEDICAL AND DRUG HISTORY

(Tick if appropriate)

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>Lobotomy</td>
<td>Sydenham's chorea</td>
</tr>
<tr>
<td>E.C.T.</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Insulin coma treatment</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Metrazol coma</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Temporal lobe epilepsy</td>
</tr>
<tr>
<td>Cerebral arteriosclerosis</td>
<td>Abnormal E.E.G</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>Bell's palsy</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>Congenital neurologic disease</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Concussion, contusion</td>
</tr>
<tr>
<td>Uraemia</td>
<td>Korsakoff's psychosis</td>
</tr>
<tr>
<td>Senile dementia</td>
<td></td>
</tr>
</tbody>
</table>

### Other Medical History:

### Antipsychotic Therapy: (list drug/drugs and length of treatment)

### Anti-Parkinsonian Drug Therapy: (list drug and length of treatment)

### Other Drugs Administered:

### Current Medication:

### Other Relevant Information:

### Length of Stay in Hospital:
APPENDIX 3

ABNORMAL INVOLUNTARY MOVEMENT RATING SCALE

Definitions

FACIAL AND ORAL MOVEMENTS

1. **Periocular Area**

   **Blinking of Eyes**
   
   Repetitive and more or less continuous or in bursts. To be distinguished from tics which occur episodically.

   **Tremor of Eyelids**
   
   Isolated tremor, more frequently bilateral but can occur unilaterally. Usually seen when eyes are closed. Fine in character.

2. **Movements of the Lips**

   **Pouting of the Lower Lip**
   
   A thrusting out of the lower lip as in solemnness.

   **Puckering of Lips**
   
   Drawstring or pursing action of the lips.

   **Smacking of Lips**
   
   Brisk separation of lips which produces a sharp sound.

3. **Chewing Movements**

   Self explanatory.
4. **Sweet in Mouth Sign (Bon Bon)**

Tongue movement within the oral cavity which produces a bulge in the cheek giving the impression the patient has a hard sweet tucked in his cheek. Occasionally a repetitious sweeping movement of the tongue over the buccal lining which also pushes out the mouth.

5. **Tongue Protrusion**

- **Clonic** - a rhythmic in and out movement of the tongue.
- **Tonic** - a continuous protrusion of the tongue.
- **Fly Catcher** - a sudden shooting out of the tongue from the mouth at irregular episodes.

6. **Tongue Movements**

- **Tongue Tremor**

Fine tremor observed with the mouth open and tongue within the buccal cavity.

- **Choreoathetoid Movements of the Tongue**

A rolling, worm-like movement of the tongue muscles without displacement of the tongue from the mouth. The tongue may rotate on its longitudinal axis. Observed when the mouth is opened.

7. **Axial Hyperkinesia** (patient standing)

A front to back hip rocking movement. Resembles copulatory movements. Differs from the rocking movement where it is the upper torso which has to and fro movement.
8. **Rocking Movement**

A rhythmic to and fro movement of the upper torso which occurs from a repeated bending of the spinal column in the lumbar region. Different from Axial Hyperkinesia where the hips move to and fro.

9. **Torsion Movements**

Twisting undulant movement of the upper or lower part of the trunk (shoulder or hip girdle) resulting from mobile, spastic movements of the axial and proximal muscles. The movements are not fast and they involve large portions of the body.

**EXTREMITIES MOVEMENTS**

10. **Movement of Fingers and Wrists**

**Choreiform Movements**

In fingers, wrists, arms. Variable, purposeless, coarse, quick and jerky movements which begin suddenly and show no rhythmicity. They vary in distribution and extension.

**Athetoid Movements**

In fingers, wrists, arms. Continuous rhythmic, slow, writhing, worm-like movements. They almost invariably appear together with Choreiform Movements.

**Finger Counting**

Rhythmic rubbing of the thumb against the middle and index finger.

**Caressing Face and Hair**

Gives the impression of being absent-minded or vernous mannerism; has the appearance of being purposeful.
Rubbing of Thighs

Hands rub the outside or tops of thighs. Sporadic and non-rhythmic.

11. Movements of Ankles and Toes

Rotation and/or Flexion of the Ankles

Self-explanatory

Toe Movements

Slow rhythmic, retroflexion, usually of the big toes although other toes can also be involved.

12. Stamping Movements

Stamping Movements (Standing)

Weight is shifted back and forth from one foot to the other when patient stands.

Stamping Movements (Sitting)

Flapping or tapping of the whole foot on the floor when the patient is sitting, or may comprise an alternate toe and heel tapping.

ENTIRE BODY MOVEMENTS

13. Akathisia

An inability to sit or stand still.

Source: Adapted from Rockland Research Institute Tardive Dyskinesia Rating Scale (Definitions).
6 March 1980

To: General Practitioners providing services for residents in Surrey County Council Homes for the Elderly.

Dear Doctor

As you will know, in the mid 1950s the tranquilliser drugs dramatically changed the treatment of mental illness. They have been widely used in psychiatric hospitals where previously physical restraint played a prominent part. Use has also extended to the treatment of confusion and agitation in the elderly.

Some years after the introduction of the tranquillisers, it was observed that some of those who had been on treatment for at least six months began to develop involuntary muscular movements, e.g. a pronounced continuous chewing movement or frequent ejection of the tongue. Many people have tended to accept these movements as part of the illness process and, in fact, they can occur in people who have never received tranquillisers.

Much research has been done in psychiatric hospitals to determine the prevalence of these movement disorders, but very little work has been done to assess how much is present in the elderly as a group and how many of these have been on tranquillisers.

There are some 1600 residents in the County's Homes for the Elderly and as a PhD research student of Surrey University I am planning to carry out a study to obtain information that will fill these gaps in the total picture.

Approval has been obtained from the County's Social Services Department and the Area Specialist in Community Medicine to undertake this work in the Part III Homes, and will consist of a simple test procedure which does not involve physical contact with the residents.

In those residents showing abnormal involuntary movements it would be necessary to establish whether or not they have had any antipsychotic drugs in the past 7 years and I would be grateful if you would allow me to obtain this information from the Officer in Charge/Matron of the respective homes. I appreciate there may be gaps in treatment records, and in this event the resident would be classified in a separate sub-group.

If you would like further information on the proposed project please let me know. In any event, I would be pleased to forward you a report on the findings of the study.

Yours sincerely

Member Social Services Committee, S.C.C.
and Surrey Area Health Authority.
To: Officers in Charge
Homes for the Elderly

Dear Officer in Charge,

As you may know the tranquilliser drugs have revolutionised the treatment of mental illness. They have been widely used in psychiatric hospitals where previously physical restraint played a prominent part. Use has also extended to the treatment of confusion and agitation in the elderly.

Some years after the introduction of the tranquillisers, it was observed that some of those who had been on treatment for at least six months began to develop involuntary muscular movements, e.g. a pronounced continuous chewing movement or frequent ejection of the tongue. Many people have tended to accept these movements as part of the illness process and, in fact, they can occur in people who have never received tranquillisers.

Much research has been done in psychiatric hospitals to determine the prevalence of these movement disorders, but very little work has been done to assess how much is present in the elderly as a group and how many of these have been on tranquillisers.

As you will appreciate, there are some 1600 residents in the County's Homes for the Elderly and I am planning to carry out a study, under the aegis of the University of Surrey, to obtain information that will fill these gaps in the total picture.

I would plan to explain the details of the survey to a staff meeting at your Home to indicate what is involved for your residents and what action will be required by members of staff. I should be glad to explain the results of a pilot study which I have already completed with a group of elderly ladies in a hospital setting, where there was considerable interest and co-operation from residents and staff alike. There is a fairly simple test procedure, but without your support the whole test would not be possible. A report on this pilot study is attached, and could be shown to your visiting doctors, who have been sent a letter (copy enclosed) informing them of the project.

Mr Lillington did write to you in March of last year indicating his agreement to the study being carried out in the County's Homes for the Elderly, and I am now ready to commence this stage of the project and would hope to contact you within the next few months.

Looking forward to meeting you.

Yours sincerely

A.J. Blowers

c.c. Mr B.R. Lillington
Dr. B. Westworth


TARDIVE DYSKINESIA AND THE MENTALLY HANDICAPPED

Dear Sir,

Most surveys have been carried out among long-stay psychiatric hospital populations of chronic schizophrenics where phenothiazines have frequently been used for long periods of time.

