

**A STUDY OF THE ACUTE  
NEUROLOGICAL SIDE EFFECTS IN  
HOSPITALIZED PSYCHIATRIC  
PATIENTS RECEIVING NEUROLEPTIC  
DRUG TREATMENT**

by

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## ABSTRACT

Neuroleptic drugs are essential in the treatment of schizophrenia and many other psychiatric disorders. These drugs do however cause a wide range of side effects which can be very distressing to patients. In particular the acute neurological side effects of parkinsonism, akathisia and dystonia, which are termed extrapyramidal syndromes, can be a limiting factor in the use of these drugs (Weiden et al 1987).

Fort Napier Hospital is a large psychiatric referral hospital and the majority of patients admitted require neuroleptic drug treatment. Extrapyramidal side effects are regularly seen amongst these patients. This study was designed to discover the incidence of parkinsonism, akathisia and dystonia amongst patients treated with neuroleptic drugs and what specific factors were responsible for these side effects.

Relevant literature on this topic was reviewed and comparable studies done in America, Europe and South Africa are discussed.

The study sample consisted of one hundred patients who were examined regularly over a two week period for signs of parkinsonism, akathisia, or dystonia which were rated quantitatively according to specific rating scales. Patient and drug variables were then analysed to assess what factors were responsible for these side effects.

The incidence of drug-induced parkinsonism was 29%, akathisia 35% and dystonia 20%. Combinations of these three syndromes were observed resulting in an overall incidence of 47%.

High potency drugs such as haloperidol and trifluoperazine were responsible for a large percentage of all the side effects, while of the low potency drugs, thioridazine produced less side effects than chlorpromazine. Oral drugs combined with

intramuscular depot drugs resulted in a high incidence of side effects.

The phase of treatment was clinically important with dystonia occurring more often within the first three days of treatment, akathisia within ten days and parkinsonism after ten to fourteen days.

Other factors that were studied included the patients age, sex and prior history of neuroleptic-induced neurological side effects. Due to the predominantly young patient population in this study, the mean age of those patients who developed parkinsonism was 26,7 years, akathisia 27,5 years and dystonia 25,8 years. These side effects were seen more commonly in males than in females. Of the 27 patients in this study who had a prior history of neurological side effects , 15 (56%) developed similar side effects following re-exposure to neuroleptic drugs.

Conclusions derived from this study include the need for clinicians to select the correct type and dose of neuroleptic for individual patients in order to minimise the development of neurological side effects. Accurate, early diagnosis of side effects by regular examination of patients is necessary for effective patient management. Clinicians should be made more aware of the side effects that can develop with the use of neuroleptic drugs and the effect these side effects have on patients.

SUPPORTING SERVICES

In this research the statistical planning and analyses, and recommendations arising from these analyses, have been done in consultation with the  
Institute of Biostatistics  
of the  
Medical Research Council, Durban.

## PREFACE

This study represents original work by the author and has not been submitted in any form to another University. Where use was made of the work of others it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Psychiatry, University of Natal, under the supervision of Dr S.V.Moodley.

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## CHAPTER 1

### INTRODUCTION

#### 1.1 OVERVIEW

Neuroleptic drugs have played an important part in the treatment of schizophrenia and many other psychiatric disorders for almost four decades. The introduction of chlorpromazine in the 1950's revolutionized psychiatry and allowed many thousands of patients to be discharged from psychiatric hospitals. The development of depot preparations such as fluphenazine decanoate during the 1960's vastly improved the compliance of patients on long term drug treatment. A variety of neuroleptic drugs, with different chemical properties, have been introduced since then. Associated with the use of most of these drugs remains the problem of extrapyramidal side effects including parkinsonism, akathisia, dystonia and tardive dyskinesia. For the purposes of this study, only the acute neurological side effects are reviewed.

The clinical presentations of these drug-induced side effects are distinguished by certain neurological signs and symptoms. Parkinsonism is clinically similar to idiopathic parkinsons disease and is characterized by tremor, rigidity and bradykinesia. Akathisia involves an objective state of motor restlessness and a subjective feeling of unease with a constant desire to move. Dystonia involves involuntary muscle spasms of the face, eyes, tongue, neck or limbs. These neuroleptic-induced side effects can be very distressing to patients and can lead to poor compliance with future treatment programmes.

Review of the literature reveals that a number of studies have been conducted on drug-induced extrapyramidal side effects over the last thirty years. The incidence of these side effects is influenced by a number of variable factors which include the patients age, sex and individual vulnerability combined with the drug type, dose and phase of treatment (Sovner and DiMascio

1978 p.1021). This is further compounded by differences in methodological procedures, definitions and patient populations used in studies on this topic which makes comparison of the different studies difficult.

In general, the studies done on patients receiving high and low potency drug combinations, such as chlorpromazine and fluphenazine, showed incidence rates for extrapyramidal side effects ranging from 37% (Decina et al 1992) to 61,9% (Ayd 1983 p.86). Patients receiving only low potency drugs, such as chlorpromazine, showed a low (10,6%) incidence of side effects (Swett 1975), while patients treated with high potency drugs, such as haloperidol, were found to have incidence rates of 95 - 100% (Chiles 1978, Neborsky et al 1981). Studies looking specifically at the incidence of akathisia range from 19% (Barnes 1989) to 75% (Van Putten et al 1984). Dystonia incidence rates with high potency drugs, such as haloperidol, range from 31% (Addonizio and Alexopoulos 1988) to 94% (Boyer et al 1987), while with high and low potency combinations, such as chlorpromazine and haloperidol, rates ranged from 10,1% (Swett 1975) to 20,9% (Stramek et al 1986).

The age and sex of patients treated with neuroleptics influences the incidence of side effects with dystonia occurring more commonly in young individuals, particularly young males, while parkinsonism is seen more often in older age groups and akathisia in middle aged females (Ayd 1983 p.87).

Individual vulnerability plays an important part in the development of extrapyramidal syndromes and a prior history of these side effects may predict an increased propensity for patients to develop this problem on re-exposure to neuroleptic drugs (Keepers and Casey 1991).

The phase of treatment influences the clinical presentation of these side effects with dystonia likely to occur within the first few days of treatment while akathisia and parkinsonism occur over the next few weeks to months (Tarsy 1984).

There have been very few published studies done on drug-induced neurological side effects in South Africa. Holden et al (1984) conducted a survey of tardive dyskinesia amongst inpatients at Valkenberg hospital in Cape Town and found the incidence of this disorder to be 17%. Myslobodsky et al (1986) looked at parkinsonian symptoms in patients with tardive dyskinesia and found that 28 (57%) of the 49 patients in the study exhibited various parkinsonian symptoms which were attributed to the high doses of neuroleptics such as fluphenazine used in these patients.

Acute extrapyramidal side effects have been reported to occur in up to 62% of psychiatric patients receiving neuroleptic treatment (Ayd 1983 p.86). This represents a significant clinical problem that warrants further study especially in South Africa where little research has been conducted on this subject.

## 1.2 AIMS AND HYPOTHESES

The aims of this study were to:

1. Discover the incidence of parkinsonism, akathisia and dystonia in a group of hospitalized psychiatric patients receiving neuroleptic drug treatment.
2. Examine the factors responsible for these specific extrapyramidal syndromes.
3. Compare the results of this study with those found in similar studies reported in local and international literature.

It was hypothesized that:

1. There would be a relatively high incidence of parkinsonism, akathisia and dystonia amongst the patients in this study.
2. The incidence of these side effects would be influenced by the type, dose and route of administration of the neuroleptic drugs used.

3. The age, sex and individual vulnerability of the patients would influence the presentation of these specific side effects.

The results of this study could be used to assist clinicians in the early diagnosis and management of these iatrogenic conditions.

