Schizophrenic Patients' Experiences

of

Neuroleptic Medication

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy by

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1995

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Chapter 3: Compliance with Neuroleptic Therapy

Abstract

This thesis provides an overview of schizophrenia, drug treatment of schizophrenia and compliance with neuroleptic medication. These subjects are covered in the introductory review Chapters (1 to 3). Chapter 4 gives a general overview of the research to be carried out. Four studies comprise the work which are described in the subsequent chapters. Chapter 5 describes a Q-methodological study of schizophrenic patients' attitudes to neuroleptic medication. In this study it was found that attitudes to neuroleptics cannot be simplified along a unidimenisonal continuum. A conflict was observed between mental health workers' perceptions of compliance when viewed from a personal as opposed to a professional perspective. In the second study reported in Chapter 6, a scale, the Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS), was designed and validated for schizophrenic patients to self-rate neuroleptic side effects. Chapter 7 describes a postal survey of psychiatrists, senior registrars and registrars in the Merseyside area. Psychiatrists' estimations of the average prevalence and distress of neuroleptic side effects experienced by schizophrenic patients, as well as their likelihood of informing patients about side effects, are reported. Psychiatrists' estimations of prevalence but not distress correlated with patients' self-reports. Chapter 8 describes a longitudinal study of patients' attitudes to neuroleptic medication. Patients who were prescribed neuroleptic medication for the first time were compared with a group who had been prescribed neuroleptics for at least three years. There was little difference between the two groups except that the Long-Term group experienced significantly more negative symptoms. Attitudes to medication measured at six month follow-up were predicted by side effects and dysphoria measured at the initial assessment.

Acknowledgements

I am indebted to Dr Steve Pleece who stimulated my interest in Psychiatry. I am also indebted to Professor Richard Bentall, without whose encouragement, supervision and enthusiasm this thesis would not have been possible.

This work was supported by the Department of Health Pharmacy Practice Enterprise Scheme, and I am grateful to Jeannette Howe and others for giving me the opportunity to have carried out this interesting work.

Thanks are due also to Mike Dewey and Dr Brian Farragher for statistical advice and to Katheryn, Mary and Lyndsay for all their help over the years.

I am thankful for the support, encouragement and patience of friends and family too numerous to mention but especially to James, Gill, Darice, Frog, Anthea, Paul and most of all Crispin, whose patience and understanding are beyond measure.

CHAPTER 1

Classification and Aetiology of Schizophrenia: An Overview

1.1 Introduction

The schizophrenic disorders are perhaps the least understood of psychiatric conditions, and their status remains a matter of controversy, both in terms of describing and categorising them, and also in terms of their aetiology. These issues have been recently discussed (Bentall, 1993; Chadwick, 1993; Claridge, 1993; Farmer, Jones, Williams, & McGuffin, 1993; Johnstone, 1993a). This thesis focuses on patients' experiences of neuroleptic medication, undoubtedly the most widely used treatment for schizophrenic disorders. In this introductory chapter the history of the schizophrenia concept, research into the aetiology of the schizophrenic disorders, current diagnostic criteria for schizophrenia, and some of the social consequences of these disorders are reviewed. This overview is necessarily limited for reasons of space. Main themes will be highlighted but no attempt will be made to provide a comprehensive review of past and present schizophrenia research.

1.2 An Historical Perspective of Schizophrenia

In 1898 Kraepelin described *dementia praecox* in an attempt to classify mental disease, bringing together a number of previously described syndromes; démence précoce, hebephrenia, catatonia, and dementia paranoides. When these words are translated directly; dementia means madness or insanity and

praecox consists of prae (before) plus coquere (to cook or to boil) which can be translated as premature. In this definition Kraeplin was describing an intellectual deterioration which occurred initially in young adults. In classifying dementia praecox Kraeplin described a mental weakness which was characterised by certain psychological symptoms such as hallucinations, delusions, distorted emotional expression, disorders of attention, negativism, sterotypies of motion and attitude, lessened capacity for work, disorders of judgement and a dilapidation of the thought processes. His definition in 1913 was as follows:

> "Dementia praecox consists of a series of clinical states which have as their common characteristic a peculiar destruction of the internal connections of the psychic personality with the most marked damage of the emotional life and of volition."

More recent accounts of schizophrenia encompass many of these symptoms. Kraepelin indicated that the condition started early in adulthood and that the prognosis in most cases was poor. The emphasis within Kraepelin's definition was therefore on a chronic course and poor outcome as well as specific characteristic symptomatology. Kraepelin assumed that the aetiology of illness was of a physical nature and postulated the existence of metabolic disorders resulting in auto-intoxication.

Bleuler added to the work of Kraepelin by focusing on symptoms which he perceived as fundamental in cases of dementia praecox. In 1911 Bleuler suggested that the term dementia praecox should be superseded by the term schizophrenia and indicated that the primary symptomatology included i) the presence of logically unrelated ideas which are related in the patient's mind; ii)

the use of symbols instead of everyday language and the condensation of thought processes and iii) the frequent use of alliteration. He indicated that the disease was characterized by a specific type of alteration of thinking, feeling, and relation to the external world. He considered autism, delusions, hallucinations, negativism, stereotypies and catatonia to be secondary symptoms. In particular Bleuler emphasized the *splitting of personality* in sufferers of schizophrenia, markedly between the emotional and intellectual aspects of the personality. For Bleuler, the most important symptom was the fragmentation in the formulation and expression of thought which he referred to as a loosening of associations. Bleuler also considered that schizophrenia was of organic origin stating that it was less a deficiency than an intoxication.

A further influential attempt at classifying symptoms of schizophrenia was carried out by Schneider in 1959. Schneider emphasized symptoms of schizophrenia which could be diagnostically discriminating and which could be reliably observed. Schneider moved away from emphasising avolition and dissociative processes as his predecessors had, and identified delusions and hallucinations as first rank symptoms of schizophrenia. He outlined implausible or bizarre delusions and hallucinations, such as thought withdrawal, thought insertion, thought broadcasting, hallucinations providing a running commentary on the persons actions and externally controlled thought and movement, as being particularly characteristic of schizophrenia and toxic psychotic syndromes.

Modern conceptions of schizophrenia have evolved directly from the contributions of Kraepelin, Bleuler and Schneider. For example, the Present

State Examination (PSE), a widely used psychiatric assessment schedule developed by Wing, Cooper, & Sartorius (1974) explicitly incorporates Schneiderian principles. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders which has gone through a series of revisions (American Psychiatric Association; 1968, 1980, 1987, 1994), and which has been widely used to classify psychiatric disorder in the USA and other countries, both recognises the distinction which Kraepelin drew between affective schizophrenic disorders, and also emphasises Schneiderian symptoms in its' definitions of schizophrenic disorders. The World Health Organisation's International Classification of Disease (ICD), which has also undergone various revisions (World Health Organisation; 1977, 1990) also makes use of Kraepelinian, Bleulerian and Schneiderian concepts.

1.3 The aetiology of schizophrenia

A number of factors have been implicated in the aetiology of schizophrenia including biological factors, such as genetic influences and brain abnormalities, and environmental factors, such as family environment, maternal viral infection and birth difficulties. It is not known if a single factor is implicated in the aetiology of schizophrenia, but the heterogeneity in the clinical presentation of the disorder suggests that there may be a number of factors involved.

Biological factors

1.3.1 Dopamine Hypothesis

For many years it has been hypothesised that part of the aetiology of schizophrenia is mediated by a defect in the dopamine neurotransmitter pathway. This theory has until recently has been a focus of research in explaining the aetiology of schizophrenia and in the search for improved treatments. In 1988 Andreasen states;

> "The most widely accepted hypothesis concerning neurochemical mechanisms in schizophrenia is the dopamine hypothesis which suggests that symptoms of schizophrenia are at least partially caused by a functional hyperactivity in the dopamine system in the brain."

This hypothesis originated from early observations that dopamine agonists and agents which facilitate a release of dopamine, such as amphetamine, can induce a psychosis apparently indistinguishable from acute paranoid schizophrenia (Connell, 1958; Randrup & Munkvad, 1965). In parallel to this it was known from quite early on that neuroleptic drugs, which had been empirically determined to reduce schizophrenic symptoms, affected dopamine metabolism. Carlsson & Lindqvist (1963) found that small doses of chlorpromazine and haloperidol elevated the plasma levels of 3-methoxytyramine (a metabolite of dopamine) in mouse brain. It was thought that the increase in the metabolite was due to feedback activation of catecholaminergic neurones as a result of post-synaptic blockade of dopamine receptors by neuroleptic drugs. Unfortunately much of the detailed neurotransmitter work has been carried out in animals and the results extrapolated to humans, which raises questions about

the validity of conclusions made.

The dopamine hypothesis still receives support from members of the scientific community. In a recent review, Sunahara, Seeman, Van Tol, & Niznik (1993) stated that the dopamine hypothesis is still supported by a range of evidence, particularly that;

a) all clinically effective antipsychotic agents selectively bind to and block dopamine D2 receptors at molarities which correlate well with clinically effective antipsychotic doses;

b) radioligand binding assays using various tritiated neuroleptics on post-mortem brain tissues from schizophrenic patients show a selective elevation of dopamine D2-like receptors; and

c) positron emission tomography studies on living neuroleptic naïve subjects also show an elevation in D2-like receptors.