So far few studies have involved the equally long-stay populations of mental handicap hospitals where chronic shortage of staff, inadequate diversional activities and inappropriate environments have frequently necessitated the non-specific use of antipsychotic medication to reduce behaviour disturbances. Routine review of prescriptions in mental handicap hospitals has not always been adequate; it has been our experience that prescriptions may be repeated at infrequent intervals with little thought for their continuing need. In the past anticholinergic drugs were often given routinely, and the mentally handicapped, because of the supervision of their drug taking, probably reach a high degree of compliance.

Many mentally handicapped have congenital or long-standing brain damage, and because of the increasing life span the geriatric population of mentally handicapped individuals is increasing so that between 10 per cent and 24 per cent of patients in most long-stay hospitals are over 65 years.

Surveys for abnormal movements in these patients should therefore yield fruitful results, although such surveys will challenge our diagnostic skills as by no means will all the movement disorders be tardive dyskinesia: the involuntary movements of the cerebral palsies must be distinguished.

In a small survey of the total population in one long-stay female ward in a mental handicap hospital where ages ranged from 42 to 87 years (mean of 65 years) and time spent in hospital ranged from 2 to 50 years (mean of 32 years) and mental ages ranged from less than 5 years to dull normality, 9 had received antipsychotic medication in the past 7 years. Obvious movements suggestive of tardive dyskinesia were found in 49 per cent and mild abnormal movements of the face, tongue, jaws and hands were found in a further 37 per cent. All 9 who had received antipsychotic medication, and 25 out of 31 who had not received medication had abnormal movements; in this small number there was no significant relationship to medication history, nor to age. This survey was primarily a pilot scheme to assess the level of co-operation one could expect from such a population. With appropriate techniques and much encouragement all patients in the survey completed the examination, based on the technique described by Sovner (1978), using the Abnormal Involuntary Movements Scale (NIMH, 1975) with appropriate simplification assuming low cognitive abilities (Blowers and Bicknell, 1979).

With the slight improvements in the mental handicap services and the greater emphasis on daily activity programmes, many of the behaviour disturbances formerly treated by medication are being successfully dealt with by methods not requiring medication. Many mentally handicapped people are being maintained in the community in more appropriate environments than were hitherto available in long stay wards. Those who are admitted to hospital are experiencing a service that continues to improve. We believe therefore that further work could usefully be done with this group of mentally handicapped individuals who are with us now, as with a more progressive philosophy of care and increased resources the opportunity to study such a group should fortunately disappear.

D. J. BICKNELL
A. J. BLOWERS

Botleys Park Hospital,
Chertsey, Surrey

References


The Relevance of Antipsychotic Medication in Tardive Dyskinesia in the Elderly

A. J. Blowers and Joan Bicknell
THE RELEVANCE OF ANTIPSYCHOTIC MEDICATION IN TARDIVE DYSKINESIA IN THE ELDERLY

A.J. BLOWERS† AND JOAN BICKNELL‡
†Department of Human Biology and Health, University of Surrey, Guildford, Surrey, U.K.; ‡Botleys Park Hospital, Chertsey, Surrey, U.K.

INTRODUCTION

Tardive dyskinesia has been generally regarded as a complication of long-term antipsychotic therapy. It appears to be more prevalent in the elderly. Female patients have been considered more prone to the disorder than males and in particular chorea was more common in women than in men. Following screening of the adult population of a large mental hospital, some 360 patients (11%) were found to have symptoms of tardive dyskinesia, and, from a representative group chosen together with a matched control group, female patients were found to be over-represented. The present study was undertaken to establish the prevalence of tardive dyskinesia in a small population of elderly, female patients in a hospital for the mentally handicapped and to observe whether there were any differences between those who had received antipsychotic medication during the past seven years and those who had not.

MATERIALS AND METHODS

Forty-one female patients, the total population available from one ward, were included in the study. Ages ranged from 42-87 years with a mean of 65.5 years. Time spent in the present hospital ranged from 2-50 years with a mean of 31.6 years.

Assessment of dyskinetic symptoms

The patients were examined individually using a modification of the technique described by Sovner based on the A.I.M.S. (Abnormal Involuntary Movements Scale) examination devised by the National Institute of Mental Health and referred to by Cardos et al. Details of abnormal involuntary movements were recorded using a modification of the Abbreviated Dyskinesia Rating Scale of the Rockland Research Institute. Medical and drug history for the past seven years were also recorded.
RESULTS

Examination of the current medical status revealed that 3 patients had involuntary movements of long standing. One of these showed symptoms indistinguishable from tardive dyskinesia of 43 years duration. She had received chlorpromazine more than 7 years ago, but was excluded from the study as her disorder was present before phenothiazines were available as therapeutic agents. The other two patients had symptoms more typical of a cerebellar disorder and they had received no medication in the last 7 years. Two patients had Parkinson's disease, one was arteriosclerotic, and the other postencephalitic, the latter improving with L-dopa. Two patients were epileptic and were on anti-convulsants, and eight were mildly hypertensive and obese, and were controlled by diuretics and anti-hypertensives. Three were receiving treatment for depression or anxiety and two maintained euthyroid with thyroxine therapy. Four patients received iron for anaemia and two, analgesics for osteoarthritis.

Of the 40 patients remaining in the study, 31 patients had received no antipsychotic medication (phenothiazines, butyrophenones or thioxanthenes) during the previous 7 years.

Nine patients had received one or more antipsychotic preparations at some time during this period. Five had received thioridazine alone, two haloperidol, one haloperidol followed by thioridazine and one flupenthixol. In addition, these nine patients had received antidepressants (5 prescriptions), antiparkinsonian drugs (5 prescriptions), minor tranquillizers (5 prescriptions) and barbiturates (2 prescriptions).

Scoring for abnormal movement was completed for each patient who was then assigned to one of two groups, group A which included those who had no antipsychotic medication for 7 years and group B involving those who had received antipsychotic medication in the past 7 years. A variety of abnormal movements were seen in patients in both groups. Abnormalities most commonly seen were movements of the lips, pouting, puckering and smacking, tongue protrusion with abnormal movements, choreoathetoid movements of the tongue, chewing movements and abnormal movements of the fingers and wrists. In the 31 patients who had not received antipsychotic medication, 25 had abnormal movements noted and in the 9 patients who had received antipsychotic medication, all patients had some noted abnormal movements. Each group was subdivided into those below 65 years and those above 65 years, the means of scores were calculated, the standard deviations and standard errors, tables A & B.
TABLE A - GROUP A (31 PATIENTS - NO ANTIPSYCHOTIC MEDICATION)

<table>
<thead>
<tr>
<th>Age</th>
<th>No.</th>
<th>Mean</th>
<th>S.D.</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 65</td>
<td>13</td>
<td>2.69</td>
<td>2.14</td>
<td>0.59</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>18</td>
<td>3.78</td>
<td>3.66</td>
<td>0.86</td>
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<tr>
<td>All ages</td>
<td>31</td>
<td>3.32</td>
<td>3.11</td>
<td>0.56</td>
</tr>
</tbody>
</table>

TABLE B - GROUP B (9 PATIENTS - ANTIPSYCHOTIC MEDICATION RECEIVED)

<table>
<thead>
<tr>
<th>Age</th>
<th>No.</th>
<th>Mean</th>
<th>S.D.</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 65</td>
<td>4</td>
<td>5.25</td>
<td>3.30</td>
<td>1.65</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>5</td>
<td>5.20</td>
<td>3.49</td>
<td>1.56</td>
</tr>
<tr>
<td>All ages</td>
<td>9</td>
<td>5.22</td>
<td>3.19</td>
<td>1.06</td>
</tr>
</tbody>
</table>

The age distribution is similar for the two groups (mean age of 65.3 years for Group A and 65.7 years for Group B). Differences between the four mean scores are not statistically significant at the 5% level but there is a trend for the scores to be greater in group B, than in group A, and a trend for the score to increase with age, but neither of these were very pronounced.