## CHAPTER 2

### REVIEW OF LITERATURE

Drug-induced extrapyramidal disorders have been studied by researchers from a number of different disciplines including psychiatry, neurology and clinical psychopharmacology. Review of the literature reveals that studies on this subject vary in methodological procedures, definitions and patient populations used. In reviewing the available information on parkinsonism, akathisia and dystonia, each syndrome is discussed under the following headings:

- 1 Clinical Features
- 2 Pathophysiology
- 3 Epidemiology
- 4 Factors Influencing Clinical Presentation
  - 4.1 Age
  - 4.2 Sex
  - 4.3 Drug Treatment
  - 4.4 Phase of Treatment

#### 2.1 PARKINSONISM

##### 2.1.1 Clinical Features

Neuroleptic-induced parkinsonism is characterized by tremor, rigidity and bradykinesia which may be seen individually or in combination. The tremor is of moderate to high frequency and is seen during movement as well as rest. It is usually seen in the hands and arms but in severe cases may involve the tongue, jaw and lower extremities (Sovner and DiMascio 1978 p.1023).

Rigidity of the limbs can be elicited on passive movement and may be of the cogwheel type. Characteristic parkinsonian postural and gait abnormalities such as flexion of the trunk and limbs and shuffling propulsive or retropulsive gait can be seen in severe cases.

Bradykinesia is the earliest, most common sign observed and may consist of expressionless faces, slow movements, reduced armswing and soft, monotonous speech.

### 2.1.2 Pathophysiology

The pyramidal and extrapyramidal systems are closely integrated and control strength and coordination of movement. The extrapyramidal system involves inputs from multiple brainstem and deep cortical nuclei that modulate pyramidal function. Pharmacologic studies have focused on the striatum (caudate and putamen) where there are high concentrations of dopamine and acetylcholine. Biochemical imbalance of the dopaminergic - cholinergic system leads to abnormal, involuntary movement disorders. Neuroleptic drugs cause blockade of post synaptic dopamine receptors and this results in an underactivity of striatal dopaminergic function (Marsden and Jenner 1980). The effect of this is extrapyramidal dysfunction and the clinical signs of parkinsonism.

### 2.1.3 Epidemiology

One study that is often quoted in the literature on this subject is that of Ayd (1961), where 15,4% of 3775 patients treated with neuroleptics developed parkinsonism. He continued his work over the next twenty years and gathered data on a further 5 000 patients treated with neuroleptics and discovered that 13,2% of this group developed drug-induced parkinsonism (Ayd 1983 p.86). These surveys involved large numbers of chronic patients treated with a range of different neuroleptics for periods of up to 5 years. Donlon and Stenson (1976) studied 175 hospitalized schizophrenic patients on neuroleptic treatment and found that 28,8% developed parkinsonism. More recent studies by McCreadie et al (1992) found that 27% of 146 schizophrenic outpatients on neuroleptic drugs showed signs of parkinsonism. Chakos et al (1992) studied 70 patients treated with fluphenazine over a ten week period and found that 34% of the sample developed parkinsonism.



The increasing incidence of parkinsonism in patients treated with neuroleptics over the last decade may be due to the increased use of high potency drugs and depot preparations. The use of more sensitive rating scales and more refined research criteria may have also influenced these results.

#### 2.1.4 Factors influencing clinical presentation

##### 2.1.4.1 Age

Ayd (1961) reviewed 582 patients with drug-induced parkinsonism and compared the incidence of this syndrome with the age of the patients. There was an increased incidence in patients over the age of 40 years, reaching a peak in the 70 to 79 year age group which is similar to the age range for patients with idiopathic parkinsons disease. Other researchers (Donlon and Stenson 1976, Chakos et al 1992) studying younger patient populations do not specify the age range of those patients who developed drug-induced parkinsonism. This syndrome is however commonly seen in young individuals treated with neuroleptics and thus age alone is not the only factor influencing the clinical presentation of parkinsonism (Sovner and DiMascio 1978 p.1027).

##### 2.1.4.2 Sex

Ayd (1961) reported that women were twice as likely to develop parkinsonism following neuroleptic drug treatment compared to men. This was based on data from 582 patients treated with seven different neuroleptic drugs. The doses used for males and females were however not equivalent. There have been no controlled studies done on the effect of gender on the incidence of acute extrapyramidal side effects. The sex of the patient is only one of the factors that influences the incidence of side effects such as parkinsonism (Marsden et al 1975 p.231).

#### 2.1.4.3 Drug Treatment

The reported incidence of drug-induced parkinsonism varies from study to study and one of the factors responsible for this is the type of neuroleptic used. Studies done on patients receiving high and low potency drugs, such as chlorpromazine and fluphenazine, showed incidence rates for parkinsonism ranging from 13,2% (Ayd 1983 p.86) to 27% (McCreadie et al 1992). Where high potency drugs, such as haloperidol or fluphenazine have been used, the incidence rates for parkinsonism range from 34% (Chakos et al 1992) to 40% (Binder and Levy 1981). This can be explained to some degree by the relatively higher anticholinergic properties of the low potency drugs such as chlorpromazine and thioridazine compared to the high potency drugs such as haloperidol and fluphenazine (Snyder et al 1974). The dose of neuroleptic used also appears to influence the incidence of these side effects with the middle dosage range of each drug having the highest incidence of extrapyramidal side effects (Sovner and DiMascio 1978 p.1026).

#### 2.1.4.4 Phase of treatment

Signs of parkinsonism may begin within a few days of drug treatment with a gradual increase in incidence so that up to 75% of cases appear by one month (Marsden et al 1975 p.230). The development of parkinsonism may be more rapid with severe signs developing over days following depot preparations such as fluphenazine decanoate (Ayd 1975). Sudden discontinuation of concurrent anticholinergic drug treatment may also lead to a recurrence of parkinsonism features in predisposed individuals (Manos et al 1981).

## 2.2 AKATHISIA

### 2.2.1 Clinical Features

Akathisia is a movement disorder with two major components : an objective state of motor restlessness and a subjective feeling of unease with a desire to move. The motor component is characterized by an inability to stand still, purposeless limb movements, pacing or shifting from foot to foot. The restlessness is not localized to any part of the body and may range from nonspecific fidgety movements to a state of constant movement. The subjective state of restlessness is usually described as a feeling of uneasiness or tension and can be very distressing to patients. They may also suffer from initial insomnia because they cannot lie motionless in bed long enough to fall asleep (Ratey and Salzman 1984).

### 2.2.2 Pathophysiology

Akathisia occurs in some individuals following treatment with neuroleptic drugs. The exact pathogenesis is not known, but the most plausible current hypothesis put forward by Marsden and Jenner (1980) implicates competitive blockade of mesocortical post synaptic dopamine receptors by neuroleptic drugs. Blockade of dopamine receptors in the striatum and mesolimbic areas such as the nucleus accumbens produces inhibition of locomotion, while the reverse occurs with blockade of mesocortical dopamine systems (Marsden and Jenner 1980). Further research is required to confirm this hypothesis.

### 2.2.3 Epidemiology

Van Putten and Marder (1986) state that akathisia is under-recognized and that this has been due to the lack of clear operational definitions. The diagnosis of akathisia has tended to rely on questioning about a patient's inner restlessness, but reliance on a patients subjective feelings alone does not

lead to reliable diagnosis. Barnes (1989) developed a rating scale for drug-induced akathisia which incorporates both subjective and objective features and appears a more reliable method of diagnosing this disorder.

Estimates on the incidence of akathisia vary a great deal. Gibb and Lees (1986) believe that as many as 50% of patients on chronic neuroleptic therapy could have mild akathisia. Ratey and Salzman (1984) report that 20-45% of patients on neuroleptic treatment have definite signs and symptoms of akathisia. In a prospective study of acute inpatient admissions by Braude et al (1983), the incidence of akathisia was found to be 25%. Figures as high as 75% have been reported (Van Putten et al 1984) with the use of drugs such as haloperidol. Marsden et al (1975 p.234) believe that incidence figures of 20% are generally accepted by researchers in this field.