It has been found that amphetamine can exacerbate psychoses in a person diagnosed as schizophrenic and this fact has been cited as evidence to support the notion that schizophrenia can be explained by an overactivity of dopamine receptors (Iverson & Iverson, 1981). However in a review of previous research, Van Kammen, Docherty, Marder, Schulz, Dalton, & Bunney (1982) identified 12 studies of 285 patients and of these only 25% of the total sample showed a worsening of psychosis when challenged with amphetamine, with 46% who showed no change and 29% who actually improved. Further evidence lent support to the dopamine hypothesis in a clinical trial of the therapeutic efficacy of optical isomers of flupenthixol. Johnstone, Crow, Frith, Carney, & Price (1978) compared the effects of the cis (α) isomer of Flupenthixol

with the trans (ß) isomer on clinical symptoms of schizophrenia. The cis isomer which has much greater antidopaminergic activity compared with the trans isomer showed significantly greater clinical efficacy than either the trans isomer or placebo. In the late 1970's further evidence in support of the dopamine theory was obtained from studies which showed an increase in the numbers of D_2 receptors in the basal ganglia of schizophrenic patients (Lee, Seeman, Tourtellotte, Farley, & Hornkiewicz, 1978; Owen, Cross, Crow, Longden, Poulter, & Riley, 1978). The finding of an increase in D_2 receptor binding in the brains of schizophrenic subjects has been replicated in a number of studies (Hess, Bracma, Kleinman, & Creese, 1987; Mackay, Bird, Spokes, Rossor, Iversen, Creese, et al., 1980). However these results have not always been replicated in drug free schizophrenic subjects. For example Farde, Wiesel, Hall, Halldin, Stone-Elander, & Sedvall (1987) used Positron Emission Tomography (PET) imaging in young untreated schizophrenic subjects and did not find an increase in D_2 receptors. Farde concluded that D_2 up-regulation was a consequence of neuroleptic treatment.

Another piece of evidence which has been cited in support of the dopamine hypothesis of schizophrenia is the observation that metabolites of dopamine such as homovanillic acid are lowered in patients with a diagnosis of schizophrenia (Davidson & Davis, 1988; Karoum, Karson, Bigelow, Lawson, & Wyatt, 1987). However there are wide variations in the composition of subjects within these studies and some of the studies have been carried out in neuroleptic treated subjects which makes interpretation complex. More recent studies have not found a statistically significant reduction of homovanillic acid

levels in schizophrenic patients and have found no association between homovanillic levels and psychopathology (Koreen, Lieberman, Alvir, Mayerhoff, Loebel, Chakos, et al., 1994; Pickar, Breier, Hsiao, Doran, Wolkowitz, Pato, et al., 1990).

There is considerable discrepancy between the results obtained in this area and controversy surrounding the dopamine hypothesis is great at present. Where studies show a link between dopamine activity and psychotic symptoms the changes are not uniformly observed in all patients studied; there is considerable heterogeneity of results with a considerable overlap with the normal range of measured values (Jackson, 1990). Also, although dopamine receptor occupancy of neuroleptic drugs has been correlated with daily therapeutic dose (Creese, Burt, & Snyder, 1976), there are no published studies which demonstrate a relationship between dopamine receptor occupancy and clinical psychopathology. In one positron emission tomography study, lack of neuroleptic response was not related to lack of occupancy of dopamine D2 receptors (Wolkin, Barouche, Wolf, Rotrosen, Fowler, Shuie, et al., 1989). However the most compelling evidence against the dopamine hypothesis is that atypical neuroleptic agents are as effective and sometimes more effective than the traditional neuroleptics which have disparate neurotransmitter activity. This fact has led to a reformulation of the role of dopamine in the aetiology of schizophrenia (Kerwin, 1994).

1.3.2 Genetics

For many years there has been interest in the possibility of schizophrenia being a genetically inherited disorder. Early studies suggested that schizophrenia aggregated in families (e.g. Rudin, 1916), and even led some authors to call for the sterilization of schizophrenic patients and their relatives in order to prevent future schizophrenic births (Kallman, 1938). However these studies were methodologically weak for a number of reasons. Often a normal control group was not included and subjects were not assessed and diagnosed by blind raters. Also operationalised diagnostic criteria had not been defined at that time and so were not used in these studies. However, more recent studies which have employed operationalised diagnostic criteria, blind ratings and a normal control group indicate that the prevalence of schizophrenia is higher in the first-degree relatives of schizophrenic probands than of control probands (Baron, Gruen, Rainer, Kane, Asnis, & Lord, 1985; Gershon, DeLisi, Hamovit, Nurnberger, Maxwell, Schreiber, et al., 1988; Kendler, Gruenberg, & Tsuang, 1985). The fact that schizophrenia is more common in the relatives of individuals diagnosed as schizophrenic does not provide unequivocal evidence that there is a genetic linkage for schizophrenia but it does suggest that this may be the case.

There are a number of difficulties in carrying out genetic studies in schizophrenia. For example, schizophrenia may be a heterogenous disorder (discussed below) and this makes the identification of genetic determinants difficult. Discrepancies between different proposed diagnostic criteria for schizophrenia (also discussed below) also makes genetic findings difficult to

interpret. There may also be heterogeneity at the genetic level, i.e. different families may carry different susceptibility genes (Kendler & Diehl, 1993). It is also possible that gene carriers do not necessarily manifest clinical signs of schizophrenia or that some individuals may manifest signs of schizophrenia due to environmental influence, but not carry genetic aberrations.

A great deal of evidence has been gathered over the years to demonstrate that there is a higher rate of schizophrenia in monozygotic twin probands of schizophrenic subjects than dizygotic twin probands. Although these concordance rates are well below 100%, for example 4% -15% for dizygotic twins and 14% -59% for monozygotic twins (Onstad, Skre, Edvardsen, Torgersen, & Kringlen, 1991), these observations do seem to suggest that a genetic influence is present in the aetiology of schizophrenia. An obvious objection to twin studies such as these, is that twins will have a very similar environmental influence and therefore adoptive studies may reveal a more accurate picture of the genetic influence. Studies in which subjects are separated from their biological parents have shown that the prevalence of schizophrenia is higher in the offspring of schizophrenic parents compared to non-schizophrenic parents (Heston, 1966; Rosenthal, Wender, Kety, Welner, & Schulsinger, 1971; Tiernari, Wynne, Moring, Lahti, Naarala, Sorri, et al., 1994).

Although few would argue that some kind of genetic contribution is implicated in the development of schizophrenia there is continuing debate about the strength of that contribution (Rose, Lewontin, & Kamin, 1984). There have been criticisms of the methodology used in twin studies, for example the inclusion of other related conditions such as manic depression or personality

disorder or indefinite diagnosis. It has been argued that if these borderline cases are excluded from the calculation of concordance rates that the statistical difference between the schizophrenic and control subjects disappears (Lidz & Cook, 1981; Rose, et al., 1984). There is also debate over the correct way of calculating concordance rates. Some researchers prefer probandwise rather than pairwise concordance rates (Torrey, 1992), whilst other researchers suggest that the proband calculation overestimates the genetic contribution (McGue, 1992), as twin pairs independently identified can be counted twice.

A number of possibilities exist for the way in which schizophrenia could be genetically transmitted. The most simple model is that schizophrenia is transmitted by a single gene in Mendelian fashion. Alternatively there could be a multifactorial polygenic model in which aberrations in a number of chromosomes is necessary before schizophrenia is evident. Neither of these models has been substantiated and there is an absence of a consistent and generally accepted model of genetic transmission in schizophrenia. One study found a significant linkage of schizophrenia to a region on chromosome 5 (Sherrington, Brynjolfsson, Petursson, Potter, Dudleston, Barraclough, et al., 1988) but this has never been replicated despite a number of attempts (Crowe, Black, Wesner, Andreasen, Cookman, & Roby, 1991; Detera-Wadleigh, Goldin, Sherrington, Encio, de Miguel, Berretini, et al., 1989; Kennedy, Guiffra, Moises, Cavalli-Sforza, Pakstis, Kidd, et al., 1988; St Clair, Blackwood, Muir, Baillie, Hubbard, Wright, et al., 1989). There are a number of factors which suggest that a single Mendelian gene linkage is not present in schizophrenia. If a single gene existed for schizophrenia it could not be said to be fully penetrant due to the concordance rate in monozygotic twins being considerably below 100%, and

this is not usual for a Mendelian disorder. Also in simple Mendelian transmitted disorders such as cystic fibrosis, typical symptoms of the disorder are only present when the "disease gene" is present, whereas symptoms of schizophrenia can occur as a result of metabolic conditions or pharmacological toxicity. Mendelian conditions tend to be rare, aetiologically homogenous and diagnostically distinct from related conditions, which clearly cannot be said for schizophrenia (Kendler & Diehl, 1993). Although in recent years there have been a number of important improvements in methods and concepts molecular biology and statistical genetics, the genetic contribution to schizophrenia remains elusive.

1.3.3 Brain Neuroanatomy and Neuromorphology

A number of neuroanatomical abnormalities have been reported in schizophrenic patients and this research has progressed in recent years due to advances in imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). The most common neuroanatomical change found in schizophrenia is enlarged cerebral ventricles either in area or volume (Weinberger, 1984). This increased ventricular size has been associated with deficit symptoms, cognitive impairment and poor response to pharmacotherapy (Nasrallah & Coffman, 1985). Suddath et al. in 1990, in a study of monozygotic twins discordant for schizophrenia, found enlargement of the lateral and third ventricles in schizophrenics but not in their non-schizophrenic siblings. Many other neuroanatomical changes have been identified in schizophrenic patients including widening of sulci and fissures (Raz, 1993; Rubin et al, 1993). MRI

scans have also demonstrated decreased cerebral volume in schizophrenic subjects as compared to normal controls (Andreasen et al. 1986) and this has been attributed to neurodevelopmental abnormalities. Other reported abnormalities include cerebellar dysfunction (Taylor, 1991) and medial temporal lobe hypoplasia (Roberts, 1991). These findings are evidence to some researchers that schizophrenia is associated with neurodevelopmental abnormalities and may be of genetic origin (Bogerts, 1993). However there are problems with research of this kind. Firstly a great majority of the schizophrenic subjects have been consuming neuroleptic medication and in a proportion of cases for many years. Therefore it is difficult to ascertain if the neuroanatomical changes are due to the "disease" or due to changes evoked by neuroleptic medication. Secondly neuroanatomical changes can occur in the brain subsequent to psychological changes in mood or excitement and are thus not specific to schizophrenia. Therefore it is difficult to establish if the neuroanatomical changes occur prior or consequent to presentation of psychotic symptoms. Finally although some researchers report differences in the morphology and anatomy of schizophrenic brains there is usually overlap with the characteristics of the brains of normal controls. Often the changes reported are relatively small and only 6 to 40% of schizophrenics may exhibit such changes (Syvalahti, 1994).