DISCUSSION

 Whilst it is generally accepted that tardive dyskinesia occurs as a result of long-term antipsychotic medication there is evidence to suggest that the disorder can occur in persons who have never received these compounds.¹⁴,¹⁵ Naturally occurring involuntary movements might be diagnosed as tardive dyskinesia and this might explain the unusually high prevalence of the disorder in some studies of drug and non-drug treated patients.¹⁶ Over enthusiasm about diagnosing tardive dyskinesia has been suggested as a reason for mistaking other types of unusual motor activity for this condition.¹⁷

Whilst the results presented here point to a high prevalence rate in elderly female patients they are comparable with figures obtained by Jus et al.¹⁸ who, with careful screening, eliminated abnormal movements found in other neurological disorders, and showed a prevalence rate of 60% in the 50 to 69 years age group, and in those of 70 years and above the rate had risen to 75.6%. The prevalence rate in this study was 77.3% in the 50 to 69 years age group, and 80% in the 70 years and above group.
Within its limitations this present study has shown a level of dyskinesia in patients who have never received antipsychotic medication that is not significantly different to that of a small group who have received antipsychotic medication over a period of several years. Of the nine patients who had received antipsychotic medication the two showing the highest dyskinetic movements (Score = 9), were receiving haloperidol, whereas those receiving thioridazine produced lower scores. In fact, in the treated group, the two showing the least dyskinetic movements (Scores 2 and 1) were from patients who had received thioridazine for 7 years and 17 years respectively. In animal model experiments, it has been shown that thioridazine induced an increase in dopamine-receptor sensitivity which was significantly less intense and of shorter duration than that induced by haloperidol, and the observation made that the tendency of a drug to increase dopamine-receptor sensitivity has been related to its propensity to induce tardive dyskinesia in man, and on this basis it may be expected that tardive dyskinesia following treatment with thioridazine will be rare and less intense than those seen after classical neuroleptics.

REFERENCES

13. Rockland Research Institute, Personal communication.
Dear Sir,

Following an earlier pilot study in elderly patients in a mental handicap hospital (Bicknell and Blowers, 1980), we have recently carried out a prevalence study of abnormal involuntary movements in 12 local authority residential homes for the elderly. A total of 500 subjects, 138 males and 362 females were included in the study. They were rated individually for abnormal movements using a modification of the AIMS examination (NIMH, 1975).

Abnormal involuntary movements were observed in 179 (35.8 per cent) of the 500 subjects. These movements were mostly mild in severity, but orofacial involvement was present in 140 (28 per cent).

In the 122 (24.4 per cent) subjects who had received antipsychotic drugs for a minimum period of three months, abnormal involuntary movements were present in 59 (48.4 per cent), and in the 378 (75.6 per cent) subjects who had no recorded history of antipsychotic medication, abnormal movements were present in 120 (31.7 per cent). The Chi square test (Kirkwood, 1981), indicated that the difference in prevalence of abnormal movements between subjects who had received antipsychotics and those who had never been exposed to these compounds, was statistically significant (P <0.001), thus confirming the association of dyskinetic movements with antipsychotic medication.

The presence of spontaneous dyskinesia in 120 (31.7 per cent) of the 378 subjects who had never received antipsychotic medication confirms an earlier study in which 38 (18 per cent) of 211 residents who had never been treated with an antipsychotic drug showed dyskinetic movements (Bourgeois et al., 1980).

The Task Force of the American Psychiatric Association (1980) reporting on late neurological effects of antipsychotic drugs suggested that the ageing brain may have an increased likelihood of antipsychotic related dyskinesias, especially of the oral region, and also drew attention to the fact that in the elderly, studies had shown that the prevalence of spontaneous buccolingualomasticatory movement abnormalities, is close to that found in antipsychotic treated geriatric patients.

Our own study has shown that in a group of elderly subjects, age range 59–102 years (mean 82.7 years) there is a considerable prevalence of spontaneous dyskinesias, and that antipsychotic drugs do seem to increase the risk of developing dyskinesias during old age.

A. J. Blowers
Department of Human Biology and Health,
University of Surrey, Guildford, Surrey

R. L. Borison
Medical College of Georgia,
Atlanta, Georgia, USA

C. M. Blowers
Maudsley Hospital, London SE5

D. J. Bicknell
St George’s Hospital, London SW17

References
Abnormal orofacial movements

Abnormal involuntary movements, particularly in the orofacial region, are not uncommon in the elderly, and a visit to the day room of any home for the elderly will soon confirm this.

Spontaneous lingual-facial-buccal movements

The syndrome of spontaneous lingual-facial-buccal movements is characterised by uncontrolled movements of the tongue, lower facial (oral or buccal) muscles, and the jaw or masticatory muscles. The tongue may exhibit a choreoathetoid or writhing movement, readily observed when the mouth is open, and it may be thrust out in either a fly-catcher movement or complete protraction. Lip movements include smacking, pouting, and puckering, and eye movements such as excessive blinking or blepharospasm may occur.

The pathophysiology of spontaneous lingual-facial-buccal dyskinesia is suggested by Weiner and Klawans (Journal of the American Geriatrics Society, 1973, XXI, 314-320) as being related to altered responsiveness of dopamine receptor sites.

Tardive dyskinesia

Reports of persistent abnormal involuntary movements associated with long-term treatment with antipsychotic medication began to appear in the 1950s. The dyskinetic movements are similar to those of the spontaneous syndrome, and the main area of involvement is the orofacial region. Numerous studies have shown a prevalence of the disorder ranging from 0.5 per cent to 56 per cent in patients treated with prolonged antipsychotic medication, and there is evidence to suggest that the movements occur with increasing frequency with age.

A recent study undertaken by the author (not yet published) has shown that in 500 subjects who were resident or receiving day care in homes for the elderly, abnormal involuntary movements were present in 179 (36 per cent). In the 122 subjects who had a history of antipsychotic medication 59 (48 per cent) had dyskinetic movements, and in the 378 subjects who had never received antipsychotic medication 120 (32 per cent) had dyskinetic movements. Orofacial involvement was present in approximately 80 per cent of those who had dyskinesia, whether spontaneous or in association with antipsychotic drugs.

Fig 1: A technique used for detecting abnormal movements, which may disappear under stress, is to distract the patient by asking her to look at pictures of animals and recall at least three species after the pictures have been removed. This will unmask them.
Treatment
Most of the orofacial dyskinesias seen in the above study were mild, and the subjects were unaware of the presence of the movements. Treatment is probably inappropriate and, in any case, likely to be ineffective.

In a leading article (British Medical Journal, 1981, 282, 1257-1258) reference was made to the fact that many remedies have been tried in treating tardive dyskinesia, but none is effective. Promising results in uncontrolled studies have not been confirmed under double-blind conditions. Increasing the dosage of antipsychotic drugs only postpones the risk, since further, and perhaps more, severe dyskinesia may develop later. Anticholinergic drugs will exacerbate established tardive dyskinesia, and their long-term use for controlling drug-induced parkinsonism should be avoided.

Table 1: Severity of abnormal involuntary movements with antipsychotic medication

<table>
<thead>
<tr>
<th>Antipsychotic compound</th>
<th>Number of patients</th>
<th>Dyskinetic mean score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more compounds</td>
<td>31</td>
<td>3·55</td>
</tr>
<tr>
<td>Trifluoperazine + tranylcypromine</td>
<td>1</td>
<td>3·00</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>4</td>
<td>2·75</td>
</tr>
<tr>
<td>Promazine</td>
<td>17</td>
<td>2·15</td>
</tr>
<tr>
<td>Flupenthixol</td>
<td>2</td>
<td>1·50</td>
</tr>
<tr>
<td>Perphenazine + amitriptyline</td>
<td>4</td>
<td>1·80</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>27</td>
<td>1·06</td>
</tr>
<tr>
<td>Fluphenazine + nortriptyline</td>
<td>2</td>
<td>1·00</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>18</td>
<td>0·64</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>13</td>
<td>0·27</td>
</tr>
</tbody>
</table>

Prophylaxis
Preventive measures, such as using antipsychotic drugs only when clearly indicated, and using the lowest effective daily dosage, will minimise the incidence of tardive dyskinesia. There appears to be a relationship between drug-induced parkinsonism and tardive dyskinesia, and Klawans, Goetz, and Perl (American Journal of Psychiatry, 1980, 137, 900-908) suggest the use of thioridazine because it has the lowest incidence of drug-induced parkinsonism, and is also a much weaker blocker of striatal dopamine receptors than other antipsychotics.