#### 2.2.4 Factors influencing clinical presentation

##### 2.2.4.1 Age

Review of the literature reveals that there is some variation in the age of patients who develop akathisia following neuroleptic drug treatment. Ayd (1961) noted that akathisia can occur at any age, but is more prevalent amongst middle aged patients. Marsden et al (1975 p.234) report that the incidence of akathisia is fairly uniform between the ages of 12 and 65 years. Ratey and Salzman (1984) believe that akathisia is more common in the elderly with a peak incidence in the eighth decade. Further studies on the effect of age on the incidence of akathisia are needed to clarify this issue.

##### 2.2.4.2 Sex

The effect of gender on the incidence of akathisia has not been clearly demonstrated. Studies done on patients with akathisia (Braude et al 1983, Gibb and Lees 1986) do not comment on the

incidence of akathisia according to patients sex. Akathisia has been reported to occur more commonly in female patients than in males following neuroleptic drug treatment (Ayd 1961). This survey did not however control for the dose of neuroleptic used. Marsden et al (1975 p.234) feels that female patients receive somewhat higher doses of neuroleptics than males and this may influence the incidence rates. Controlled studies would be needed to answer this question.

#### 2.2.4.3 Drug treatment

Akathisia is probably the most common neurological side effect that develops following treatment with neuroleptic drugs (Marsden et al 1975 p.234). The incidence of akathisia does however vary according to the potency of drug used. Van Putten et al (1984) studied the incidence of akathisia in two populations of newly admitted schizophrenic patients: one group was treated with haloperidol and the other group received thiothixene hydrochloride at fixed doses. 75% of the patients who received haloperidol developed akathisia by the seventh day compared to only 46% of those patients who received thiothixene. Low potency drugs such as thioridazine are less likely to produce akathisia than the high potency drugs such as haloperidol, while depot preparations such as fluphenazine decanoate are not more liable to evoke akathisia than other potent oral drugs (Ayd 1975). The dose of drug used is also an important factor and although there is no direct linear relationship, lower doses of neuroleptics produce less akathisia.

#### 2.2.4.4 Phase of treatment

Ayd (1961) noted that akathisia generally precedes drug-induced parkinsonism in time of onset and that the incidence of akathisia increases with time so that about 50% of such reactions occur within the first month of treatment with oral neuroleptics. Following a dose of intramuscular fluphenazine decanoate, 90% of the cases of akathisia develop within one to

four days (Ayd 1975).

Braude et al (1983) studied 104 patients on neuroleptic drug treatment and found that 26 (25%) developed akathisia. All of these patients showed signs of akathisia after large increases in drug dosage which usually occurred in the first 10 days of treatment. Akathisia can however develop within hours of starting treatment as was shown by Van Putten et al (1984) where patients started on oral haloperidol were observed to have clinical signs of akathisia within six hours of the first dose.

## 2.3 DYSTONIA

### 2.3.1 Clinical Features

The typical presentation of dystonia is one of intermittent or sustained muscular spasms leading to abnormal postures or facial movements. The clinical presentation depends on which muscle groups are involved; when the muscles of the head and face are involved, facial grimacing, tics, tongue protrusion, forced jaw opening, distortions of the lips, oculogyric crises or other aversive eye movements may occur. Involvement of the neck muscles produces torticollis or retrocollis and involvement of the pharyngeal muscles can produce dysphasia or respiratory distress while involvement of the trunk or limbs leads to abnormal postures and limb movements (Tarsy 1984).

### 2.3.2 Pathophysiology

The physiology of dystonic reactions has been studied by Marsden and Jenner (1980) who proposed the following process. Neuroleptic drugs cause a dopamine blockade which leads to compensatory changes in pre and post synaptic dopamine receptors. As the neuroleptic concentration decreases after acute administration, super-sensitive post synaptic dopamine receptors are left exposed. Any dopamine that is then release

provokes an enhanced response at these receptors. The clinical result of this complex process is seen as acute dystonic reactions. Why only some individuals develop these side effects has not been clearly demonstrated and may represent an idiosyncratic reaction or a dose dependent condition (Marsden and Jenner 1980).

### 2.3.3 Epidemiology

The incidence of dystonia has been well documented by many researchers. In the early 1960's Ayd (1961) noted that 2,3% of 3775 patients developed dystonia following phenothiazine treatment. A study by Swett (1975) of 1152 psychiatric patients treated with neuroleptic drugs, revealed that 10,1% developed dystonia. A further study by Ayd (1983 p.86) found that 11,9% of the patients developed dystonia, while more recent studies by Khanna et al (1992) found incidence rates for dystonia of 20%. Figures as high as 94% have been reported in patients treated with haloperidol (Boyer et al 1987). There is a consensus of opinion that the increased incidence figures since the 1960's are due to the increasing use of high potency drugs and depot neuroleptics.

### 2.3.4 Factors influencing clinical presentation

#### 2.3.4.1 Age

Studies over the past thirty years have confirmed that the incidence of dystonia is higher in younger individuals. A study of extrapyramidal reactions in adolescents treated with high potency antipsychotics by Chiles (1978) revealed that 7 (64%) of 11 patients aged 13 - 18 years developed dystonic reactions. Addonizio and Alexopoulos (1988) compared drug induced dystonia in young and elderly patients and found that 31% of the young patients (mean age 26 years) developed dystonia compared to only 2% of the elderly patients (mean age 69 years). This study controlled for the type and dose of drugs used in the two groups.

Why neuroleptic induced dystonia occurs less frequently in the elderly remains unclear. It is possible that age related degeneration of the striatum may diminish dopaminergic activity which may decrease the likelihood of dystonia (Addonizio and Alexopoulos 1988).

#### 2.3.4.2 Sex

Ayd's (1983 p.87) surveys of extrapyramidal side effects found that dystonic reactions were twice as common in males than in females. Arana et al (1988) reviewed the available literature on acute dystonias and found that the incidence of dystonia is higher in male patients especially younger men. One has to also consider that young, hostile male patients frequently receive higher doses of neuroleptics which may influence the incidence figures in this group of patients (Chakos et al 1992).

#### 2.3.4.3 Drug treatment

Swett (1975) investigated the relative incidence of dystonia according to type of neuroleptic used and found the incidence with haloperidol to be 16%, trifluoperazine 8,2%, chlorpromazine 3,5% and thioridazine 0,6%. Arana et al (1988) reviewed a number of studies on dystonia and found that the incidence of dystonia in studies using high and low potency neuroleptics was 14,8% while in studies using only high potency neuroleptics, this figure was 51,2%. Boyer et al (1987) found the incidence of dystonia in a group of young adults treated with haloperidol to be 94%. These findings indicate that the incidence of dystonia with different neuroleptics seems to parallel the differential incidence of drug-induced parkinsonism with high potency drugs causing a higher incidence of side effects than the low potency drugs (Goetz and Klawans 1981).



The dose of drug used is also important with high doses or rapid increases in dose leading to a higher incidence of dystonia. Swett (1975) found that doses of chlorpromazine greater than 300mg per day caused significantly more dystonic episodes than if doses of 100mg per day or less were used.

#### 2.3.4.4 Phase of treatment

Dystonic reactions usually begin within hours of starting neuroleptic treatment with the majority occurring within the first few days. Marsden et al (1975 p.232) report that approximately 50% of dystonic reactions will occur within forty eight hours and up to 90% within five days of starting drug treatment. They may either remit or fluctuate spontaneously over several hours but often reappear on increasing the dose of neuroleptic. Depot preparations given intramuscularly may produce acute dystonias within 12 - 24 hours of each administration (Ayd 1975). New dystonic reactions are rare after the first few weeks of treatment and are not often seen in chronic patients on maintenance treatment.