As well as reporting neuroanatomical and neuromorphological changes occurring in the brains of schizophrenic subjects, some studies have reported functional changes. Changes in neuronal activity have been reported using techniques such as electroencephalograms (EEG's) (Barrett, McCallum, & Pocock, 1986), studies of evoked potentials (Blackwood, St Clair, Muir &

Duffy, 1991) and magnetoencephalography (MEG) (Tiihonen et al., 1992). Changes in cerebral blood flow have been investigated using techniques such as single photon emission computerised tomography (SPECT) (Sauer, Schroder, Henningsen, & Wilhelm, 1990) and positron emission tomography (PET) (Gur, Resnick, Alavi, Gur, Caroff, Dann, et al., 1987). However the results of numerous studies employing these techniques do not provide unequivocal evidence for consistent functional changes in the brains of schizophrenic patients. One finding which has been repeated is that there is low relative glucose metabolism in the frontal regions and this was first described by Ingvar and Franzen in 1974 who used the xenon-113 technique. A follow up study 18 years after this initial study in the same group of patients replicated these findings and concluded that changes in cerebral regional blood flow are constant in chronic schizophrenics (Cantor et al. 1991). Decreased regional cerebral blood flow in schizophrenic patients as compared to controls has been replicated in a number of studies (Buchsbaum, Ingvar, Kessler, Waters, Cappelletti, van Kammen, et al., 1982; Gur & Pearlson, 1993; Rubin, et al., 1994). In one study the specific symptom syndromes of psychomotor poverty, disorganisation, and reality distortion were associated with specific patterns of perfusion of regional locations in the brain. For example psychomotor poverty and disorganisation were associated with altered perfusion at different loci in the prefrontal cortex, and reality distortion was associated with altered perfusion in the medial temporal lobe (Liddle et al., 1992). Similar to the neuroanatomical studies one of the main criticisms of these studies is that often subjects who take part in the research have been exposed to neuroleptic medication over many years. In a recent review Chua & McKenna (1995) concluded that the only well established structural brain abnormality in schizophrenia is lateral ventricular

enlargement; this is modest and there is a large overlap with the normal population.

Environmental Factors

1.3.4 Prenatal Effects

a) Prenatal Viral Infections

The most frequently cited prenatal factor which has been implicated in the aetiology of schizophrenia is influenza infection in the second trimester of pregnancy. Thus Mednick reported that foetuses of mothers who were in the second trimester of pregnancy during the 1957 influenza epidemic were more likely in subsequent life to be admitted to a psychiatric hospital with a diagnosis of schizophrenia (Mednick, Machon, Huttunen & Bonett, 1988). This finding has been replicated (Sham et al., 1992). The increased incidence of schizophrenia in the offspring of mothers who were in the second trimester during an influenza epidemic was found in one study to be gender specific to females born in England and Wales (Takei et al., 1994). The influenza theory is particularly blighted with methodological problems. The studies which cite the increase in schizophrenia after influenza epidemics tend to correlate factors such as the number of deaths associated with the epidemic with the number of babies born shortly after the epidemic who subsequently develop schizophrenia in adulthood. However this does not take into account the relationship between actual contraction of the influenza virus and consequent development of schizophrenia and this makes assertions of causality difficult to

substantiate (Crow, 1994). In a study of 945 mothers who actually contracted influenza during the 1957 epidemic, the proportion of their offspring who went on to develop schizophrenia was not significantly different to a non-infected control group (Crow & Done, 1992). Recently a Dutch study showed that schizophrenic patients who were in their 2nd trimester of foetal life during the peak of the 1957 influenza epidemic were at no greater risk than controls of developing schizophrenia (Selten & Slaets, 1994). Another flaw in this theory is that although births occurring after the 1957 influenza epidemic were associated with an increased prevalence of schizophrenia, no relationship has been demonstrated between development of schizophrenia and the influenza epidemics of 1944 and 1951 which resulted in more fatalities (Crow, 1994). This could possibly be explained by gene mutations in the influenza virus but this theory is to date unproven. Although some authors assert that a proportion of schizophrenic births are associated with the influenza virus (Sham, et al., 1992), others have revealed inconsistencies in this theory and have questioned the methodologies used (Crow, 1994).

b) Seasonality of Birth

It has been shown in a number of studies that the proportion of births of babies who develop schizophrenia later in life is disproportionately higher in late winter and early spring (Machon, Mednick & Schulsinger, 1983; Torrey, Torrey & Petersen, 1977) and these results have been replicated even when controlling for the age incidence effect (Rodrigo, Lusiardo, Briggs, & Ulmer, 1992). The reason for this phenomenon is not known but various factors have been proposed to be involved, including infectious agents (such as influenza as

previously mentioned), nutritional factors, temperature variations at the time of conception, environmental factors and an interaction of these factors with genetic influences (Delisi & Crow, 1986). Not all studies which have investigated the effect of season of birth have replicated the finding that babies who subsequently develop schizophrenia are more likely to be born in late winter and early spring. For example Kim, Lee, Lim, Noh, & Park (1994) in a Korean study of 1606 schizophrenic patients and 4582 controls found that there was no significant difference in the month of birth between the two groups. The studies which have replicated or failed to replicate the season of birth effect for schizophrenia suggest that the effect is significant only in the Northern hemisphere (Berquier & Ashton, 1991). The geographic variation in the finding of season of birth effect and in the geographic variation in the prevalence of schizophrenia have been cited as evidence of viral aetiology in the development of schizophrenia (Delisi & Crow, 1986). However other authors have concluded that no research to date has irrefutably indicated an infectious or autoimmune aetiological process in schizophrenia and suggest that schizophrenia is more likely to be a heterogenous disorder resulting from interactions between multiple factors (Kirch, 1993).

1.3.5 Environmental Stress

A number of studies have investigated the role of life stressors, such as bereavement, divorce or being made redundant, in the emergence of psychotic symptoms. When comparing people with a diagnosis of schizophrenia to those with other psychiatric diagnoses such as depression, there does not seem to be a consistent association with increased number of life event stressors (Paykel,

1979). It has been demonstrated that there is a greater association between life events and depression than life events and schizophrenia (Tennant, Bebbington, & Hurry, 1981).

Comparisons have also been made between the amount of life stressors experienced by people with a diagnosis of schizophrenia and normal control samples. For example Jacobs & Myers (1976) compared life stressors in a group of 62 first episode psychosis in-patient admissions with an age and sex matched randomly selected control group. A highly statistically significant increase in the number of life events was found for the patient group compared to the control group for a period of one year before interview/admission. Other studies have also shown an increase in life events prior to onset of psychotic symptoms compared to control groups (Schwartz & Myers, 1977) but this has not always been replicated (Al Khani, Bebbington, Watson, & House, 1986).

Perhaps the most useful observations about the relationship between life events and psychotic symptoms have been obtained in temporal studies of the relationship between variation of life stressors and worsening of psychotic symptoms, so using individuals with a diagnosis of schizophrenia as their own control. For example in an early study Brown & Birley (1968) found an increase in significant life events in the three week period before relapse. This study was carried out retrospectively, that is, subjects were asked to retrospectively report life events preceding the onset of psychoses, and there is an obvious methodological weakness with such an approach. However some prospective studies have been carried out (Bebbington, Wilkins, Jones, Foerster, Murray, Toone, et al., 1993; Ventura, Nuechterlein, Lukoff, & Hardesty, 1989)

and these have also shown a significantly increased number of life events in the weeks before onset of psychosis. In a large collaborative World Health Organisation study, Day et al. (1987) found that in six of nine catchment areas from around the world, life events were significantly more likely to occur in the six week period preceding psychotic relapse. Although the exact relationship between life stressors and psychotic symptoms is not certain there is some evidence which suggests that there is a link between life events and the emergence of psychotic symptoms. However, it is important to note that not all individuals who suffer even extreme life stressors necessarily exhibit psychotic symptoms, and further work is required to investigate the contribution of life events to the emergence of psychotic symptoms.

Although the number of methodologically sound studies which investigate the role of life stressors in schizophrenia are limited, a considerable amount of research has been carried out into the role of family stressors, particularly 'expressed emotion'. Expressed emotion is a term to describe intense emotional overinvolvement or criticism from a near relative or spouse. This concept originated from early work by Brown, Carstairs, & Topping (1958) which found that, contrary to expectation, patients who were discharged back to live with their spouse or parents were subject to a higher level of morbidity than those patients who were discharged to lodgings or to live with siblings. It also appeared that the amount of time spent with either parents or spouse was significant in terms of morbidity and this observation led the authors to speculate that there may be some aspects of interfamilial relationships which affect psychiatric relapse. Subsequently a more carefully controlled prospective study to investigate the influence of family relationships on relapse of

schizophrenic patients was carried out. The researchers attempted to measure the amount of emotion expressed about the patient by relatives, dominance of the individuals involved, and hostility. It was found that a combination of high hostility and high levels of emotion expressed about the patient predicted a high rate of relapse (Brown, Monck, Carstairs, & Wing, 1962). Although the measures used in this study were rudimentary and not validated, further work led to the development of the Camberwell Family Interview, which was explicitly designed to measure expressed emotion (Brown & Rutter, 1966). Studies using this and more recently developed measures have generally replicated the observation that increased levels of contact with high expressed emotion relatives is a predictor of poor outcome in schizophrenia. A particularly influential study in this area was carried out by Vaughn & Leff (1976) who demonstrated that high expressed emotion and prolonged time periods spent with stressor relatives was associated with higher relapse rates. These authors also found that neuroleptic medication had a stress protective effect by reducing the rate of relapse in households were the measured expressed emotion was high. More recent studies have shown that individuals who live in low expressed emotion households relapse significantly less than those in high expressed emotion households, and also that expressed emotion can fluctuate and so is not a static attribute of the home environment (McCreadie, Robertson, Hall, & Berry, 1993; Tarrier, Barrowclough, Vaughn, Bamrah, Porceddu, Watts, et al., 1988). Some authors have suggested that expressed emotion reflects in some part the response of the family to an individual with a psychotic illness, although this has not been scientifically demonstrated (Birchwood & Smith, 1987; Macmillan, Gold, Crow, Johnson, & Johnstone, 1986). Intervention studies which are aimed at reducing expressed emotion using various

psychological techniques with a view to reducing relapse rates have met with success (Falloon, Boyd, McGill, Razani, Moss, & Gilderman, 1982; Leff, Kuipers, Berkowitz, Ebstein-Vries, & Sturgeon, 1982).