Following drug withdrawal the syndrome temporarily worsens, presumably because of the better access of dopamine to striatal receptors, but after a few weeks it will diminish. In the elderly both spontaneous dyskinesias and drug-induced dyskinesias are more common and the irreversibility of the latter is less likely, possibly due to degenerative changes in the basal ganglia of the brain. It now seems generally accepted that antipsychotic drugs should only be used when clearly indicated and the daily dosage kept as low as possible. Early detection of tardive dyskinesia is important and medication should be withdrawn if possible.

A J Blowers
Dept Human Biology and Health
University of Surrey
EPIDEMIOLOGY OF TARDIVE DYSKINESIA IN THE ELDERLY

A. J. Blowers
Department of Human Biology and Health, University of Surrey, Guildford, Surrey, England.

Summary—In a study of 500 subjects in residential homes for the elderly, abnormal involuntary movements were found in 35.8%. In those subjects who had received antipsychotic medication 48.4% had dyskinetic movements, and in those who had never received antipsychotic medication 31.7% had dyskinetic movements. The difference in prevalence of movements was statistically significant.

Analysis of data following the examination of drug histories of patients receiving antipsychotic medication for a minimum period of 3 months, suggested that those who had received thioridazine were least likely to develop tardive dyskinesia.

Problems in conducting and interpreting results of epidemiological studies are discussed.

Since the first reports of abnormal involuntary persistent movements, often of a lingual-facial-buccal nature, began to appear (Ey, Faure and Rappard, 1956; Hall, Jackson and Swain, 1956; Schonecker, 1957) numerous prevalence studies have been undertaken. Klawans, Goetz and Perlik (1980) in reviewing some of these studies, observed that the prevalence of tardive dyskinesia ranged from 0.5 to 56% of patients treated with prolonged antipsychotic medication.

A number of studies have shown that involuntary movements similar to tardive dyskinesia have been observed in elderly subjects who have never been exposed to antipsychotic medication (Crane and Smeets, 1974; Bourgeois, Bouilh, Tignol and Yesavage, 1980; Blowers and Bicknell, 1980). A preliminary report of a study of 500 subjects in residential homes for the elderly indicated a prevalence rate of dyskinetic movements of 35.8% (Blowers, Borison, Blowers and Bicknell, unpublished).

This paper presents further details of the prevalence study (Blowers et al., unpublished) and considers the problems in conducting and interpreting results of epidemiological studies of tardive dyskinesia in the elderly.

METHODS

Five hundred subjects, 138 males and 362 females, who were resident or receiving day care in homes for the elderly were included in the study. Ages ranged from 59 to 102 years with a mean of 82.7 years. The subjects were examined individually for abnormal involuntary movements using a modified A.I.M.S. examination (National Institute of Mental Health, 1975), and these movements were rated on the Rockland Dyskinesia Scale (Simpson, Lee, Zoubok and Gardos, 1979). Medical and drug histories were also recorded.

RESULTS

Abnormal involuntary movements mostly mild in severity were observed in 179 (36%) of the 500 subjects included in the study. In the 122 subjects who had a history of antipsychotic medication 59 (48%) had dyskinetic movements, and in the 378 subjects who had never received antipsychotic medication 120 (32%) had dyskinetic movements.

In the 59 subjects in the antipsychotic treated group who had dyskinetic movements, orofacial involvement was observed in 48 (81%) and in the 120 subjects who had no history of antipsychotic drugs, 92 (77%) had orofacial dyskinetic movements. In both groups choreoathetoid tongue movements were most frequently observed, and the individual orofacial movements are shown in Table 1.

Whilst the majority of subjects in the study were showing only mild dyskinesia, in the antipsychotic-treated group, 12 of 122 subjects had total dyskinetic scores of between 5 and 9, and 3 subjects had total scores in excess of 10. In the group who had not been exposed to antipsychotic medication, 7 of 378 had

<table>
<thead>
<tr>
<th>Table 1. Rockland scale orofacial movements in antipsychotic and non-antipsychotic treated subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rockland item</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>One or more orofacial movement</td>
</tr>
<tr>
<td>Choreoathetoid tongue movements</td>
</tr>
<tr>
<td>Lip movements</td>
</tr>
<tr>
<td>Chewing movements</td>
</tr>
<tr>
<td>Tongue protrusion</td>
</tr>
<tr>
<td>Periorcular movements</td>
</tr>
<tr>
<td>Bonbon sign</td>
</tr>
</tbody>
</table>

1339
total dyskinetic scores of between 5 and 9, and 3 had scores in excess of 10.

Analysis of antipsychotic drug history has shown that of the 91 subjects who had received only one compound, the 13 who had received thioridazine had the lowest dyskinetic scores. In the thioridazine group, 10 of 13 subjects had no dyskinetic movements.

**DISCUSSION**

In an overview of the changing epidemiology of tardive dyskinesia, Jeste and Wyatt (1981) referred to the reported rising prevalence among patients treated with antipsychotics. They also suggested that epidemiological studies of drug-induced tardive dyskinesias should be complemented by similar work on spontaneously occurring dyskinesias to show that the risk of drug-induced illness is significantly greater than the baseline risk of developing dyskinesia. The present study in 12 homes for the elderly was conducted under conditions where information on drug treatment was not known until after all of the residents of each home had been rated for dyskinetic movements. The Chi Square test (Kirkwood, 1981) indicated that the difference in prevalence of dyskinesias between subjects who had received antipsychotic drugs and those who had never been exposed to these compounds was statistically significant ($P < 0.001$). The lower proportion of patients with dyskinesia in the study not treated with antipsychotics thus further confirms the relationship between tardive dyskinesia and antipsychotic medication, and this association has been strongly supported (Baldessarini, 1974).

It is suggested that some of the epidemiological studies that have reported a high prevalence of tardive dyskinesia may reflect an increasing sensitivity to minor degrees of possible movement abnormality (Task Force, 1980). Methodological differences include diagnostic criteria, severity of dyskinesia and type of dyskinesia, and account for the wide variations in prevalence rates (Jeste and Wyatt, 1981).

In an earlier study (Blowers and Bicknell, 1980), dyskinesias seen in patients treated with thioridazine were less frequent and of lower severity than those seen in patients treated with haloperidol. The absence of dyskinesia in 10 of the 13 subjects who had received thioridazine in the current study complements results obtained from animal studies, in which it has been shown that the dopamine receptor sensitivity produced by thioridazine is significantly less intense and of shorter duration than that produced by haloperidol (Sayers, Bürki, Ruch and Asper, 1977) and by haloperidol and fluphenazine (Borison and Blowers, 1981).

_Acknowledgements_—I am most grateful to Professors Joan Bicknell and Richard Borison for continued encouragement and support, to Dr Alick Munro for helpful criticism and to Mrs R. Trumper for preparing the manuscript.

**REFERENCES**


Co-dergocrine (Hydergine) in the treatment of tardive dyskinesia

SUDHIR C. RASTOGI,1 ANTHONY J. BLOWERS2 AND ALAN C. GIBSON3

From Herrison Hospital, Dorchester, Dorset

SYNOPSIS In a double-blind, placebo-controlled study with co-dergocrine in the treatment of tardive dyskinesia in a group of elderly chronic psychiatric patients the reduction of dyskinetic scores in the group receiving active medication was slightly greater than that in the placebo group; however, this difference did not reach a level of statistical significance. It is suggested that further work could be undertaken with a longer period of treatment, and at a higher dosage level of co-dergocrine, in a younger patient sample.

INTRODUCTION

Since reports of tardive dyskinesia associated with antipsychotic drugs first appeared (Ey et al. 1956; Hall et al. 1956; Schonecker, 1957), many drugs have been suggested for its treatment. To date, no generally satisfactory treatment has been demonstrated (Mackay et al. 1980).