## 2.4 COMBINED NEUROLOGICAL SYNDROMES

Dystonia, parkinsonism and akathisia can develop as individual side effects in the absence of the others, but all of the possible combinations of these reactions are commonly seen. In a study of 70 patients receiving fluphenazine, Chakos et al (1992) found that 38% of the patients had one form of acute extrapyramidal side effect while 21% had two forms and 3% all three forms of side effect. In Donlon and Stenson's (1976) study of 175 patients, 12 (7%) showed combined signs of parkinsonism and dystonia. Patients may develop the neurological side effects simultaneously or at different times during their treatment with neuroleptics.

## 2.5 PRIOR HISTORY OF NEUROLOGICAL SIDE EFFECTS

Susceptibility to extrapyramidal side effects varies widely amongst patients treated with neuroleptic drugs. Without reliable methods of predicting these side effects, many patients are unnecessarily treated with prophylactic anticholinergic medications. In an attempt to predict future vulnerability to these side effects, Keepers and Casey (1991) studied 62 patients who had a prior history of extrapyramidal side effects and found that 84% of these patients developed side effects on re-exposure to neuroleptic drugs. This result supports the hypothesis that patients with a history of extrapyramidal syndromes are at greater risk for future side effects due to their individual susceptibility. Possible reasons for this include variations in drug metabolism, neurotransmitters, micro-anatomy of the basal ganglia or that neuroleptic exposure produces a reverse tolerance to extrapyramidal syndromes (Keepers and Casey 1991). Further research is need to clarify this problem.

## CHAPTER 3

### PATIENTS AND METHODS

#### 3.1 COMPOSITION OF STUDY SAMPLE

This was a prospective study conducted over a three month period at Fort Napier Hospital. The study sample consisted of all patients admitted to the hospital who met the following criteria:

- 1) patients who clinically required neuroleptic drug treatment
- 2) patients who had not been treated with depot neuroleptic preparations in the month prior to admission
- 3) patients who had not been on regular oral antipsychotic treatment in the two weeks prior to admission
- 4) patients who did not require anticholinergic, antidepressant, anticonvulsant or anxiolytic drugs in combination with the prescribed neuroleptic drug treatment
- 5) patients with no clinical signs of any other neurological disorder involving the extrapyramidal system
- 6) patients with no clinically significant extrapyramidal side effects on admission

All patients in the study sample were over sixteen years of age and included both males and females.

#### 3.2 CONSENT PROCEDURES

On admission each patient was interviewed and those who met the study criteria were asked to give written consent (Appendix A) for inclusion in the study.

Informed consent was obtained where possible by explanation of the procedure to the patient by a Zulu speaking staff member. This included the reasons for the study, the examination procedures and the freedom to withdraw from the study at any time without prejudice to their further management.

If the patient was unable to give written consent, attempts were made to obtain consent from accompanying relatives. If this was not possible consent was obtained from the medical superintendent.

### 3.3 RATING SCALES

To objectively measure the different extrapyramidal syndromes, specific rating scales were used. Each patient was examined by the author to avoid any inter-rater variability.

#### 3.3.1 Parkinsonism

In assessment of neuroleptic induced parkinsonism, the rating scale for extrapyramidal side effects (Appendix B) by Simpson and Angus (1970) was used. This rating scale includes the following ten items: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, salivation.

Each item is rated from 0 to 4, where 0 is normal and 4 the extreme of that particular condition. Each patient was examined and a net score obtained by adding the scores of the ten items and dividing by ten. This was then recorded as follows: 0 - 0,9 normal, 1 - 1,9 mild parkinsonism, 2 - 2,9 moderate parkinsonism, 3 - 3,9 marked parkinsonism and 4 extreme parkinsonism.

### 3.3.2 Akathisia

The rating scale for drug-induced akathisia (Appendix C) by Barnes (1989) was used for the assessment of akathisia. Using this protocol each patient was examined for objective signs of restlessness while seated, standing and involved in activities. The individuals were also interviewed and questioned about subjective feelings of restlessness. These features were rated according to a global clinical assessment of akathisia where 0 indicated no sign of akathisia and 5 severe akathisia.

### 3.3.3 Dystonia

For this condition each patient was examined and questioned about any dystonic movements since starting treatment. This was combined with nursing observation reports on the patient since admission. If dystonic movements had occurred, they were recorded according to type (body part involved) and the day on which they started. Dystonia was recorded as either being present or absent and not graded according to severity. This information was recorded on a data sheet (Appendix D).

## 3.4 DATA COLLECTION PROCEDURES

Each patient was interviewed and information obtained on prior psychiatric treatment with neuroleptic drugs, any prior history of extrapyramidal syndromes and any present neurological side effects. A physical examination was performed on each patient looking particularly for the neurological features described in the rating scales. These examinations were done on admission and on day 5, 10 and 14 where possible. Examinations after day 14 were not always possible as a large percentage of the patients were discharged from hospital after 2 to 3 weeks of treatment.

The scores obtained from each examination were recorded on a composite data sheet (Appendix E). The patients current drug treatment was recorded including drug type, dose and route of administration. The total daily drug dose was converted to chlorpromazine equivalents (Davis 1976).

### 3.5 STATISTICAL ANALYSIS

The statistical analysis was conducted under the direction of Miss E Gouws at the Institute of Biostatistics of the medical research council Durban. Descriptive statistics were used to analyse the specific variables influencing the extrapyramidal syndromes and where relevant the Chi Square technique was used to determine statistical significance. Duncans multiple range test was used to compare the effect of the various drugs on the examination scores obtained.

## CHAPTER 4

## RESULTS

## 4.1 SAMPLE DETAILS

404 patients were admitted to the admission wards of Fort Napier hospital over the three month study period. Of this number, 100 patients met the criteria for inclusion into the study. This group consisted of 67 males and 33 females ranging in age from 17 to 65 years with a mean age of 29,4 years. A breakdown by age and sex is shown in TABLE I from which it can be seen that 52 (52%) of the patients were aged 20 to 29 years. This group consisted of 39 males and 13 females while 31 (31%) of the patients were aged 30 to 39 years and this included 18 males and 13 females. There were only 6 patients aged less than 20 years and 3 patients aged over 50 years.

TABLE I

Distribution of patients according to age and sex.

AGE GROUP (YEARS)	NUMBER OF PATIENTS		
	MALE	FEMALE	TOTAL
< 20	5	1	6
20 - 29	39	13	52
30 - 39	18	13	31
40 - 49	3	5	8
50 - 59	1	1	2
60 - 69	1	0	1
TOTAL	67	33	100

#### 4.2 NEUROLEPTIC DRUGS USED

The types of drugs and dosages used in this study are shown in TABLE II.

TABLE II

##### Drug types and dosage

DRUG TYPE	NO OF CASES TREATED	DOSE RANGE (mg/day CPZ equiv)	MEAN DOSE (mg/day CPZ equiv)
Thioridazine	11	50 - 600	345
Thioridazine + IM drug	3	350 - 700	583
Chlorpromazine	34	200 - 1200	531
Chlorpromazine + IM drug	28	250 - 1000	630
Trifluoperazine	5	300 - 600	490
Trifluoperazine + IM drug	3	300 - 700	500
Haloperidol	11	225 - 2000	1157
Haloperidol + IM drug	3	350 - 2100	1183
Zuclopenthixol Decanoate IM	2	100	100

(IM - IntraMuscular)

11 patients were treated with thioridazine, mean dose 345 mg/day, 34 patients with chlorpromazine, mean dose 531 mg/day, 5 patients with trifluoperazine, mean dose 490 mg/day and 11 patients with haloperidol, mean dose 1157 mg/day. 2 patients were treated with Zuclopenthixol depot alone, mean dose 100mg/day. (Doses converted to chlorpromazine equivalents.)



Chlorpromazine was prescribed more often than any other drug in this study with 34 patients receiving chlorpromazine alone and 28 patients receiving combinations of chlorpromazine and intramuscular drug.

The combinations of oral and intramuscular drugs used are shown in TABLE III.