An interesting point is that there is a high prevalence of previous childhood abuse has been reported in adults with psychotic symptoms. Goff, Brotman, Kindlon, Waites, & Amico (1991b) found that 43% of 61 chronically psychotic in-patients reported childhood abuse and more recently Greenfield, Strakowski, Tohen, Batson, & Kolbrener (1994) in a study of 38 patients admitted for first episode psychosis found that 20 reported childhood abuse. Dissociative symptoms such as alterations in sense of reality identity and memory can overlap with and are sometimes difficult to distinguish from psychotic symptoms. There is relatively little research in this area and further work would be of great benefit in trying to elucidate the aetiology and appropriate treatment of schizophrenia.

Migration has also been postulated to increase the incidence of schizophrenia. For example there is a higher rate of first incidence of schizophrenia in Caribbean born immigrants and second generation Caribbeans in Manchester and Camberwell compared to other cultural groups (Cochrane & Bal, 1989; Harrison, Owens, Holton, Neilson, & Boot, 1988). Studies which have investigated the incidence of schizophrenia in Asian born individuals have shown more variability (Pilgrim & Rogers, 1993), and some studies have shown an increased incidence of schizophrenia in Asians (Shaikh, 1985). Higher rates of schizophrenia and other related diagnoses have been found in Irish immigrants (Cochrane & Bal, 1989). These findings are difficult to interpret due

to methodological difficulties, such as diagnostic criteria, sampling and there are inconsistencies in the studies. For example some studies include only people who have not been born in the UK and others include second generation immigrants. There are also problems with hospital admission records which are often incomplete or missing. However one study which found an increase in the rates of diagnosis of schizophrenia was a carefully controlled prospective study carried out in Nottingham (Harrison, et al., 1988) and this study found an increased rate, particularly in second generation Afro-Caribbeans. It has been suggested that the increased incidence in diagnosis of schizophrenia and related disorders in Afro-Caribbeans may be a consequence of discrimination and subsequent stress and increased social deprivation in this population (Pilgrim & Rogers, 1993).

1.4 Conceptual Models of Schizophrenia

A number of conceptual models of schizophrenia have been proposed over the years and on inspection of these, a dichotomy of opinion is apparent between those theorists who favour biological theories for the aetiology of schizophrenia and those theorists who favour the idea that environmental factors are fundamental in the aetiology. It may be the case that schizophrenia is of heterogenous aetiology and some theories encompass aspects of both perspectives. The following section will give a very brief overview of some of the main hypotheses which have been suggested with regard to schizophrenia.

1.4.1 Schizophrenia as a Distinct Disease

There are a number of exponents of the concept of schizophrenia as a single disease. It is proposed that although the aetiology of schizophrenia is unknown at present, it will one day be reduced to a cause which will lead us to the optimum treatment of the disease (Johnstone, 1993a). In this model schizophrenia is thought to be a disease of the nervous system, and although the aetiology is not known at present a simplified explanation will become available to us with the help of modern technology. An inherent problem in this model is that researchers do not always define or interpret a "disease" or "illness" in the same way. Thus disease can be described as a structural or functional abnormality of cells, tissues, organs or bodies, as a lesion or as a defined by Scadding in 1967:

> "The sum of abnormal phenomena displayed by a group of living organisms in association with a specified common characteristic or set of characteristics by which they differ from the norm for their species in such a way as to place them at a biological disadvantage".

This definition and other similar definitions have been used either to promote or refute schizophrenia as a disease. At the root of opinions which advocate or oppose the disease model is a belief or disbelief in a biological cause of schizophrenia. Thus authors such as Johnstone (1993a) believe that the evidence for a biological cause is strong and that even if this turns out not to be the case, that using a disease model of schizophrenia is helpful to the clinician, sufferers of schizophrenia and their relatives.

An interesting and alternative disease model has been proposed by

Claridge (1990) who compared schizotypal personality with blood pressure. In both of these cases there is a continuum of each phenomena in the normal population so for example it is difficult to define high blood pressure within a distinct range. If the higher extremes of either high blood pressure or schizotypal personality occurs in the presence of certain stressors there is an increased likelihood of developing a "disease". Thus in the case of high blood pressure, stress, high fat diet, smoking and high consumption of alcohol can lead to an increased risk of stroke and cardiac disease. Claridge compares this to a schizotypal personality which with the presence of biological vulnerability (genetic risk) and life stresses such as high expressed emotion greatly increase the risk of a schizophrenic break down. He based this theory on the fact that research in non-psychiatric populations has identified people with psychotic traits who do not have a psychiatric diagnosis and function well in the community. This theory is also supported by the fact that children with a high (genetic) risk of developing schizophrenia do not always go on to do so in later life. He concedes however that it is difficult to compare physical illnesses with those that affect the mind, as the brain is a highly complex and unique organ, in which small changes in its physiology can affect massive changes throughout the body.

At the other extreme Szasz has argued that the concept of mental illness is scientifically unviable and socially harmful (Szasz, 1973). He asserts that in medicine an illness is a consequence of physicochemical disturbances which are identified by means of physical disturbances. This may be in the form of signs such as fever or symptoms such as pain. However a mental illness is diagnosed on the basis of mental symptoms which depend on the patients communications

about themselves and their world. Mental symptoms are intrinsically linked to the legal, psychosocial and ethical context in which they occur and in this way can only be considered as symptoms if they differ from the beliefs of the observer (for example a psychiatrist). Szasz states that whilst a disturbance in a persons visual field can be explained by a lesion in the central nervous system, a belief in catholicism, communism or that the world is flat cannot and should not be explained in such terms. He also argues that a diagnosis of a mental illness involves a covert comparison of the ideas of the patient and those of the observer, and that the function of diagnosis is to licence social control. As Szasz asserts that beliefs, which are an integral factor in the diagnosis of schizophrenia, cannot be explained by a defect or disease in the nervous system he believes that it is erroneous to expect that a medical intervention could remedy mental illness which is viewed as a psychosocial ethical and legal deviation. Szasz prefers to think of schizophrenia as a problem in living or in the intercommunication between people rather than an illness. This viewpoint is forceful and controversial and Szasz has stated that a belief in mental illness is an heir to a belief in demonology and witchcraft. In this context Szasz acknowledges that personal unhappiness and socially deviant behaviour do exist but that these phenomena should not be categorized as a mental illness. According to Szasz mental illness is a myth which is used in order to disguise and soften the blow of moral conflicts in human behaviour.

More recently Szasz has criticised the diagnosis of "crazy talk" as mental symptoms (Szasz, 1993) asserting the lack of evidence for abnormal physiological processes causing these symptoms. Szasz also refers to the gift of speaking with tongues (glossolalia) which is not widely seen as requiring

treatment and reasserts the importance of values and context for diagnosing symptoms. Szasz has bravely attempted to question and criticise the foundations of psychiatric diagnosis and theory. However he has been severely criticized by many authors within the psychiatric establishment (Hamilton, 1973; Roth, 1973). For example Leff (1993) commenting on the "crazy talk" paper, makes the point that glossolalia lasts for only a few minutes, whereas speech disorder associated with schizophrenia lasts for days, weeks, or even years. Bentall & Pilgrim (1993) comment that whilst Szasz has made a significant contribution in pointing out the importance of values in psychiatric decision making, there are weaknesses in his arguments. For example Szasz fails to recognise that such values and social contexts also affect decision making in physical disease, and his definition and viewpoints of the illness concept are too simplistic.

1.4.2 Subtypes of Schizophrenia

The hypothesis of Crow that schizophrenia is comprised of two sub-types; type I and type II is well known (Crow, 1980). Symptoms characteristic of type I are positive symptoms particularly hallucinations, bizarre behaviour and thought disorder. In this acute type, symptoms respond well to treatment and there is an absence of intellectual impairment. Crow hypothesised the putative pathology of this type to be an overactivity of dopamine receptors. Type II schizophrenia is characterised by predominantly negative and chronic symptomatology such as blunted affect, withdrawal, avolition and poverty of speech. These symptoms tend not to respond well to neuroleptic treatment and intellectual impairment is sometimes present (Angrist, Rotrosen, & Gershon,

1980; Johnstone, et al., 1978). Crow postulated that pathology of type II schizophrenia was cell loss and structural changes within the brain.

There have been criticisms of this theory, for example Goldberg (1985) who asserted that negative symptoms do respond to neuroleptic treatment. It is also difficult to accurately define response of negative symptoms to neuroleptic treatment (Angst, Stassen, & Woggon, 1989). Negative symptoms are difficult to assess and may be more difficult to distinguish between aspect of a persons premorbid personality and those which are a consequence of schizophrenia or drug treatment.

There has been little research to support Crow's hypothesis. In one study which used factor analysis of data from the Present State Examination of people with a diagnosis of schizophrenia, three factors were identified , two of which reflected the positive and negative typology of Crow and a third factor associated with cognitive and verbal disorganisation (Liddle, 1987). This has been replicated in a number of studies (Frith, 1992; Malla, Norman, Williamson, Cortese & Diaz, 1993). Studies carried out using non-schizophrenic volunteers have indicated that schizotypal traits may also fit the three dimensional model (Bentall, Claridge, & Slade, 1989; Chapman, Chapman, & Miller, 1982).