The ergot derivative co-dergocrine appears to play a role in cerebral synaptic transmission and has been shown in vitro to displace dopamine and haloperidol from their specific binding sites in the caudate nucleus (Goldstein et al. 1978), and in vivo to produce an acceleration of noradrenaline turnover and a slowing of dopamine and serotonin brain turnover, suggesting noradrenaline antagonism, dopamine agonism and serotonin antagonism (Loew et al. 1979).

While it might be expected that dopamine agonists would markedly exacerbate tardive dyskinesia, it has been shown that apomorphine actually reduced dyskinetic movements (Smith et al. 1977). It has been postulated that a low dose of the dopamine agonist, bromocriptine, may lead to predominant stimulation of the pre-synaptic inhibitory dopaminergic receptor, thus reducing pre-synaptic dopamine release (Barnes et al. 1978). It was felt that the dopamine agonist effect of co-dergocrine merited study in the treatment of tardive dyskinesia.

Results from uncontrolled studies with co-dergocrine in the treatment of tardive dyskinesia have been promising (Gomez, 1977; Hajioff, 1978), and the present study was undertaken to evaluate the compound under double-blind conditions.

METHOD

Clinical population

Forty chronic in-patients (17 male and 23 female) were included in the study. The following criteria for admission were established: (1) the presence of persistent involuntary movements predominately in the orofacial region and unrelated to idiopathic or drug-induced Parkinsonian movements; (2) movements had been present for at least 1 year and were considered to have resulted from antipsychotic drug administration; (3) antipsychotic drug treatment had lasted for a period of at least 1 year. Of the 40 patients selected, case-note diagnoses were: schizophrenia (29), dementia (5), depressive psychosis (3), oligophrenia (2), bipolar affective psychosis (1). The mean age was 69·9 years (range 41–91) and the median period of psychiatric hospitalization was 26·7 years (range...
S. C. Rastogi, A. J. Blowers and A. C. Gibson

Table 1. Comparison of groups and treatments

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Placebo</th>
<th>Overall means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±s.e.)</td>
<td>69·7 (±2·1)</td>
<td>70·0 (±2·6)</td>
<td>69·9</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/12</td>
<td>11/10</td>
<td>18/22</td>
</tr>
<tr>
<td>Mean pre-drug</td>
<td>10·1 (±1·1)</td>
<td>8·7 (±0·7)</td>
<td>9·4</td>
</tr>
<tr>
<td>score (±s.e.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number in group</td>
<td>19</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Reduction of scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre→first 6 weeks</td>
<td>3·79</td>
<td>2·48</td>
<td>3·10</td>
</tr>
<tr>
<td>Standard error</td>
<td>0·92</td>
<td>0·95</td>
<td></td>
</tr>
<tr>
<td>Reduction of scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre→second 6 weeks</td>
<td>4·37</td>
<td>3·14</td>
<td>3·72</td>
</tr>
<tr>
<td>Standard error</td>
<td>0·95</td>
<td>0·82</td>
<td></td>
</tr>
</tbody>
</table>

1–55). All patients had been treated with a variety of antipsychotic drugs (mean 3·8 compounds) during their psychiatric care. Background antipsychotic and antiparkinsonian medication was held constant throughout the study.

Informed consent was obtained from patients participating in the study and approved by the patient’s psychiatric consultant.

Study design

A double-blind, placebo-controlled parallel group procedure was used. Patients were randomly allocated to two groups, one of which received co-dergocrine, 4·5 mg tablets once daily for 6 weeks, and the other received an identical placebo tablet for the same period. The 2 raters, ward staff and patients were blind to the treatment procedure.

Rating procedures

Patients were examined individually under standard conditions, at approximately the same time of day, by 2 raters using the AIMS examination (NIMH, 1975) combined with the abbreviated Rockland Tardive Dyskinesia Rating Scale (Simpson et al. 1979). Ratings were carried out prior to entry into the study, at the conclusion of the 6-week drug treatment period, and again at 6 weeks after completion of the drug treatment period to observe any possible carry-over effect.

Statistical analysis

Due to the random allocation of patients to the 2 groups it was necessary to ascertain the importance of sex ratio, mean age and pre-treatment scores between the 2 groups. This was obtained by using generalized linear models (Nelder & Wedderburn, 1972) to perform the analysis on decreases in scores over the study period.

RESULTS

The decreases in the scores of dyskinetic movements were obtained after the 6-week medication period in both the group receiving active medication and the placebo group. The improvement in the active treatment group was reflected in a mean reduction of 3·79 from the pre-treatment mean score of 10·1 (±1·1). In the placebo group the mean reduction was 2·48 from a pre-treatment mean score of 8·7 (±0·7). At the end of the further 6-week period following the drug treatment phase, a small additional improvement in mean scores was seen in the co-dergocrine group of 0·58 and in the placebo group of 0·66. The comparability of the groups and of treatments is shown in Table 1. Both results indicated that there were no sex differences present in the data. However, the use of the pre-drug score as a covariate indicates that it has a significant effect in both cases: thus, the higher the pre-drug score, the greater the improvement in scores between (1) pre-drug and after week 6, and (2) pre-drug and after week 12. A significant effect was also noted when age was used as a second covariate ($P < 0·01$ for pre-drug and after week 6, and $P < 0·05$ for pre-drug and after week 12), indicating that the improvement in scores is reduced as age increases. The reduction in scores in the active group was slightly higher than the placebo group for both periods, but this did not reach a level of statistical significance.
Co-dergocrine in tardive dyskinesia

DISCUSSION

In reviewing all the studies on antipsychotic drug-induced tardive dyskinesia published in the English literature up until August 1978, Jeste & Wyatt (1979) observed that there is, as yet, no single satisfactory method of treating the disorder, and that, until recently, most of the treatment studies were conducted on a small number of patients and were uncontrolled. This observation has been further emphasized by others (Committee on Safety of Medicines, 1979; Mackay et al. 1980). The present study has shown that, under double-blind conditions, improvement in tardive dyskinesia did not reach a level of significance between co-dergocrine and placebo. The patient sample in this study included a high proportion of chronic schizophrenics who had been in institutional care for many years. Of the 40 patients in the study, 35 had been in psychiatric hospitals for more than 10 years and 24 for more than 20 years. Thirty-three patients had been treated with 3 or more different antipsychotic agents during their illness, and 38 had been prescribed one or more antiparkinsonian drugs. Ten patients had been previously treated unsuccessfully with tetrabenazine and/or sodium valproate for their tardive dyskinesia. In addition, 25 patients were over the age of 70, and it would seem unlikely that any drug would produce improvement in a group where tardive dyskinesia was probably irreversible.

In this study a daily dosage of 4-5 mg of co-dergocrine was employed. A preliminary report of a further double-blind study, in which a daily dose of 6 mg of co-dergocrine was used, showed an impressive trend in the effect of co-dergocrine over placebo in the analysis of results in the first 8 patients who had completed the trial (Chien et al. 1980).

Further studies with a longer period of treatment and at a higher dosage level in a younger patient sample should be undertaken.

We wish to express our gratitude to the doctors, nurses and pharmacists at Harrison Hospital for their kind cooperation; to Mr P. Jones for the statistical analysis; and to Mrs R. Trumper for the preparation of the manuscript.

REFERENCES


Site Specific Action of Neuroleptic Drugs in the Brain

... an epidemiologic and clinical review

Richard L. Borison, M.D., Ph.D.
Psychiatry Service, VA Downtown Medical Centre
Medical College of Georgia
Augusta, Georgia

Anthony J. Blowers,
Department of Human Biology and Health
University of Surrey, Guildford
Surrey, England

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at the American Psychiatric Association 135th Annual Meeting
Toronto, Canada, May 17–20, 1982
PUBLIC HEALTH ISSUES REGARDING EXTRAPYRAMIDAL SIDE EFFECTS

1. Dystonic reactions are distressing to patients and account for a large non-compliance rate in taking antipsychotic medication.

2. Dystonic reactions involving the laryngeal muscles produce laryngospasm which can be life threatening.

3. Drug-induced parkinsonism occurs in a high percentage of patients receiving piperazine phenothiazines or butyrophenones. The diagnosis is often missed because akinesia/bradykinesia is the most common parkinsonian sign, and tremors are relatively uncommon.

4. Patients with drug-induced parkinsonism are more prone to injury by falling and food aspiration due to swallowing difficulties.