TABLE III

**Drug combinations used**

INTRA-MUSCULAR DRUG TYPE	NUMBER OF CASES					TOTAL
	COMBINED WITH					
	NO ORAL DRUG	THIORIDAZINE	CPZ	TFP	HALO-PERIDOL	
Zucloperthixol acetate	0	1	8	2	2	13
Zucloperthixol acetate + Zucloperthixol decanoate	0	0	3	0	0	3
Zucloperthixol decanoate	2	0	2	0	1	5
Flupentixol decanoate	0	2	3	1	0	6
Fluphenazine decanoate	0	0	12	0	0	12
Total	2	3	28	3	3	39

CPZ - Chlorpromazine  
TFP - Trifluoperazine

The intramuscular drugs used included zuclopenthixol acetate, zuclopenthixol decanoate, flupenthixol decanoate and fluphenazine decanoate combined with thioridazine, chlorpromazine, trifluoperazine or haloperidol. Analysis of this data was not undertaken as most of the subgroup samples were too small for statistical analysis and it was not possible to control for many of the variable factors related to the use of these drugs.

TABLE IV

**Drugs used according to patient sex**

DRUG TYPE	NUMBER OF MALE CASES TREATED	% OF MALES IN STUDY	NUMBER OF FEMALE CASES TREATED	% OF FEMALES IN STUDY
Thioridazine	7	11	4	12
Thioridazine & IM drug	2	3	1	3
Chlorpromazine	18	27	16	49
Chlorpromazine & IM drug	18	27	10	30
Trifluoperazine	3	4	2	6
Trifluoperazine & IM drug	3	4	0	0
Haloperidol	11	16	0	0
Haloperidol & IM drug	3	5	0	0
Zuclopenthixol Decanoate IM	2	3	0	0
Total	67	100	33	100

(IM - IntraMuscular)

A breakdown of the drugs used according to the sex of the patients is shown in TABLE IV. Of note is that 16 (49%) of the

females in the study were treated with chlorpromazine compared to 18 (27%) of the males, while 11 (16%) of the males were treated with haloperidol and no females in the study received haloperidol. 7 (11%) of the males were treated with thioridazine compared to 4 (12%) of the females in the study. 3 (4%) of the males were treated with trifluoperazine compared to 2 (6%) of the females in the study. Only 2 (3%) males received zuclophenthixol decanoate alone.

#### 4.3 PARKINSONISM

##### 4.3.1 Incidence

With reference to TABLE V it can be seen that of the 100 patients in the study, 21 (21%) developed mild parkinsonism, 5 (5%) moderate and 3 (3%) marked parkinsonism. This gives a total of 29 (29%) patients with drug-induced parkinsonism. There were no cases of extreme parkinsonism while 71 (71%) patients had no clinically significant signs of parkinsonism.

TABLE V

#### Severity of parkinsonism

PARKINSONISM SEVERITY	RATING SCALE SCORE	NUMBER OF CASES		TOTAL
		MALE	FEMALE	
Extreme	4	0	0	0
Marked	3+	2	1	3
Moderate	2+	3	2	5
Mild	1+	19	2	21
Nil	0+	43	28	71
		67	33	100

#### 4.3.2 Age

The age range for the 29 cases of parkinsonism was 18 to 38 years with a mean age of 26,7 years. Breakdown by sex is shown in TABLE VI where it can be seen that the mean age for the males was 27,1 years and females 24,4 years.

TABLE VI

#### Age of parkinsonism cases

SEX	NUMBER OF CASES	AGE RANGE (YEARS)	MEAN AGE (YEARS)
MALE	24	18 - 38	27,1
FEMALE	5	19 - 31	24,4
TOTAL	29	18 - 38	26,7

#### 4.3.3 Sex

Of the 67 males in the study, 24 (35,8%) developed signs of parkinsonism while only 5 of the 33 females (15,2%) showed these signs.

#### 4.3.4 Drug treatment

The incidence of parkinsonism according to type of drug used is shown in TABLE VII. There were no cases of parkinsonism observed with the use of thioridazine alone or in combination with an intramuscular drug. 12% of the patients developed parkinsonism when treated with chlorpromazine, while 25% showed these signs after receiving chlorpromazine plus an intramuscular drug. A high incidence (60 - 100%) of

parkinsonism was observed with the use of trifluoperazine and haloperidol especially when combined with an intramuscular drug. There were no cases of parkinsonism seen when zuclopenthixol decanoate was used alone.

TABLE VII

**Parkinsonism according to drug type**

DRUG TYPE	NUMBER OF CASES TREATED	PARKINSONISM	
		NUMBER OF CASES	%
Thioridazine	11	0	0
Thioridazine & IM drug	3	0	0
Chlorpromazine	34	4	12
Chlorpromazine & IM drug	28	7	25
Trifluoperazine	5	3	60
Trifluoperazine & IM drug	3	3	100
Haloperidol	11	9	82
Haloperidol & IM drug	3	3	100
Zuclopenthixol Decanoate IM	2	0	0

(IM - IntraMuscular)

**4.3.5 Phase of treatment**

Clinical examinations were conducted on day 1, 5, 10 and 14 where possible. Parkinsonism scores increased steadily from day 10 onwards with the majority of significant scores obtained on day 14.

#### 4.4 AKATHISIA

##### 4.4.1 Incidence

As can be seen in TABLE VIII, of the 100 cases in the study 24 showed mild akathisia, 10 moderate and 1 marked akathisia. This is a total of 35 cases (35%) with clinical signs of akathisia. 18 cases had questionable signs of akathisia and 47 no signs of akathisia.

TABLE VIII

##### Severity of akathisia

AKATHISIA SEVERITY	RATING SCALE SCORE	NUMBER OF CASES		TOTAL
		MALE	FEMALE	
Severe	5	0	0	0
Marked	4	1	0	1
Moderate	3	7	3	10
Mild	2	16	8	24
Questionable	1	9	9	18
Absent	0	34	13	47
		67	33	100

##### 4.4.2 Age

The age range for the 35 cases of akathisia was 19 to 50 years with a mean age of 27,5 years. Breakdown by sex is shown in TABLE IX where it can be seen that the mean age of the male patients was 26,3 years compared to 30 years for the female patients.

TABLE IX**Age of akathisia cases**

SEX	NUMBER OF CASES	AGE RANGE (YEARS)	MEAN AGE (YEARS)
MALE	24	19 - 40	26,3
FEMALE	11	19 - 50	30
TOTAL	35	19 - 50	27,5

**4.4.3 Sex**

Of the 67 males in the study, 24 (35,8%) developed signs of akathisia while 11 of the 33 females (33,3%) showed these signs.

**4.4.4 Drug treatment**

The incidence of akathisia according to type of drug used is shown in TABLE X. No cases of akathisia were observed with the use of thioridazine alone. 10 (29%) of the 34 cases treated with chlorpromazine developed akathisia while 11 (39%) of the 28 patients treated with chlorpromazine combined with an intramuscular drug developed akathisia. 7 (64%) of the 11 patients treated with haloperidol developed akathisia.

**4.4.5 Phase of treatment**

Clinical examinations were conducted on day 1, 5, 10 and 14 where possible. Scores for akathisia were on average highest by day 10 of treatment and by day 14 there was some reduction in the scores.

TABLE X

## Akathisia according to drug type

DRUG TYPE	NUMBER OF CASES TREATED	AKATHISIA	
		NUMBER OF CASES	%
Thioridazine	11	0	0
Thioridazine & IM drug	3	1	33
Chlorpromazine	34	10	29
Chlorpromazine & IM drug	28	11	39
Trifluoperazine	5	2	40
Trifluoperazine & IM drug	3	1	33
Haloperidol	11	7	64
Haloperidol & IM drug	3	2	66
Zuclopenthixol Decanoate IM	2	1	50

IM - IntraMuscular

#### 4.5 DYSTONIA

##### 4.5.1 Incidence

Of the 100 cases in the study 20 (20%) developed dystonic reactions. A breakdown of the types of dystonia observed is shown in TABLE XI and from this it can be seen that the majority (12) involved the tongue.