In the light of recent advances in developing effective anti-psychotic drugs which do not exert a dominant effect at dopamine D_2 receptors, and the fact that there is not a clear dichotomy of response of positive and negative symptoms to neuroleptic drugs, it seems probable that Crow's hypothesis is not adequate to explain variation in schizophrenic symptoms. Although it has been

useful attempt to sub-classify schizophrenia, Crow's hypothesis has been severely criticised because it is too restrictive (De Leon, Simpson, & Peralta, 1992) and is likely to be too simple. Von Knorring & Lindstrom (1995) in a recent review of principal components factors analyses of Positive and Negative Syndrome Scale (PANSS) data concluded that a five factor pyramidal model comprising positive, negative, excited, anxious/depressive and cognitive factors explains a greater proportion of variation in schizophrenic symptoms and that all five of these factors are responsive to drug treatment. The number of dimensions which are legitimately included in any model of schizophrenia is not certain, but the body of evidence which lean toward a more complex than two dimensional model suggests that psychotic symptoms exhibit a complex heterogeneity.

1.4.3 Vulnerability Model of Schizophrenia

The stress diathesis model of schizophrenia incorporates the interaction between a genetically transmitted vulnerability, and intrinsic or extrinsic stressors that can trigger a psychotic episode. This model was first proposed by Meehl in 1962, who described a biological continuum of "schizotaxia" which was a genetic dimension that could develop into schizophrenia in certain environments. However in an environment where certain stressors were not present this predisposition could be expressed as schizotypy. Schizotypy can be described as certain types of cognitive or behavioural traits, similar to psychotic symptoms, which may be present in otherwise healthy individuals. Schizotypy overlaps with what is perceived as more "normal" in behaviour and could include highly creative individuals, religious or political fanatics or

individuals who are highly mystic. Meehl regarded schizotaxia as an inherited aberration in neuronal cell function which manifested itself in varying degrees of schizotypy. The schizotypal source traits of cognitive slippage, anhedonia, ambivalence and interpersonal aversiveness would develop into full blown schizophrenia, only in the presence an adverse interpersonal environment, particularly a schizophrenogenic mother. Schizotaxia was viewed as an inherited vulnerability factor necessary for the development of schizophrenia. However not all "schizotaxic" individuals would subsequently develop schizophrenia. This viewpoint was expressed in order to explain the less than 100% concordance rate in twin studies and has been the root of the polygenic diathesis stress model which has received considerable interest from researchers over the years. Zubin & Spring (1977) further contributed to the theory that schizophrenia resulted from a combination of predisposition (usually considered to be genetic but factors such as perinatal complications may also contribute), and environmental factors. Nuechterlein & Dawson (1984) have suggested that some deficits fit into a "mediating vulnerability" pattern. This is some cognitive deficit which is present in remission but worsens during a psychotic episode. The clinical significance of this model is that vulnerability factors could be identified in people and coping strategies and environmental changes carried out in order to prevent psychotic relapse. It has also been suggested that psychological treatment of underlying cognitive deficits would be of benefit to individuals who experienced psychotic symptoms (Green, 1992). The vulnerability stress model is compatible with the dimensional models of Claridge and Liddle (previously described) and also with literature on stress, in that individuals with high schizotypy are vulnerable to stress.

1.4.4 Individual Symptoms

In contrast to a number of traditional approaches to schizophrenia, a number of researchers have argued that it may be more helpful to consider individual symptoms of schizophrenia such as delusions or hallucinations, rather than to group symptoms together under the syndrome of schizophrenia. Thus research into aetiology and treatment would tackle separately individual symptoms. The argument for this approach stems from the observation that the concept of schizophrenia does not have strength as a scientific construct due to problems of low reliability and validity. For example the concordance between the categorical systems which classify schizophrenia is not high (Brockington, Kendell, & Leff, 1978) and it has been found that operationalised diagnoses are not stable (Kendell, Brockington, & Leff, 1979). The diagnosis of schizophrenia has also been shown to have poor predictive validity, and psychosocial factors are better predictors of short term outcome than symptom variables (Hawke, Strauss, & Carpenter, 1975).

It has been argued that the problems of validity of diagnosis of schizophrenia have hindered research and that instead of carrying out research into the problem of schizophrenia, it would be more helpful to abandon an attempt to use a diagnosis and instead to carry out research into individual symptoms (Bentall, Jackson, & Pilgrim, 1988; Persons, 1986; Slade & Cooper, 1979). It has also been argued that both symptoms and syndromes of schizophrenia should be studied (Frith, 1992).

1.5 Social Aspects of Schizophrenia

Space prevents a thorough discussion of the social aspects of schizophrenia. Some aspects have already been mentioned in the case of migration, cultural background, life stress and family interactions in the above text. Social factors are known to play a major part in the aetiology of many diseases and psychological phenomena, and it is therefore not surprising that social aspects are important with regard to the development of schizophrenia. Some aspects of socially derived stress have been discussed previously but one omission is the fact that the prevalence of schizophrenia is higher in people from lower socio-economic backgrounds. This was found to be the case as early as 1939 when Faris & Dunham found that the rate of diagnosis of schizophrenia was seven times higher in poor inner-city districts compared with middle-class suburban areas. Faris asserted that poverty and social isolation were stressors involved in the aetiology of schizophrenia in vulnerable individuals. This theory is known as the social isolation theory (Faris, 1944) and the role of social isolation in the aetiology of schizophrenia has been both confirmed and refuted in research carried out since its conception. The social drift theory is based on the assumption that people who have a diagnosis of schizophrenia are not necessarily born in a low socio-economic environment. In this theoretical model it is hypothesised that the experience of psychotic symptoms and their adverse effects on social functioning and employment opportunities, results in a drift into lower socio-economic circumstances (Pilgrim & Rogers, 1993). Whilst it is widely agreed that schizophrenia is over-represented in poorer populations, the theories accounting for this situation whether "drift" or "stressor" are not decisive.

People from higher socioeconomic backgrounds have been found to have the same level of negative experiences, but more positive experiences than contemporaries from lower socioeconomic backgrounds. For this reason it has been suggested that, because people of lower socioeconomic status have fewer positive events to buffer the negative life events, they are more vulnerable to mental distress (Myers, 1975). Whilst it is clear that there is an association between the prevalence of schizophrenia and social factors, the precise role of social factors in the aetiology of schizophrenia is unknown.

1.6 Criteria for Diagnosing Schizophrenia

Previous work has shown that the reliability in diagnosing schizophrenia is not always high. For example in the 1930's and 1940's there was a significant difference between the first admission rates for schizophrenia for the United Kingdom compared with the United States (Bellack, 1958). At that stage the reasons for this discrepancy were unclear, and further studies were carried out. Thus, Cooper, Kendell, Gurland, Sharpe, Copeland, & Simon (1972) used a standardised interview to diagnose schizophrenia and found comparable rates of schizophrenia in the USA and the UK. The World Health Organisation also carried out a very large study of over a thousand patients in nine different countries (World Health Organisation, 1973). In this, researchers used a structured interview which was coded on a computerised scoring programme. In seven of the countries there was good agreement between the research teams' diagnoses and the local psychiatrists'. However in the United States and in what was then the United Socialist Soviet Republic, local psychiatrists diagnosed schizophrenia comparatively more often than researchers.

In order to increase the reliability of the diagnosis of schizophrenia, a number of bodies developed operational criteria which describe a list of symptoms which must be present in order to diagnose a disorder. Some of these systems of operational criteria will be described in detail below.

ICD-10 Criteria

The "Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Deaths", 10th revision or ICD 10 (World Health Organisation, 1990) is a medical classification system which encompasses psychiatry. ICD 10 classifies schizophrenia as a type of psychosis, describing schizophrenic psychoses as a disorder which involves fundamental disturbance of personality, characteristic distortions of thinking and perception, often a sense of being controlled by alien forces, delusions which may be bizarre, disturbed perception, abnormal affect out of keeping with the situation, and autism. In this classification system the diagnosis should not be restricted to conditions running at a protracted, deteriorating, or chronic course. Under ICD 10 criteria, a diagnosis of schizophrenia can be made if at least one of a core group of symptoms; thought insertion, delusions of control, hallucinatory voices giving a running commentary or persistent delusions ***or*** at least two of the following symptoms; persistent hallucinations, thought disorder, incoherence, catatonic behaviour, negative symptoms or consistent deterioration in personal behaviour. These symptoms must have been present for at least one month to give a diagnosis of schizophrenia. If symptoms have been present for less than one month, a diagnosis of acute schizophrenia-like psychotic disorder should be made, which may be reclassified as schizophrenia

if symptoms persist for more than one month.

The classification of schizophrenia is divided into various sub-types as described below;

F20.0 *Paranoid schizophrenia* characterised by relatively stable delusions particularly of persecution and may be accompanied by hallucinations.

F20.1 *Hebephrenic schizophrenia* in which affective changes are prominent, delusions and hallucinations fleeting and fragmentary, behaviour irresponsible and mannerisms common.

F**20.2** *Catatonic type* characterised by prominent psychomotor disturbances often alternating between extremes such as hyperkinesia and stupor.

F20.3 *Undifferentiated schizophrenia* in which the general diagnostic criteria for schizophrenia are met but the diagnostic specifications for the above sub-types are not met, or aspects of more than one diagnoses are met without a clear predominance for one subtype. This diagnosis excludes residual schizophrenia and post psychotic depression and should only be made after an attempt to classify under categories F20.0 to F20.2.

F20.4 *Post-schizophrenic depression* is characterised by a depressive episode which may be prolonged subsequent to a schizophrenic illness. Some schizophrenic symptoms may still be present (usually negative) but these are not a dominant feature.

F20.5 *Residual Schizophrenia* A chronic form of schizophrenia in which symptoms persist from the acute phase but are less distinct. Negative symptoms are prominent within this diagnosis.

F20.6 *Simple schizophrenia* in which delusions and hallucinations are not in evidence. There is an "insidious but progressive development of oddities of

conduct, inability to meet the demands of society and decline in total performance". Negative symptoms may be present.