5. Patients with the bradykinesia of drug-induced parkinsonism are often misdiagnosed as being depressed (postpsychotic depression) or catatonic.

6. Akathisia is experienced as the most discomforting side effect from antipsychotic medication, and results in poor compliance with taking medication.

7. Drug-induced akathisia may precipitate violent behavior in patients, and may appear to worsen the patient’s psychosis.

8. The use of antiparkinsonian anticholinergic drugs to treat acute extrapyramidal side effects is often associated with an antagonism of antipsychotic action.

9. Antiparkinsonian anticholinergic drugs may promote the induction of tardive dyskinesia, and are commonly used as street drugs of abuse.

10. Chronic antipsychotic drug use may result in tardive dyskinesia occurring in 24–56% of patients.

11. Tardive dyskinesia is reversible in its early stages, but often becomes irreversible while being masked by antipsychotic medication.

12. Tardive dyskinesia can lead to life threatening respiratory and gastrointestinal complications.

13. Gait disturbances leading to falling and injury, as well as swallowing difficulties may occur as a result of tardive dyskinesia.

14. Tardive dyskinesia may decrease life expectancy.
PURPOSE
To determine whether antipsychotic drugs have a differential effect on the neurochemistry and functions of various brain areas. These effects on various brain areas account for differentiation of the side effect profile of various antipsychotic drugs.

METHOD
In order to demonstrate a site-specific action for various antipsychotic agents, we have conducted both human and animal studies. If atypical neuroleptics truly have a specific action on the limbic rather than the striatal dopamine receptors they should then be unable to produce a striatal dopamine receptor denervation hypersensitivity which occurs secondary to receptor blockade in the corpus striatum.

ANIMAL STUDIES
The behavioral effects of various antipsyycotic drugs on dopamine receptor blockade was measured after their direct injection into discrete dopamine containing brain areas of the extrapyramidal and limbic systems.

□ Comparison of various antipsychotic drugs in their abilities to produce a dopamine receptor hypersensitivity as assessed by the preclinical model for tardive dyskinesia.

□ White male Sprague-Dawley rats were used in an animal paradigm for tardive dyskinesia (Tarsy and Baldessarini 1973).(32)

□ In this model animals received daily chronic administration of an antipsychotic drug over a 3 week period after which the animals then received daily saline injections over five days.

□ To assess dopamine receptor sensitization, animals were challenged with a direct dopamine agonist (i.e. apomorphine) in a dose which per se fails to produce behavioral activation.

HUMAN STUDIES
Dopamine receptor blockade in the human limbic and extrapyramidal systems assessed by radio-receptor assay.

□ In biochemical tests, human brain material was collected within 6 hours of death and areas from the limbic system including the nucleus accumbens, olfactory tubercle and extrapyramidal system including caudate nucleus, putamen were dissected.

□ Tissues were homogenized and prepared in a sodium phosphate buffer. Receptor ligand binding was carried out using (3H) spiroperidoi (Field, Reisine and Yamamura, 1977)(13) and specific binding was ascertained using butaclamol.
Preclinical model for extrapyramidal system function

The stereotyped (repetitive purposeless movements) behavior demonstrated by a rat has been used as an animal model for tardive dyskinesia. This behavior can be induced by chronic treatment with antipsychotic drugs, and like tardive dyskinesia in many animals with stereotyped behavior shows evidence in their extrapyramidal systems of having hypersensitive dopamine receptors.

Haloperidol and extrapyramidal dopamine receptor hypersensitivity

![Graph showing the effects of haloperidol on stereotyped behavior in rats.](image)

The effects of haloperidol on stereotyped behavior in rats can be observed. Animals were chronically treated with haloperidol, treatment was discontinued, and extrapyramidal dopamine receptor hypersensitivity was assessed. As can be seen, at three and seven days after stopping haloperidol treatment, there is a significant sensitization of dopamine receptors, as measured by stereotyped behavior. This hypersensitivity has normalized after fourteen days.
**Haloperidol and extrapyramidal dopamine receptor hypersensitivity at higher doses**

When the experiment was repeated with a somewhat higher dose of haloperidol, the behavioral sensitivity has increased in both duration and intensity.

**Fluphenazine and extrapyramidal dopamine hypersensitivity**

A similar response is elicited when animals have been treated with fluphenazine hydrochloride. We again see evidence of an extrapyramidal dopamine receptor hypersensitivity which mimics that found in patients with tardive dyskinesia.
Thioridazine and extrapyramidal dopamine hypersensitivity

Although thioridazine is also capable of producing a sensitivity response of dopamine receptors, it is very short lived. Antipsychotic drugs with potent clinical extrapyramidal side effects, such as fluphenazine and haloperidol, produce a longer duration of receptor sensitization when compared with thioridazine. This suggests that with some antipsychotic drugs there may be difficulty in reversing long term extrapyramidal effects.
Blockade of dopamine action in the limbic system by antipsychotic drugs

The ability of a dose of systemically administered antipsychotic drug to block the behavioral activity induced by the direct (bilateral) administration of dopamine into the limbic system (nucleus accumbens) of rat brain was plotted. These results have been compared with the daily effective antipsychotic dose of each drug. We see that there is a linear relationship, demonstrating that the antipsychotic actions of these drugs is related to their abilities to block dopamine in the limbic system.
In this figure we have plotted the ability of a dose of systemically administered antipsychotic drug to block the behavioral activity induced by the direct (bilateral) administration of dopamine into the striatum (caudate-putamen nucleus) of the rat brain. These results have again been compared with the daily effective antipsychotic dose of each drug. A linear relationship for the majority of antipsychotic drugs was found, however, thioridazine, clozapine, and sulpiride, all fall to the left of the line. This demonstrates that these three antipsychotic drugs have much less potent effects in blocking dopamine receptors in the extrapyramidal system. Furthermore, this demonstrates that the therapeutic antipsychotic effects of these drugs is not correlated to their ability to produce extrapyramidal side effects.
Comparison of extrapyramidal and limbic systems actions caused by antipsychotic drugs in the rat brain

This figure compares the ability of antipsychotic drugs, in the rat, to block the actions of dopamine in the striatum or extrapyramidal system, and in the limbic system. Those drugs which fall into the upper lefthand corner are those drugs which are more potent in the blocking extrapyramidal rather than limbic dopamine receptors. Those drugs which fall into the lower right hand corner, are those compounds which are more potent in blocking dopamine in the limbic rather than extrapyramidal system.
Direct measurement of dopamine receptor blockade in the rat brain

<table>
<thead>
<tr>
<th>IC$_{50}$ (nM)</th>
<th>Striatal</th>
<th>Limbic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olfactory Tubercle</strong></td>
<td><strong>Nucleus Accumbens</strong></td>
<td><strong>Caudate-Putamen</strong></td>
</tr>
<tr>
<td>Clozapine</td>
<td>16</td>
<td>240</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1000</td>
<td>80</td>
</tr>
</tbody>
</table>

IC$_{50}$ Limbic/IC$_{50}$ Striatal
Values less than 1 indicate a preferential binding to receptors in the limbic structures.