##### 4.5.2 Age

The age range for the 20 cases of dystonia was 18 to 49 years with a mean age of 25,8 years. Breakdown by sex is shown in TABLE XII where it can be seen that the mean age of the male patients was 25,1 years and the females 27,3 years.



TABLE XI

## Dystonia types

TYPE OF DYSTONIA	NUMBER OF CASES		TOTAL
	MALE	FEMALE	
Tongue	10	2	12
Mouth	1	0	1
Jaw	2	0	2
Neck	1	1	2
Mouth and Tongue	0	2	2
Occulogyric	0	1	1
TOTAL	14	6	20

TABLE XII

## Age of dystonia cases

SEX	NUMBER OF CASES	AGE RANGE (YEARS)	MEAN AGE (YEARS)
MALE	14	18 - 34	25,1
FEMALE	6	19 - 49	27,3
TOTAL	20	18 - 49	25,8

## 4.5.3 Sex

Of the 67 males in the study, 14 (20,8%) developed dystonic reactions while 6 (18,2%) of the 33 females developed this side effect. The different types of dystonias according to patient sex are shown in TABLE XI. Of note is that 10 (71%) of the 14 male patients had dystonias involving the tongue.

#### 4.5.4 Drug treatment

The incidence of dystonia according to type of drug used is shown in TABLE XIII. No cases of dystonia were observed with the use of thioridazine alone or in combination with an intramuscular drug.

4 (12%) of the 34 patients treated with chlorpromazine developed dystonic reactions while 9 (32%) of the 28 patients treated with chlorpromazine and intramuscular drug developed dystonic reactions. 5 (45%) of the 11 cases treated with haloperidol developed dystonias.

TABLE XIII

#### Dystonia according to drug type

DRUG TYPE	NUMBER OF CASES TREATED	DYSTONIA	
		NUMBER OF CASES	%
Thioridazine	11	0	0
Thioridazine & IM drug	3	0	0
Chlorpromazine	34	4	12
Chlorpromazine & IM drug	28	9	32
Trifluoperazine	5	2	40
Trifluoperazine & IM drug	3	0	0
Haloperidol	11	5	45
Haloperidol & IM drug	3	0	0
Zuclopenthixol Decanoate IM	2	0	0

(IM - IntraMuscular)

#### 4.5.5 Phase of treatment

17 (85%) of the 20 cases of dystonia occurred within the first 72 hours of treatment while the remainder occurred within 5 days.

#### 4.6 COMBINED NEUROLOGICAL SYNDROMES

There were 29 (29%) cases of parkinsonism, 35 (35%) cases of akathisia and 20 (20%) cases of dystonia in this study. These figures do not however reflect those patients who developed more than one neurological syndrome. With reference to TABLE XIV it can be seen that there were various combinations of the three syndromes including 9 (9%) patients with combined parkinsonism, akathisia and dystonia, 11 (11%) with parkinsonism and akathisia, 4(4%) with parkinsonism and dystonia and 4 (4%) with akathisia and dystonia.

TABLE XIV

#### Combined Neurological syndromes

NUMBER OF CASES	S Y N D R O M E S		
	PARKINSONISM	AKATHISIA	DYSTONIA
53	-	-	-
5	✓	-	-
11	-	✓	-
3	-	-	✓
11	✓	✓	-
4	✓	-	✓
4	-	✓	✓
9	✓	✓	✓
100	29	35	20

✓ present

- absent

As can be seen in TABLE XV, 53 (53%) of the patients did not develop clinically significant extrapyramidal syndromes while the 47 (47%) who did consisted of 19 (19%) with one syndrome, 19 (19%) with two syndromes and 9 (9%) with three syndromes.

TABLE XV

**Number of neurological syndromes**

NUMBER OF SYNDROMES	NUMBER OF CASES	PERCENTAGE
0	53	53
1	19	19
2	19	19
3	9	9
TOTAL	100	100

**4.7 PRIOR HISTORY OF NEUROLOGICAL SIDE EFFECTS**

Of the 100 patients in the study, 46 gave a history of prior treatment with neuroleptic drugs. Of this group 27 (59%) had developed neurological side effects as a result of their treatment. Of these 27 patients, 15 (56%) developed side effects in this study. These included various combinations of neurological syndromes with no one type predominating.

## CHAPTER 5

## DISCUSSION OF RESULTS

## 5.1 SAMPLE DETAILS

404 patients were admitted to Fort Napier hospital over the three month study period. This included 302 males and 102 females of which 67 males and 33 females were included in the study. These patients were mainly young adults with 52% being aged 20 - 29 years and 31% aged 30 - 39 years. The mean age of the male patients was 28,4 years compared to 31,3 years for the females. This study sample reflects the predominantly young patient population treated at this hospital.

Review of the literature shows that besides some large surveys (Swett 1975, Ayd 1983 p.86), most of the studies done on extrapyramidal side effects involved small samples of young to middle aged patients (McEvoy 1983, Arana et al 1988).

## 5.2 NEUROLEPTIC DRUGS USED

Two types of low potency drugs, thioridazine and chlorpromazine, and two high potency drugs, trifluoperazine and haloperidol, were used alone or in combination with intramuscular drugs. To allow comparison between drugs, the mean daily dose of each drug was converted to chlorpromazine equivalents. With reference to TABLE II (page 22) it can be seen that there were differences between the mean daily dose of each drug, with haloperidol being used in much higher doses (1157mg/day, chlorpromazine equivalents) compared to thioridazine (345mg/day, chlorpromazine equivalents).

The number of patients treated with each drug was unequal with varying combinations of oral and intramuscular drugs being used. Chlorpromazine was used more often than any other oral drug. There were also differences in the type of drug used to

treat male and female patients as can be seen in TABLE IV (Page 24) where 16% of the males in the study were treated with haloperidol while no females received haloperidol. These differences may reflect the prescribing habits of the clinicians involved or as Chakos et al (1992) notes that agitated young male patients often receive larger doses of higher potency drugs than do females. Ideally the type and dose of neuroleptics used in a study of extrapyramidal side effects should be controlled. This is not always possible for ethical reasons and only a few such studies are reported in the literature (Garver et al 1976, Van Putten et al 1984). Other studies have attempted to compare the incidence of neurological side effects with varying doses of one neuroleptic drug (Levinson et al 1990). There is however a definite need for more controlled studies on the incidence of extrapyramidal side effects resulting from the use of neuroleptic drugs.

### 5.3 PARKINSONISM

#### 5.3.1 Incidence

The incidence of parkinsonism in this study was 29% which compares favourably with other studies on this subject (Donlon and Stenson 1976, McCreadie et al 1992). Previous published studies (Sheppard and Merlis 1967) indicate that between 20 and 40 percent of patients treated with neuroleptics develop parkinsonism.

#### 5.3.2 Age

Ayd (1961) found that the incidence of parkinsonism was higher in patients over the age of 40 years though in this study the mean age of the 29 patients who developed parkinsonism was 26,7 years. This may be a consequence of the predominantly young patient population in this study, given that 89% of the

patients were less than 40 years of age, though it is possible that parkinsonism is seen more commonly in young patients than has previously been reported. A larger study with a wider age range of patients would be needed to clarify this.

### 5.3.3 Sex

24 (35,8%) of the male patients in the study developed parkinsonism compared to 5 (15,2%) of the female patients. This difference is statistically significant ( $p = 0,032$ ), but may reflect the different neuroleptics used in the treatment of males compared to the females with male patients receiving more high potency drugs than the female patients. The results of this study differ from the reports in the literature (Ayd 1961) that females more commonly develop parkinsonism. Further research is required to clarify this point using equal numbers of males and females treated with a fixed dose of one drug.

### 5.3.4 Drug treatment

The parkinsonism scores for patients treated with haloperidol and trifluoperazine were significantly higher than those of patients treated with chlorpromazine and thioridazine ( $p = 0,0001$ ). This compares favourably with studies done elsewhere (Snyder et al 1974). Thioridazine in particular is unlikely to cause significant signs of parkinsonism as was shown in this study. There were however differences in the mean daily dose of neuroleptic used, with haloperidol being used in much higher doses than thioridazine. The trends observed in this study are however similar to those found in other studies (Sovner and DiMascio 1978 p.1025).