F20.8 *Other* Not classifiable under F20.0 to F20.6

F20.9 *Unspecified* "To be used as a last resort"

A fifth character can be attached to the diagnostic number to classify the time course of the condition. For example 0 which signifies continuous, through to 5 which signifies complete remission. Other related classifications include schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders, induced delusional disorder and schizoaffective disorder.

DSM IV Criteria

The diagnostic and statistical manual of mental disorders, 4th edition (DSM IV) is a system for classifying psychiatric disorders devised by the American Psychiatric Association (APA). ICD 10 is designed for administrative and epidemiological work whereas DSM IV is also recommended for research. DSM IV criteria for schizophrenia include the presence of characteristic psychotic negative and positive signs and symptoms (such as delusions or hallucinations) for an active phase of at least one month, associated with social and occupational dysfunction, and a duration of at least six months of some signs of the disorder. Thus under the DSM IV criteria a prolonged course is a fundamental part of diagnosis which differs from ICD classification. Examples of positive signs and symptoms include; delusions, hallucinations, disorganised speech and grossly disorganised or catatonic behaviour. Negative symptoms include affective flattening, alogia and avolition. A diagnosis of schizophrenia can only be made if these criteria are met and if the psychotic symptoms are not

initiated or prolonged by organic factors.

Within the diagnosis of schizophrenia according to DSM IV, there are a number of subtypes of schizophrenia which are characterised by a predominant symptomatology. For example **Paranoid Type** (295.30) is characterised by preoccupation with one or more prominent delusions or frequent auditory hallucinations in the absence of pronounced disorganised speech, disorganised or catatonic behaviour or flat or inappropriate affect. **Disorganised type** (295.10) is characterised by disorganised speech and behaviour, flat or inappropriate affect in the absence of criteria which define catatonic type. This diagnosis is often associated with an early and insidious onset, poor premorbid personality and is termed hebephrenic in other and older classification systems. In the diagnosis of **catatonic type** (295.20) marked psychomotor disturbance is the over-riding feature. For example motor immobility may be present, or conversely excessive and purposeless motor activity. This diagnosis can also be made if extreme negativism (maintaining a motionless rigid posture), bizarre or inappropriate postures and mannerisms (such as grimacing) or echolalia (repetition of words spoken by another person) or echopraxia (repetitive imitation of the movements of other) are a salient feature.

Other classifications include **undifferentiated type**, in which the criteria for schizophrenia are met but it is not possible to classify one of the sub-types outlined above, and **residual type**, in which there has been at least one previous episode of schizophrenia but there are no current prominent symptoms such as delusions or hallucinations. There is also a subtype of **schizophreniform disorder** in which the symptoms necessary for a diagnosis

of schizophrenia are met, excepting a that the duration of some of the signs or symptoms have been present for at least six months. Impaired social or occupational functioning is not required. This may be a provisional diagnosis until the disturbance persists for more than six months when the diagnosis would be changed to schizophrenia. Similarly **brief psychotic disorder** differs from schizophreniform disorder in that the duration of the symptomatology is less than one month. Other related diagnoses classified in DSM IV include schizoaffective disorder, delusional disorder, shared psychotic disorder (also referred to as folie à deux), psychotic disorder due to a general medical condition, substance-induced psychotic disorder and psychotic disorder not otherwise specified.

Other categorical systems which classify schizophrenia include; Catego (computer program which processes data from the Present State Examination, PSE), Carpenter's flexible system, Langfeldt's, Feighners's, Astrachan's, Research Diagnostic criteria, the New Haven Schizophrenia Index, and Taylor and Abram's criteria. Although these categorical systems are reliable in their own right, the agreement between them is not high when diagnosing schizophrenia (Brockington, et al., 1978; Stephens, Astrup, Carpenter, Shaffer, & Goldberg, 1982). There are some quite prominent differences between the criteria for different classification systems. For example to establish a diagnosis of schizophrenia using DSM IV or Feighner's criteria it is a requirement that a patient is ill for at least six months, whilst the Research Diagnostic Criteria requires an illness duration of two weeks.

Status of health problem

The lifetime prevalence of schizophrenia in many studies around the world has been estimated at between 0.2 and 1 %, although marked regional differences occur (Torrey, 1987). For example the prevalence of schizophrenia in Ireland has consistently been found to be higher than other parts of the world (Torrey, McGuire, O'Hare, Walsh, & Spellman, 1984). It is frequently identified in early adulthood (late teens and early twenties), although often later in females than in males (Delisi, 1992). It is slightly more common in males than females, and males may be more likely than females to have a poor response to medication and a more severe course of illness (Flor-Henry, 1985; Seeman, 1986). Schizophrenia tends to be associated with some deterioration in social functioning and can have a prolonged morbidity.

Schizophrenia is often characterised by long periods of treatment with medication as well as numerous hospital admissions. Thus, this condition is a considerable burden on National Health Service expenditure. The prominent status of schizophrenia as a current health problem is highlighted in its inclusion in "The Health of the Nation", a government white paper published in 1992. This publication recognised mental illness as a leading cause of ill-health and disability and indicated that mental illness accounts for more than 14% of certified sickness leave. The targets outlined in this white paper are;

(1) To improve significantly the health and social functioning of mentally ill people

(2) To reduce the overall suicide rate by at least 15% by the year 2000

(3) To reduce the suicide rate of severely mentally ill by at least 33% by the

year 2000.

Although this document refers to mental illness as a whole it is particularly relevant to schizophrenia regarding targets (1) and (3).

Schizophrenia is associated with a high degree of suicide even in comparison to other psychiatric diagnoses and it has been argued that suicide is the chief cause of premature death amongst schizophrenic persons (Caldwell & Gottesman, 1992). Studies have shown that about 10% of people with a diagnosis of schizophrenia take their own lives and risk factors include living alone, single status, youth and fear of further mental disintegration (Caldwell & Gottesman, 1990).

1.7 Economic Aspects of Schizophrenia

As schizophrenia is often associated with a long term morbidity and chronic long term disability, for example preventing individuals from taking up employment, it entails considerable financial costs. The costs to society encompass three main strands; direct treatment costs, indirect costs of loss of production, and intangible costs of pain and suffering to the patient and family. It is very difficult to estimate average treatment costs of schizophrenia due to the heterogeneity of the condition and response to treatment. However two main studies have attempted to carry this out (Davies & Drummond, 1994; Kavanagh, 1994). According to Davies & Drummond, the estimated direct cost of one year of treatment for one person with schizophrenia is £2,138 based on 1991/1992 prices and assuming a yearly treated prevalence of 185 400 people. For all people with schizophrenia treated in one year in the UK the total cost,

including medical and social services, has been estimated at £397 million which accounts for 1.6% of the total health care budget (Davies & Drummond, 1994). This study also provided a conservative estimate of the indirect costs of schizophrenia at £1.7 billion. This indirect cost is based on production losses as a result of unemployment and time off work due to suffering from schizophrenia. However this does not include loss of earnings of near family and significant others who care for individuals with a diagnosis of schizophrenia. It also does not include costs of premature mortality which is associated with schizophrenia. There is a wide range of needs of people with a diagnosis of schizophrenia such that 97% of total costs are incurred by less than 50% of a one year incidence cohort. Although the majority of diagnosed schizophrenics are prescribed medication only 5% of direct costs are accounted for by drug treatments.

Kavanagh (1994) used an estimated prevalence of schizophrenia of 136 000 people and breaks down their location into various sites including hospital in-patients, private households (GP care and specialist care) specialist accomodation, homeless and prison. The majority (60 000) are in private homes under specialist care. Kavanagh also breaks down the costs of schizophrenia by agency and these costs are based on 1992/1993 prices. These costs are listed in £million as;

District Health Authorities	1242
Family Health Services agencies	13
Law enforcement agencies	55
LA Social Services departments	149
Department of Employment	1
Voluntary Sector	43
Department of Social Security	885

This amounts to a total of £2388 million per annum for direct costs, which is considerably higher than that estimated by Davies & Drummond but takes into account more agencies. Kavanagh makes the point that the costs of care for the relatively small group of people treated is disproportionately high compared to other settings. In the United States it has been stated that the financial costs of schizophrenia are greater than those for cancer but that it attracts proportionally less research funds (National Foundation for Brain Research, 1992). Thus schizophrenia presents a large economic burden, and this further justifies research of this distressing condition being carried out.

1.8 Range of Previous Research

Schizophrenia has attracted a large number of researchers from diverse backgrounds including psychology, medicine, law, sociology and economics. Over many years this has led to a vast body of publications. Despite this interest schizophrenia remains an enigma. Scientists from a variety of disciplines have failed to implicate a gene for the condition; have not determined an unequivocal receptor abnormality; are developing new drugs which have differing effects to traditional drug treatments; have not revealed consistent brain abnormalities and there are no biochemical markers to aid diagnosis. In this wide surfeit of research there is a striking lack of reports from or individual case studies of people who suffer from schizophrenia. As the techniques for researching the aetiology and treatment of schizophrenia develop, it is likely that parallel research into individuals experience of psychoses and its treatment will be beneficial.

CHAPTER 2

Drug Treatment of Schizophrenia

2.1 Introduction

The mainstay of treatment of schizophrenia at the present time is neuroleptic drugs and this chapter will mainly focus on this. However, it is important to acknowledge that drug treatment is not the only therapeutic modality available to clinicians. Psychosocial treatments for psychotic patients have been attempted with varying success rates. Although early studies evaluating psychodynamic therapy largely produced discouraging findings, more recent studies of the efficaciousness of family therapy and individual cognitive-behaviour therapy have been more encouraging (Haddock & Slade, in press; Birchwood & Tarrier, 1992).