The striatum (caudate-putamen nucleus), and part of the limbic system (olfactory tubercle and nucleus accumbens) was dissected from the rat brain. In receptor binding studies, using radioactive spiroperidol, a butyrophenone antipsychotic drug, we have measured the effects of clozapine, thioridazine, and haloperidol in blocking extrapyramidal and limbic dopamine receptors. The IC$_{50}$ refers to the dose of drug needed to displace 50% of the binding of radioactive spiroperidol to the dopamine receptor. The units are in nanomolar concentration, which is believed to be the antipsychotic drug concentration in the brain that produces an antipsychotic effect. The lower the number, the more potent a drug is in blocking dopamine receptors. We have in the far right column compared the IC$_{50}$'s of these drugs in their abilities to block dopamine in the limbic and extrapyramidal systems. Those values smaller than one, indicate a preference for blocking dopamine receptors in the limbic system. As can be seen, both clozapine and thioridazine produce a selective blockade of dopamine receptors in the limbic system, whereas haloperidol produces a preferential blockade of dopamine receptors in the striatum.
Site of action preference of antipsychotic drugs in the rat brain

Bars falling above the line indicate a preference for blocking dopamine receptors in the extrapyramidal system, while those bars falling below the line indicate a preference for blockade of limbic dopamine receptors. These results are therefore correlated with the ability of an antipsychotic drug to produce extrapyramidal side effects.
Direct measurement of dopamine receptor blockade in the human extrapyramidal system

The effect of four antipsychotic drugs to block dopamine receptors in the human caudate nucleus, which is an integral part of the extrapyramidal system is examined. The IC₅₀ and y-axis again refers to the concentration of antipsychotic drug necessary to block 50% of the dopamine receptors (as assayed by displacement of radioactive spiroperidol). On the x-axis we see the average daily clinically effective antipsychotic dose of drugs. This graph demonstrates that butaclamol, an antipsychotic chemically related to haloperidol, and haloperidol, are very potent blockers of dopamine receptors in the human caudate nucleus. In contrast, clozapine, an antipsychotic drug formerly used in Europe, which never produced an extrapyramidal side effect, including tardive dyskinesia, and thioridazine, are weak blockers of dopamine receptors in the extrapyramidal system of the human brain.
The actions of the previous four drugs in their ability to block dopamine receptors in nucleus accumbens of the human brain obtained at autopsy can be seen. The nucleus accumbens is a part of the human limbic system. As compared with the previous figure, and almost straight-line relationship between these four drugs can be observed. This indicates that these drugs are all almost equally active in their abilities to block dopamine receptors in the human limbic system. Therefore, this shows that these drugs are all equally potent as dopamine receptor blockers in that area of the human brain where they produce an antipsychotic effect. Differences between these four drugs in total milligram dose administered to achieve an antipsychotic effect in man is NOT related to their potencies in blocking dopamine receptors in the limbic system but most likely due to differences in drug metabolism and distribution.
Comparison of extrapyramidal system actions caused by antipsychotic drugs in the human brain vs limbic system actions

These bar graphs represent the relationship of butaclamol, haloperidol, thioridazine, and clozapine, in their abilities to block dopamine receptors in the human extrapyramidal and limbic systems. The higher a bar is, the more potent the drug is in its actions in blocking extrapyramidal rather than limbic dopamine receptors. These results show that haloperidol has the greatest activity in preferring extrapyramidal dopamine receptors, whereas clozapine is the least potent in this regard. This data correlates excellently with the fact that haloperidol and butaclamol produce many extrapyramidal side effects, whereas clozapine and thioridazine produce few or no extrapyramidal side effects.
We have taken the same data, and now represented it as the preference of an antipsychotic drug to block limbic system, rather than extrapyramidal system dopamine receptors. We again see that thioridazine and clozapine are the most potent in this regard; demonstrating that they are potent antipsychotic drugs with few extrapyramidal side effects. Furthermore, our dopamine receptor studies in the human brain demonstrate that the lack of extrapyramidal side effects is correlated to a poor blockade of dopamine receptors in the extrapyramidal system, and is independent of any anticholinergic properties of any of these compounds, as the addition of benztropine (Cogentin) fails to affect dopamine receptor binding.
The 'Atypical' Antipsychotic Drugs

On the feature of dopamine supersensitivity that must be considered in the attempt to evaluate animal models of mechanisms underlying T.D., is the differential ability of various classes of neuroleptics to induce supersensitivity, the recent publication of the A.P.A. task force report on Tardive Dyskinesia states:(1)

"Another feature of dopamine supersensitivity that must be considered in the attempt to evaluate animal models of mechanisms underlying TD is the differential ability of various classes of neuroleptics to induce supersensitivity. Since certain "atypical" antipsychotic drugs (notably thioridazine, clozapine, and sulpiride) are relatively less likely to induce acute extrapyramidal effects in patients, or presumably analogous actions in animals (such as inducing catalepsy or antagonizing dopamine receptor agonists), it has been suggested that they may produce tardive dyskinesia less often than other neuroleptic agents. This prediction seems to be supported by clinical experience with thioridazine compared with many other antipsychotic agents, although this point has not been evaluated critically. Clozapine and sulpiride have not been associated with tardive dyskinesia, although they are experimental drugs and have not yet been used for prolonged periods in many patients."

The Anticholinergic Properties of Thioridazine

Even though it has sometimes been alleged that thioridazine is much more anticholinergic than other neuroleptics, a thorough review of the data reveals that thioridazine is not substantially more anticholinergic than other neuroleptics.

As an example, utilizing a standard anticholinergic cluster (blurred vision, constipation, dry mouth and nasal stuffiness), Galbrecht and Klett (1968)(12) found the following prevalences: fluphenazine, 15%; thioridazine, 19%; and chlorpromazine, 21%. Similarly, Lasky(21) et al (1962) showed prevalences for fluphenazine at 24%, thioridazine at 31% and chlorpromazine at 45%. 

Low Incidence of EPS with Thioridazine

Based on 22 years’ experience, and continuing review of the literature, it can be concluded that thioridazine has the lowest incidence of extrapyramidal reactions of any antipsychotic agent available in this country. It has particularly significantly fewer of these reactions than the low mg high potency neuroleptics. This conclusion is virtually universally accepted. (2, 5–9, 14, 16–18, 21,22,24,25,27,30,31,34)

CONCLUSIONS

Extrapyramidal side effects may become irreversible and even occasionally life threatening. Beyond medical problems, extrapyramidal side effects may interfere with patient compliance in taking medication. In this exhibit we demonstrate in animals and humans, via behavior and biochemical studies, that various antipsychotic drugs produce a differential blockade of dopamine receptors in the brain. Furthermore, it is demonstrated that this differential action in the brain accounts for the differing spectrum of side effects associated with antipsychotic drugs.

The low incidence of extrapyramidal side effects found with thioridazine is due to its site specific blockade of dopamine receptors in the limbic system of the human brain. This results in effective antipsychotic actions, greater potential for recognition of reversible dyskinesias, better patient compliance and a lower incidence of recidivism.
Clinical Assessment of Dyskinesias in the Geriatric Patient

INTRODUCTION

Since the first reports of persistent, abnormal involuntary movements began to appear (Ey et al, 1956) numerous prevalence studies have been carried out. Prevalence rates of the condition, subsequently classified as tardive dyskinesia, have varied from 0.5% to 56% of patients treated with prolonged antipsychotic medication.

Several studies have shown that involuntary movements similar to tardive dyskinesia have been observed in elderly subjects who have never been exposed to antipsychotic medication (Crane & Smeets, 1974; Bourgeois et al, 1980).

Most epidemiological studies agree that advanced age is an important risk factor for the development of tardive dyskinesia (Klawans et al, 1980; Jeste and Wyatt, 1981), and we have recently investigated factors related to dyskinetic movements in geriatric patients.

MATERIAL

Five hundred patients, 138 males and 362 females, in 12 British Nursing Homes for the Elderly*, were rated for dyskinesias using the Abnormal Involuntary Movement Scale (AIMS).

Ages ranged from 59 to 102 years with a mean of 82.6 years. Medical and drug histories were subsequently recorded.

*Bishops House, Shepperton, Middlesex; Weylands, Weylndge, Surrey; The Pines, Woking, Surrey; Hale End, Woking, Surrey; Healthside, Woking, Surrey; Birchlands, Englefield Green, Surrey; Brockhurst, Ottershaw, Surrey; Glendale, Walton on Thames, Surrey; The Manor, Old Sindsor, Berkshire; Shallcross, Thames Ditton, Surrey; Thames Side, East Molesey, Surrey; Rylston,Walton on Thames, Surrey.
METHODS

Patients sat in an upright, armless chair, with hands resting on the lap and feet placed firmly on the ground.

They were invited to look at a composite picture of animals, and told that the picture would be removed after two minutes. They were then asked to recall the names of at least three different animals. While no significance was attached to the answers, the procedure was quite useful in unmasking dyskinetic movements, particularly in the orofacial region.

Using an AIMS score of 3 or greater as indicative of true tardive dyskinesia, a total of 77 (15%) patients showed dyskinetic movement.

A higher frequency of dyskinesias (20.7%) was observed in men compared with that in women (13.6%).

There were no significant differences found in dyskinesias among various age groups defined by decades.