### 5.3.5 Phase of treatment

Signs of parkinsonism were observed to increase over the two week study period with most of the clinically significant cases recorded by day 14. it is likely that if the study period had

been longer more patients would have shown signs of parkinsonism. This is supported by other studies that describe the development of parkinsonism over weeks to months (Marsden et al 1975 p.230).

#### 5.4 AKATHISIA

##### 5.4.1 Incidence

The incidence of akathisia in this study was 35% which compares favourably with other studies reported in the literature: Ratey and Salzman (1984) note that 20 to 45% of patients treated with neuroleptics may develop akathisia while Barnes and Braude (1985) found the incidence of akathisia in a group of 82 psychiatric patients to be 35%.

This result is clinically significant given that akathisia is reported to be one of the main factors leading to poor compliance with treatment programmes amongst psychiatric patients (Van Putten 1974).

##### 5.4.2 Age

Akathisia has been reported to occur in most age groups of patients treated with neuroleptics (Marsden et al 1975 p.234), though Ayd (1961) described a higher incidence of akathisia in middle aged patients. The mean age of the 35 patients who developed akathisia in this study was 27,5 years. When attempting to interpret this, one must consider that 58% of the patients in this study were less than 30 years of age. It is possible that akathisia occurs commonly in young patients but is not routinely diagnosed.



#### 5.4.3 Sex

24 (35,8%) of the male patients in the study developed akathisia compared to 11 (33,3%) of the female patients. This difference is not statistically significant, but to reliably comment on this, a larger sample of patients would be required. There are no controlled studies reported in the literature that comment on the effect of gender on the incidence of akathisia.

#### 5.4.4 Drug treatment

Patients treated with thioridazine had significantly lower scores for akathisia than those treated with the high potency drugs haloperidol and trifluoperazine ( $p = 0,0142$ ). High potency drugs are more likely to produce akathisia than the low potency drugs such as thioridazine. In this study however, the doses of drugs used were not equal with haloperidol being used in much higher doses.

Controlled studies (Van Putten et al 1984) have however shown that haloperidol does produce a high incidence of akathisia compared to other neuroleptics.

#### 5.4.5 Phase of treatment

Akathisia was seen to develop within 10 days of starting treatment with neuroleptics and often preceded the signs of parkinsonism. Van Putten et al (1984) reports that akathisia can occur within hours of starting treatment and is noticeable within days. Akathisia also occurs following increases in the dose of neuroleptic used (Braude et al 1983). These dose increases often occur during the first few weeks of treatment as was common in this study.

## 5.5 DYSTONIA

### 5.5.1 Incidence

The incidence of dystonia in this study was 20% which is comparable with other studies (using high and low potency neuroleptics) such as Stramek et al (1986) who found 20,9% of their patients developed dystonia following neuroleptic treatment. In studies using only high potency neuroleptics the incidence of dystonia has been reported to be as high as 94% (Boyer et al 1987).

### 5.5.2 Age

The mean age of the 20 patients who developed dystonic reactions was 25,8 years which included 16 patients under the age of 30 years. This trend supports the reported finding of a higher incidence of dystonia in young patients (<30 years) receiving neuroleptic drug treatment (Swett 1975, Addonizio and Alexopoulos 1988).

### 5.5.3 Sex

14 (20,9%) of the male patients in the study developed dystonic reactions compared to 6 (18,2%) of the female patients. Though not statistically significant, slightly more males than females developed dystonic reactions. Swett (1975) reports that dystonic reactions are more commonly seen in young male patients receiving neuroleptic drugs.

### 5.5.4 Drug treatment

The high potency drugs haloperidol and trifluoperazine resulted in higher rates of dystonic reactions than chlorpromazine or thioridazine. No cases of dystonia were seen following treatment with thioridazine. This conforms with other studies done on the incidence of dystonia according to drug type (see section 2.3.4.3. page 14).

### 5.5.5 Phase of treatment

85% of the cases of dystonia in this study developed within the first three days of treatment which is consistent with other studies on this subject: Stramek et al (1986) found that nearly 90% of dystonic reactions occurred by the 3rd day of treatment while Ayd (1961) found that 90% of dystonic reactions developed within the first 4½ days.

## 5.6 COMBINED NEUROLOGICAL SYNDROMES

Patients treated with neuroleptics can develop more than one type of extrapyramidal syndrome. As has been noted by Donlon and Stenson (1976), Chakos et al (1992). In this study, 47% of the patients developed more than one syndrome with 9% of these patients having three syndromes. This is clinically significant as patients may suffer a great deal of distress as a result of these side effects.

## 5.7 PRIOR HISTORY OF NEUROLOGICAL SIDE EFFECTS

Of the 100 patients in this study, 46 gave a history of prior treatment with neuroleptic drugs. Of this group, 27 (59%) had developed neurological side effects as a result of their treatment. Of these 27 patients, 15 (56%) developed side effects in this study. This is not as high a correlation as was found in the study done by Keepers and Casey (1991) (see page 16) but indicates that a prior history of neurological side effects may predict an increased vulnerability on re-exposure to neuroleptics. Clinicians should routinely ask patients about any prior history of treatment with neuroleptic drugs.

## CHAPTER 6

### CONCLUSIONS

#### 6.1 INTRODUCTION

The aim of this study was to discover the incidence of acute neurological side effects in patients treated with neuroleptic drugs and to assess the factors responsible for these side effects. The limitations of this study and the conclusions derived from the results are presented below.

#### 6.2 LIMITATIONS OF THIS STUDY

For the purposes of this study, a two week period was chosen to assess the development of acute neurological side effects following neuroleptic drug treatment. It is possible that this period was too short to fully observe the evolution of drug-induced parkinsonism and akathisia. A study period of one month would have allowed a more extensive assessment of these particular side effects. This was however not possible in this study as a large percentage of the patients were discharged from hospital after 2 to 3 weeks of treatment. Another limiting factor was that patients who had not responded to 2 weeks of treatment with a specific neuroleptic were often changed to an alternative drug which complicated the assessment of drug-induced side effects.

It was not possible to comment on the incidence of neurological side effects amongst elderly patients in this study due to the predominantly young patient population studied. Further studies on this subject should include more elderly patients to analyse the effect of age on the incidence of these side effects.

It was not possible to adequately assess the neurological side effects that resulted from the intramuscular drugs used in this study. The relatively small number of patients treated with a number of different neuroleptic drugs limited the statistical analysis. The results obtained, though not all statistically significant, did show trends which are clinically important. A larger study of more patients treated with a limited number of drugs would ensure a more comprehensive statistical analysis.

### 6.3 CONCLUSIONS

The incidence of drug-induced parkinsonism in this study was 29%, akathisia 35% and dystonia 20%. Combinations of these three syndromes were observed resulting in an overall incidence of 47%. This represents a significant clinical problem with many implications for clinicians using neuroleptic drugs.

Patients may experience physical discomfort and psychological distress due to these drug-induced side effects which may aggravate their psychiatric condition and lead to poor compliance with future treatment programmes (Van Putten 1974). Clinicians are often unaware of the problem and may misdiagnose or mistreat these side effects leading to many iatrogenic complications and unnecessary suffering by patients (Weiden et al 1987).

In this study high potency drugs such as haloperidol and trifluoperazine were responsible for a large percentage of the side effects observed while of the low potency drugs, thioridazine produced less side effects than chlorpromazine. The mean daily dose of the different drugs was however unequal with haloperidol being used in comparatively higher doses. Oral drugs combined with intramuscular depot preparations resulted in a higher incidence of side effects than the oral drugs alone.