2.2 Neuroleptic Drugs

2.2.1 History

The history of neuroleptic drugs is interesting particularly in respect of current day professional attitudes to neuroleptic treatment of schizophrenia. The first drug treatment which was used in psychiatry was reserpine, which is a derivative of the shrub Rauwolfia Serpentina. Rauwolfia had been used in India as a cure for insanity, mania, snake bites and high blood pressure, but this use was largely unknown to the western world until 1952 when reserpine was

isolated. The principle pharmacological action of reserpine is that it depletes central nervous system amines, mainly 5-hydroxytryptamine (5HT, also known as serotonin) and noradrenaline. The clinical effects of reserpine were similar to chlorpromazine but with a slower onset. Reserpine was also associated with a high incidence of side effects including precipitation of severe depression and for this reason reserpine is no longer used in the treatment of schizophrenia.

The first phenothiazine derivatives were synthesised in 1883 with the intent of developing dyes, and phenothiazine was used as an antiseptic and an anthelminthic before being withdrawn due to toxicity. Bovet in 1937 discovered the antihistamine properties of phenothiazine derivatives, and one of these derivatives, promethazine, is still used as an antihistamine today. Sedation was a known side effect of these drugs and Laborit in 1949, incorporated promethazine into his "lytic cocktail" which included a barbiturate and was intended to reduce post-operative shock. Charpentier synthesised chlorpromazine which is derivative of phenothiazine in the Rhône-Poulenc special research laboratories during research on potentiating agents in anaesthesia. Laborit discovered that this drug abolished preoperative anxiety and reduced surgical stress and postoperative shock. Laborit described the effects of chlorpromazine as inducing a state of indifference to the environment despite remaining alert and he labelled this state as "artificial hibernation" (Laborit & Huguenard, 1951).

Although it was Laborit who first identified the effects of this drug and had tried to interest psychiatrists in using the drug within their speciality, it is not him but Delay and Deniker who take the credit for the introduction of

chlorpromazine into psychiatry. Delay and Deniker first reported their results of using chlorpromazine in 1952 (Delay, Deniker, & Harl, 1952), and at the first international conferences held in Paris and Milan in 1954 in October 1955 which confirmed the indication of chlorpromazine for chronic psychoses. After this, neuroleptic usage became widespread and today almost all patients with psychotic symptoms are treated with neuroleptic drugs.

The impact of neuroleptic drugs on the course of schizophrenia has been accredited with major success by some psychiatric texts. For example Croyden Smith states that the introduction of phenothiazine drugs resulted in briefer periods in hospital and fewer patients in mental hospitals with the numbers of inpatients falling since that time (Croyden-Smith, 1982). Iverson and Iverson in 1981 claimed that the neuroleptic drugs had a dramatic impact on psychotic illnesses and that in the pre-neuroleptic era, mental hospitals were largely custodial in function. They state:

> "Since the introduction and widespread use of neuroleptic drugs, the in-patient population of such hospitals has declined dramatically".

These authors also assert that the neuroleptic drugs have a specific action on psychotic symptoms and do not have their main effect by simply "tranquillising" recalcitrant patients.

If the early reports of the effects of neuroleptic drugs are examined, however, these kinds of dramatic effects were not common-place. Undoubtedly, neuroleptic drugs were a break-through compared to treatments used in psychiatric hospitals at that time, which did not have great efficacy, and were

associated with a large number of adverse effects. Neuroleptic medication significantly reduced relapse of psychotic symptoms and rehospitalisation. At the point when neuroleptic drugs were introduced, the main physical treatments employed in psychiatric hospitals were insulin shock treatment, electroconvulsive therapy and barbiturates as well as physical restraints such as the strait jacket. Bellack in 1958 after seeing chlorpromazine in clinical use for four years had some interesting observations about the introduction of the phenothiazines into psychiatric hospitals. He made the observation that in psychotic patients treated with promazine the hallucinations did not disappear, but that individuals' emotional and physical reactions to the hallucinations were diminished. He also stated that

> "undoubtedly some proportion of improvement from drugs is due to the increased interest and attention of hospital personnel".

Bellack also perceived one advantage of the new drugs to be an elevation in staff morale. In his book, he produced a table of results for the treatment modalities used at that time. Although this cannot be viewed as an accurate or scientific study, due to the lack of double blind placebo controlled methodology it is presented here in order to give an example of the opinion of an eminent psychiatrist of the time;

Table 2.1 To Show Historical Perspective of Neuroleptic Efficacy

Type of Treatment	Number of patients treated	%complete recovery /social remission
Custodial	11 080	19
Electric shock	7 357	29
Insulin coma	9 483	48
Lobotomy	1 211	18
Chlorpromazine	2 718	38
Reserpine	1 269	25

This table seemed to suggest that the neuroleptic were responsible for complete recovery in only 38% per cent of patients treated with them which is 10% per cent less than those who recovered when treated with insulin shock treatment, a treatment which is now obsolete. One reason for this low rate could be that lower doses of neuroleptic were used in the early days, however it cannot be said that all psychiatrists hailed neuroleptics as a dramatic improvement on traditional treatments when they were introduced. Sir Aubrey Lewis was another contemporary psychiatrist who expressed the opinion:

> "If we had to choose between abandoning the the industrial rehabilitation centres and other social facilities available to us there would be no hesitation about the choice - the drugs would go"

(Lewis, 1959).

Lehmann and Hanrahan (1954) described the main effects of chlorpromazine as being a pronounced inhibitory effect on the central nervous system and that patients who previously presented management problems or were assaultive, became tractable when treated with chlorpromazine. They stated that patients treated with chlorpromazine displayed a lack of spontaneous interest in the environment and tended to remain silent and immobile, answering questions in slow monotone. These observations are similar to the early descriptions by Delay and Deniker, the psychiatrists who pioneered chlorpromazine. Interestingly Lehmann and Hanrahan provide what is probably the first description of neuroleptic induced dysphoria as follows:

> "Some patients dislike the treatment and complain of their drowsiness and weakness. Some state that they feel 'washed out,' as after an exhausting illness, a complaint which is indeed in keeping with their appearance."

This effect was seen however without a clouding of consciousness. Although some patients complained of tiredness, higher psychic functions were preserved such as sustained attention, reflection and concentration. This was a major advantage over the barbiturates which markedly impaired higher functioning. Lehmann and Hanrahan in this study report the treatment of 71 psychiatric patients, and their findings indicated that the chlorpromazine was most effective in the treatment of manic depressive patients in the manic or hypo-manic state. They stated that most of the patients who showed no lasting improvement with chlorpromazine were chronic schizophrenics and that they did not observe a direct influence of the drug on delusional systems or on hallucinatory phenomena.

There seems to be a discrepancy between the original early reports of the effects of neuroleptic treatment and the later psychiatric texts which describe their revolutionising impact. It is difficult to summarise the effect neuroleptics had on the outcome of schizophrenia as there were a number of changes in social policy at the time of introduction of neuroleptic drugs. It is known that the numbers of patients detained in psychiatric hospitals declined during the 1950's, but this decline started before the use of neuroleptic drugs in psychiatric hospitals so it is difficult to ascertain the precise effects of the drug. The proportion of schizophrenic patients living in the community before 1940 was approximately 50 to 55%, and this rose to more than 70% in the post war period. After the introduction of neuroleptic drugs this trend continued with about 85% of patients out of hospital at that time (Warner, 1985).

Another consideration is that although less psychiatric patients were

physically detained in hospital, it does not mean necessarily that their quality of life was better. The evidence from 68 follow up studies of outcome in schizophrenia suggests that the number of schizophrenic patients who fully recover has not changed since 1900 (Warner, 1985). Other authors have analysed data from twelve follow up studies, each spanning at least ten years, and found that the complete recovery rate has not changed since 1908 when Bleuler first coined the term schizophrenia (Stephens, 1970; Tsuang, 1982). In 1965 McLaughlin presented the effects of initiating neuroleptic drug treatment in a group of 100 psychiatric patients in a Philadelphia clinic. He presented clinical data on patients for eight years prior and eight years subsequent to treatment with neuroleptic drugs. McLaughlin observed that one of the most significant outcomes from the introduction of neuroleptics was the reduction in the time needed to manage psychiatric patients. In their clinic, the time needed for personnel to counsel patients was reduced from 3 hours to 45 minutes per month after the introduction of new drugs . They found that the hospitalisation rate was the same for the eight years before and after the introduction of neuroleptic treatment and that patient's adjustment to their environment remained unchanged. Ellsworth & Clayton (1960) studied discharge and readmission before and after the introduction of neuroleptics. These authors found no statistical difference between the neuroleptic and pre-neuroleptic era in terms of lengths of hospitalisation and return rate, but did find that with the use of neuroleptics wards were quieter and less ECT was used. Another important factor to consider is that although the number of hospitalised psychiatric patients decreased after the Second World War in the UK, the number of hospitalised patients in other European countries increased after the introduction of neuroleptic drugs. For example in 1951 the number of

psychiatric beds in Belgium was 19, 841 and by 1970 this figure had increased to 26, 841 (Pilgrim & Rogers, 1993).

A number of important points emerge from the inspection of these early studies. Firstly, although the introduction of neuroleptics was a pharmacological breakthrough, they were not developed with a specific pathophysiological theory in mind, and they were used initially in all psychiatric patients. They did not exhibit a uniform and predictable specific effect on psychotic symptoms or schizophrenia. They were not curative and their effects were ameliorative, often limited and unpredictable. Later the neuroleptic drugs were found (amongst many other pharmacological effects) to block dopamine receptors and it is this fact which is one of the cornerstones of dopamine theory which has been used in the search for more effective and selective neuroleptic drugs. Since the 1950's there have not been major advances in the drug treatment of schizophrenia (see later) and chlorpromazine remains the most widely used drug in the treatment of psychoses in the United Kingdom. This is quite unusual; in other areas of medicine major advances have been made, for example in the treatment of hypertension, where older drugs have fallen into disuse. Perhaps the reason for this is that dopamine blockade is not the major mechanism of action of these drugs and thus the reason for the improved effects of novel drugs (such as risperidone which is less selective at blocking dopamine receptors and more effective at blocking e.g. $5HT_2$ receptors) on the negative symptoms of schizophrenia. After many years of use of neuroleptic drugs, the mechanism of action of these drugs in treating psychoses is no clearer today than in the early 1950's, when chlorpromazine was first used in psychiatric patients.