In the 122 patients who had a history of antipsychotic medication, the prevalence of dyskinesias (23%) was statistically significant ($p<0.001$) as compared with 13% in the 378 patients who had never received antipsychotics.

There were no significant difference in the frequency of dyskinesias between males receiving antipsychotics (26.5%) and those who had not (21.6%).

However, women receiving antipsychotic drugs had almost twice the frequency of dyskinesias in comparison with those who had never been exposed to antipsychotics (21.6% vs 11.0%).
RESULTS

Recent recommendations (Klawans et al, 1980)(20) on restricting the use of antiparkinsonian drugs to situations where they are clearly indicated, and then no longer than 90 days is supported in our results.

The total use of antiparkinsonian drugs in the population studied was associated with more dyskinesias (37%) than in patients not receiving these compounds (13.4%).

Patients receiving antiparkinsonian drugs in combination with antipsychotic drugs had a significantly higher rate of dyskinesias (43.3%) than patients receiving antiparkinsonian drugs alone (22%).

The use of multiple antipsychotic agents produced more dyskinesias than the use of any single agent.

The antipsychotic drugs associated with the highest frequency of dyskinesias were haloperidol when used in combination with other neuroleptics, with and without an antiparkinsonian agent (55.6%), and trifluoperazine (40%), whereas no patient receiving thioridazine alone achieved a score of 3 on the AIMS. This is consistent with earlier work (Blowers and Bickness, 1980)(3) in which dyskinesias seen in patients treated with thioridazine were less frequent and of lower severity than those treated with haloperidol. This observation was also made by Gerlach (1979)(15).

These clinical findings were similar to those of Mukherje(23) Rosen, Cardenas, et al, who examined 153 psychiatric outpatients, on a maintenance regimen of neuroleptics, for tardive dyskinesias and parkinsonism.

### AIMS ≥ 3 For Patients on Single Neuroleptic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients with AIMS ≥ 3/Total Patients</th>
<th>Dosage Range</th>
<th>Total Ingestion</th>
<th>Length of Treatment (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>thioridazine*</td>
<td>3/13</td>
<td>30–450 mg</td>
<td>6 — 1751 gm</td>
<td>1/4 — 16</td>
</tr>
<tr>
<td>prochlorperazine</td>
<td>3/18</td>
<td>10–50 mg</td>
<td>1.3 — 27 gm</td>
<td>1/4 — 9</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>3/27</td>
<td>10–300 mg</td>
<td>2.7 — 40 gm</td>
<td>1/4 — 11</td>
</tr>
<tr>
<td>promazine</td>
<td>3/17</td>
<td>25–150 mg</td>
<td>4.5 — 216 gm</td>
<td>1/2 — 10</td>
</tr>
</tbody>
</table>

*Mellaril®*
AIMS ≥ 3 For Patients on Single Neuroleptic and an Antidepressant Agent

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients with AIMS 3/Total Patients</th>
<th>Dosage Range</th>
<th>Total Ingestion</th>
<th>Length of Treatment (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluphenazine + nortriptyline</td>
<td>1/2</td>
<td>(fluphenazine) 1.5 mg</td>
<td>1–2 gm</td>
<td>2–4</td>
</tr>
<tr>
<td>perphenazine + amitriptyline</td>
<td>3/4</td>
<td>(perphenazine) 4–6 mg</td>
<td>0.36–17 gm</td>
<td>1⁄4–8</td>
</tr>
<tr>
<td>trifluoperazine + tranylcypromine</td>
<td>1/1</td>
<td>(trifluoperazine) 2 mg</td>
<td>3 gm</td>
<td>4</td>
</tr>
</tbody>
</table>

AIMS ≥ 3 For Patients on No Neuroleptics, Multiple Neuroleptics

<table>
<thead>
<tr>
<th>Population</th>
<th>AIMS</th>
<th>Population</th>
<th>AIMS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neuroleptics</td>
<td>377</td>
<td>49 (13%)</td>
<td>haloperidol + neuroleptic(s)</td>
</tr>
<tr>
<td>+ antiparkinsonian</td>
<td>18</td>
<td>4 (22%)</td>
<td>+ antiparkinsonian</td>
</tr>
<tr>
<td>no antiparkinsonian</td>
<td>359</td>
<td>45 (13%)</td>
<td>no antiparkinsonian</td>
</tr>
<tr>
<td>Two neuroleptics</td>
<td>20</td>
<td>10 (50%)</td>
<td>haloperidol exclusive</td>
</tr>
<tr>
<td>+ antiparkinsonian</td>
<td>7</td>
<td>4 (57%)</td>
<td></td>
</tr>
<tr>
<td>no antiparkinsonian</td>
<td>13</td>
<td>6 (46%)</td>
<td></td>
</tr>
<tr>
<td>Three neuroleptics</td>
<td>11</td>
<td>5 (45%)</td>
<td></td>
</tr>
<tr>
<td>+ antiparkinsonian</td>
<td>5</td>
<td>4 (80%)</td>
<td></td>
</tr>
<tr>
<td>no antiparkinsonian</td>
<td>6</td>
<td>1 (17%)</td>
<td></td>
</tr>
</tbody>
</table>

*Haloperidol was included in this table since there was no record of its use as a single neuroleptic.

DISCUSSION

In this study tardive dyskinesia was significantly associated with the use of high-potency or high dosage neuroleptics and depot fluphenazine.

Low-potency neuroleptics were negatively correlated with moderate tardive dyskinesia.

The authors recommend that the use of neuroleptics be limited to conditions where definite indications and evidence of benefit exist. They recommend that the guidelines established by the A.P.A. Task Force on tardive dyskinesia be followed:
Suggested Guidelines for the Avoidance and Management of Tardive Dyskinesia

"1. Consider indications for prolonged neuroleptic therapy carefully; indications (chronic psychosis) should be serious, with objective evidence of benefit.

2. Seek alternative therapies in neuroses and mood and character disorders.

3. Use lower doses in elderly patients and children, strive for minimum effective doses, avoid multiple drugs, and remove antiparkinsonism agents as soon as possible.

4. Advise patients and families of risks and benefits; arrive at a mutual decision when use of neuroleptic exceeds one year. Not discussion and agreement in clinical record.

5. Examine patient regularly for early signs of choreoathetosis and orallingual dyskinesia. Consider alternative neurologic diagnoses.

6. Reevaluate and document indications and response at least every three to six months and attempt to reduce dose.

7. At earliest sign of dyskinesia, lower the dose, change to a less potent agent, or ideally stop treatment; await remission as long as psychiatric status permits.

8. Treat dyskinesia with benign agents first (diazepam, deanol, choline, or lecithin in high doses, possibly lithium); stay alert to new experimental therapies, if only to bide for time and offer hope. Reinstitute neuroleptics only as an extreme measure for disabling dyskinesias, using lowest doses feasible."

Gerlach and Simmelsgared reported in 1978 on 16 patients in a cross-over trial of thioridazine, clozapine, and haloperidol where they reported that haloperidol might have a greater tendency to induce tardive dyskinesia than thioridazine.

In a report on 44 chronically institutionalized patients who had taken only one neuroleptic on a long term basis, DeVeauh-Geiss found that patients on thioridazine cluster around the low AIMS scores, while the patients with the highest scores (30's and higher 20's) were taking high potency neuroleptics.
CONCLUSIONS

The results also compliment animal studies, in which Sayers et al (1977)\(^26\) showed that the dopamine receptor sensitivity produced by thioridazine is significantly less intense and of shorter duration than that produced by haloperidol. Borison and Blowers (1981)\(^{3a}\) reported a similar pattern in respect of thioridazine compared with haloperidol and fluphenazine.

Our data also showed that in an elderly age group, the prevalence of idiopathic orofacial dyskinesias is high (13.2%), but only women show a much higher frequency of dyskinesias after antipsychotic drug treatment which is consistent with previous epidemiological studies.

In the age range of the group we studied (59–102 years) we found no trend towards increasing dyskinesias with age.

The use of antiparkinsonian drugs and “high potency” antipsychotic agents dramatically increased the frequencies of dyskinesias.

Based upon these findings, it is hoped that it will be possible to more rationally plan the treatment regimens for geriatric patients so as to minimize the potential risks for their development of tardive dyskinesias.
REFERENCES