Careful selection of the type and dose of neuroleptic drug prescribed can minimise the chances of patients developing extrapyramidal side effects. The lowest effective dose of neuroleptic should be used where possible and more use should be made of drugs such as thioridazine which has relatively more anticholinergic properties than other neuroleptics resulting in less neurological side effects.

The age and sex of the patients being treated should be taken into consideration when prescribing neuroleptics, given that these factors can influence the type of side effects that develop. Treatment regimés should be chosen specifically for the needs of individual patients which was not the case in the majority of patients in this study.

The phase of treatment is also clinically important, as was seen in this study, with dystonia occurring more often within the first three days of treatment, akathisia within the first ten days and parkinsonism after ten to fourteen days. During this acute phase of treatment clinicians should examine their patients regularly to check for these specific side effects. Early detection and treatment of these frightening neurological syndromes will prevent unnecessary suffering and improve patients compliance with future treatment programmes.

A thorough history and clinical examination for drug-induced side effects should be an important part of the psychiatric examination. Asking about neurological side effects encountered during previous treatments can be useful. In this study, 56% of patients who had a prior history of side effects developed similar problems on being re-exposed to neuroleptics. Regular questioning about feelings of stiffness, restlessness or unusual movements in patients can aid in the diagnosis of the early, subtle signs of parkinsonism, akathisia and dystonia.

Neuroleptic drugs play an important part in the treatment of psychiatric disorders, but clinicians should never ignore the patients quality of life while on treatment. Accurate early diagnosis and treatment of drug-induced side effects is necessary for effective patient management.

## CHAPTER 7

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## APPENDIX A

## INFORMED CONSENT

1. I \_\_\_\_\_  
 hereby consent to a Clinical examination for any acute neurological drug side effects.
2. I acknowledge that I have been informed by Dr N Raymond concerning the possible advantages and possible adverse effects, which may result from the above mentioned procedure and of the ways in which it is different from the conventional procedure.
3. I agree that the above procedure will be carried out and supervised by Dr N Raymond.
4. I acknowledge that I understand the contents of this form and freely consent to the above procedure.
5. I am aware that I may withdraw my consent at any time without prejudice to my futher care.

SIGNED SUBJECT : \_\_\_\_\_

SIGNED WITNESS : \_\_\_\_\_

SIGNED RESEARCHER: \_\_\_\_\_

DATE : \_\_\_\_\_

## APPENDIX B

## RATING SCALE FOR EXTRAPYRAMIDAL SIDE EFFECTS

1. Gait - The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all for the basis for an overall score for this item. This is rated as follows:
  - 0 - normal
  - 1 - diminution in swing while the patient is walking
  - 2 - marked diminution in swing with obvious rigidity in the arm
  - 3 - stiff gait with arms held rigidly before the abdomen
  - 4 - stooped shuffling gait with propulsion and retropulsion
  
2. Arm Dropping - The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome the arms falls very slowly:
  - 0 - normal, free fall with loud slap and rebound
  - 1 - fall slowed slightly with less audible contact and little rebound
  - 2 - fall slowed, no rebound
  - 3 - marked slowing, no slap at all
  - 4 - arms fall as though against resistance; as though through glue
  
3. Shoulder shaking - The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patients' elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:

- 0 - normal
  - 1 - slight stiffness and resistance
  - 2 - moderate stiffness and resistance
  - 3 - marked rigidity with difficulty in passive movement
  - 4 - extreme stiffness and rigidity with almost a frozen shoulder
4. Elbow Rigidity - The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.) Scoring is from 0-4 as in Shoulder Shaking test:
- 0 - normal
  - 1 - slight stiffness and resistance
  - 2 - moderate stiffness and resistance
  - 3 - marked rigidity with difficulty in passive movement
  - 4 - extreme stiffness and rigidity with almost a frozen elbow
5. Fixation of position or Wrist Rigidity - The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension flexion and both ulner and radial deviation. The resistance to this procedure is rated as in Items 3 and 4:
- 0 - normal
  - 1 - slight stiffness and resistance
  - 2 - moderate stiffness and resistance
  - 3 - marked rigidity with difficulty in passive movement
  - 4 - extreme stiffness and rigidity with almost a frozen wrist
6. Leg Pendulousness - The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially

extended. It is then allowed to fall. The resistance to falling and the lack of swing form the basis for the score on this item:

- 0 - the legs swing freely
- 1 - slight diminution in the swing of the legs
- 2 - moderate resistance to swing
- 3 - marked resistance and damping of swing
- 4 - complete absence of swing

7. Head Dropping - The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:

- 0 - The head falls completely with a good thump as it hits the table
- 1 - slight slowing in fall, mainly noted by lack of slap as head meets the table
- 2 - moderate slowing in the fall quite noticeable to the eye
- 3 - head falls stiffly and slowly
- 4 - head does not reach examining table

8. Glabella Tap - Subject is told to open his eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:

- 0 - 0-5 blinks
- 1 - 6-10 blinks
- 2 - 11-15 blinks
- 3 - 16-20 blinks
- 4 - 21 and more blinks

9. Tremor - Patient is observed walking into examining room and then is reexamined for this item:
- 0 - normal
  - 1 - mild finger tremor, obvious to sight and touch
  - 2 - tremor of hand or arm occurring spasmodically
  - 3 - persistent tremor of one or more limbs
  - 4 - whole body tremor
10. Salivation - Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
- 0 - normal
  - 1 - excess salivation to the extent that pooling takes place if the mouth is open and tongue raised
  - 2 - when excess salivation is present and might occasionally result in difficulty in speaking
  - 3 - speaking with difficulty because of excess salivation
  - 4 - frank drooling



## APPENDIX C

## RATING SCALE FOR DRUG-INDUCED AKATHISIA

Patients should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example, while engaged in activity phenomena should be elicited by direct questioning.

## OBJECTIVE

- 0 Normal, occasional fidgety movements of the limbs
- 1 presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swing of one leg, while sitting, and/or rocking from foot to foot or 'walking on the spot' when standing, but movements present for less than half the time observed
- 2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
- 3 The patient is constantly engaged in characteristic restless movements, and/or has the inability to remain seated or standing without walking or pacing, during the time observed

## SUBJECTIVE

## Awareness of restlessness

- 0 Absence of inner restlessness
- 1 Non-specific sense of inner restlessness
- 2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, and/or complains of inner restlessness aggravated specifically by being required to stand still
- 3 Awareness of an intense compulsion to move most of the time and/or reports a strong desire to walk or pace most of the time

### Distress related to restlessness

- 0 No distress
- 1 Mild
- 2 Moderate
- 3 Severe

### Global clinical assessment of akathisia

- 0 Absent  
No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
- 1 Questionable  
Non-specific inner tension and fidgety movements
- 2 Mild akathisia  
Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movements present but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress
- 3 Moderate akathisia  
Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
- 4 Marked akathisia  
Subjective experience of restlessness includes a compulsive desire to walk or pace, However, the patient is able to remain seated for a least five minutes. The condition is obviously distressing

5 Severe akathisia

The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

## APPENDIX D

## DYSTONIA DATA SHEET

Observation by examiner or ward staff of any dystonic movements.

The type of movements should be described and the time of onset noted. Rated as:

- 0 absent
- 1 present

Type : \_\_\_\_\_

Onset: Day: \_\_\_\_\_ ; hr \_\_\_\_\_

## APPENDIX E

## COMPOSITE DATA SHEET

CASE NUMBER :  
 SEX :  
 AGE :  
 PRIOR HISTORY OF NEUROLOGICAL SIDE EFFECTS : YES/NO

SYNDROME	EXAMINATION NUMBER				MAXIMUM SCORE
	1	2	3	4	
PARKINSONISM					
AKATHISIA					
DYSTONIA					
TYPE ONSET					

DRUG TREATMENT

DRUG TYPE :  
 DOSE (mg/day) :  
 ROUTE OF ADMINISTRATION :  
 ORAL/INTRAMUSCULAR  
 CHLORPROMAZINE EQUIVALENCE (mg/day) :