2.2.2 Efficacy of neuroleptics in Treating Schizophrenia

There is a large body of evidence in numerous double-blind placebo controlled trials that neuroleptic medication is effective in the treatment of acute psychotic symptoms and in the prophylaxis of schizophrenia. Several reviews of placebo controlled studies show that neuroleptic medication is significantly superior to placebo in preventing psychotic relapses (Davis, 1975; Davis, Schaffer, Killian, Kinard, & Cahn, 1980; Kane & Lieberman, 1987). It has been consistently shown that the relapse rate in the first year following hospitalisation can be reduced from approximately 70% to 40% with the use of neuroleptic medication (Hogarty, 1993). The majority of clinical trials carried out have assessed response to neuroleptics in terms of clinical efficacy eg.. in reducing scores measured using the Present State Examination or the Positive and Negative Syndrome Scale. Although these measures are important validated tools for measuring psychotic symptoms, they do not include items which reflect the patient's point of view as they do not include any measure of quality of life.

2.2.3 Pharmacological Effects and Mechanism of Action of Neuroleptic Drugs

The pharmacological effects of neuroleptic drugs are diverse which confounds attempts to clarify their mechanism of action in relieving psychotic symptoms. The neuroleptics have been studied extensively with regard to their pharmacological effects and much of this experimental work has been carried out in animals. Neuroleptic drugs are known to demonstrate antihistaminic,

antiserotonergic, anticholinergic, antiadrenergic and antidopaminergic properties. These effects are thought to be responsible for the physiological and adverse effects of neuroleptic drugs. Whilst all neuroleptics are known to have some selectivity for these receptors in the brain, individual neuroleptics vary in both the extent to which they block each receptor type, and the site of action in the brain where they have an effect. For example thioridazine has a greater anticholinergic effect than other neuroleptic drugs and this results in a reduced prevalence of extrapyramidal side effects. Thioridazine also has a greater antiadrenergic effect than other neuroleptic drugs and this is thought to contribute to the high incidence of adverse sexual side effects associated with the drug (Kotin, Wilber, & Verburg, 1976). The antiemetic action of neuroleptic drugs is a consequence of blockade of dopamine receptors in the chemoreceptor trigger zone of the vomiting centre in the medullary region of the brain stem. Blockade of dopamine receptors in the nigrostriatal pathway leads to the development of extrapyramidal side effects such as parkinsonism and dystonias, and blockade of cholinergic receptors in the same pathway lead to a reduction in these effects. In a drug free state dopamine receptors in the tuberoinfundibular tract inhibit the release of prolactin, which is the hormone that stimulates milk production in mothers following childbirth. As neuroleptic drugs antagonise dopamine, this leads to reduction of inhibition of prolactin and increased levels of this hormone can lead to some of the hormonal side effects including amenorrhoea, gynaecomastia (breast growth) and galactorrhoea (milk production). The antihistamine properties of these drugs are thought to contribute to the sedative effects typical in patients treated with them.

In 1963 Carlsson and Lindqvist discovered that neuroleptic drugs increased the turnover of dopamine and noradrenaline and suggested that they did so by blocking post-synaptic catecholamine receptors. Carlsson and Lindqvist demonstrated a positive correlation between the clinical potency of neuroleptics and dopamine metabolism. It is now well established that despite the diversity in chemical structures, the traditional neuroleptic drugs do share one property, and that is blockade of dopamine receptors. At least eight subtypes of dopamine receptors have been proposed and recent advances in molecular biology have allowed the identification and characterisation of five neuronal dopamine receptor genes D_1 to D_5 (Sunahara, et al., 1993). The best known dopamine receptor types are D_1 and D_2. The classification of each receptor was based on the fact that D_1 receptors are positively coupled to adenylate cyclase and D_2 receptors are negatively coupled to adenylate cyclase (Kebabian & Calne, 1979). For many years the antipsychotic effect of neuroleptic drugs has been attributed to the blockade of D_2 receptors, corroborated by evidence that affinity for striatal dopamine D_2 receptors correlated with average clinical dose (Seeman & Lee, 1975). The theory for the clinical effects of neuroleptics being mediated by D_2 receptors has been questioned in recent years. The evidence that D_2 blockade is not the principle mechanism of action of neuroleptic drugs includes the fact that Clozapine, an atypical neuroleptic which has much less activity at D_2 receptors than traditional drugs, is a more effective antipsychotic (Kane, Honigfeld, Singer, & Meltzer, 1988). Although the focus of research to discover new neuroleptic drugs has rested on D_2 blockade for many years, there were indications that this should not necessarily have been the main line of research. For example

behavioural, biochemical, and electrophysiological evidence suggests that such a blockade occurs immediately after the administration of the first dose of a neuroleptic drug. Indeed positron emission tomography has shown that maximal occupancy of dopamine D_2 receptors is attained within a few hours of ingestion of a modest dose of haloperidol (Nordstrom, Farde, & Halldin, 1992). However in clinical practice improvement of psychotic symptoms and development of neurological side effects often takes several weeks of repeated administration of a neuroleptic drug, implicating a time dependent process in their mechanism of action. Another line of evidence which suggested that D_2 receptors were implicated in neuroleptic response was from post-mortem studies which demonstrated increased numbers of D_2 receptors in the brain tissue of schizophrenic patients. However positron emission tomography (PET) imaging studies have shown that D_2 receptor upregulation does not occur in young untreated schizophrenic patients and is therefore thought to occur as a result of drug treatment rather than an underlying pathological defect (Farde, et al., 1987). One problem is that the function of dopamine systems within the brain is not clear. Malfunctioning in nigro-striatal dopaminergic system is associated with neurological disorders characterised by movement abnormalities and in the mediation of extrapyramidal side effects of neuroleptic drugs. Another piece of evidence which conflicts with dopamine D_2 receptor blockade being the mechanism of action of antipsychotic drugs is that PET studies have demonstrated that lack of therapeutic response is not related to a lack of occupancy of D_2 receptors (Wolkin, et al., 1989). It has been suggested that the meso-limbic and meso-cortical pathways (involved in mood) are involved in the pathogenesis of schizophrenia ,and drug industries are directing research into

drugs which have a differential effect in these areas, as they are thought to have more of an effect on negative symptoms. For example clozapine exerts selective effects on meso-limbic dopamine neurones rather than striatal dopamine neurones and there is much interest in this (Lieberman, 1993).

2.2.4 Indications and clinical use of neuroleptic drugs

The indications for prescribing neuroleptic drugs include; schizophrenia, schizoaffective disorder, acute mania, Gilles de la Tourette syndrome, emesis (particularly concomitant use with an opiate analgesic in terminal care), agitation and/or anxiety symptoms (short term), challenging behaviour and intractable hiccup. Clinically the main use of neuroleptics is in the treatment and control of psychotic symptoms and in the prevention of their relapse. Neuroleptics have been shown to be significantly effective in acute episodes of schizophrenia (Cole, Kleberman, & Goldberg, 1964) and to be significantly superior to placebo in preventing relapse (Leff & Wing, 1971).

Whilst the neuroleptics reduce relapse they do not prevent relapse in all patients. In placebo controlled trials it has been estimated that over a twelve month period 30% of patients prescribed neuroleptics will relapse and 70% of patients prescribed placebo will relapse in the same time period (Davis, 1975; Kane & Lieberman, 1987; Rifkin, Quitkin, Rabiner & Klein, 1977). One problem with citing these figures, is that relapse is difficult to define and when considering just one parameter of an individual's life such as readmission to hospital, many other factors which affect a person's quality of life may be overlooked. Davis and Garver in 1978b summarised the results of 207

double-blind trials of neuroleptics compared to placebo and found neuroleptics to be superior to placebo in 86% of trials. There were 66 trials comparing chlorpromazine to placebo and 11 of these did not show a significant improvement. However in all studies which used a dose of chlorpromazine of at least 500mg per day, chlorpromazine showed a significant effect, suggesting that inadequate doses were used in some of the trials.

2.2.5 Response to Neuroleptic Drugs

Whilst neuroleptic drugs are the primary treatment of schizophrenia, there is a notable diversity in the response of individuals to treatment. There is a spectrum in the quality and quantity of the response to treatment. Approximately 20% of patients will remain floridly psychotic despite adequate neuroleptic dosage and plasma levels (Hollister & Kim, 1982; Rimon, Averbuch, Rozick, Fijman-Danilovich, Kara, Dasberg, et al., 1981). A considerable number of schizophrenic patients experience persistent delusions and hallucinations despite continued treatment with neuroleptic medication (Curson, Barnes, Bamber, Platt, Hirsch, & Duffy, 1985; Silverstein & Harrow, 1978). Of those that do respond, some will have a complete remission of symptoms, whilst others will still experience psychotic symptoms such as auditory hallucinations but will suffer less distress as a result of taking neuroleptic drugs.

2.3 Factors related to neuroleptic response

Numerous studies have investigated a multitude of factors in the hope of identifying predictors of neuroleptic response. So far, these results have been

bewildering and inconclusive, and the only factor with consistent predictive value is past response to a particular drug (Kolakowska, Williams, Arden, Reveley, Madelbrote, Jambor, et al., 1985). This has implications for prescribing and clinical use of neuroleptics. For example it is not possible for a prescriber to target a particular drug to an individual, or to predict whether a patient will respond fully, partially or not at all to treatment. Prescribing neuroleptic drugs for schizophrenic patients is therefore very much a matter of trial and error.

2.3.1 Comparative Efficacy of Individual Neuroleptic Drugs

A number of double blind placebo controlled trials have been carried out to investigate the relative efficacy of differing neuroleptics in schizophrenia but none of the traditional neuroleptics has been found to be consistently different to any other in terms of their efficacy on specific symptoms, syndromes or types of schizophrenia sub-groups (Hirsch, 1986). However Clozapine has been shown to be more effective than chlorpromazine in treating previously non-responsive schizophrenics (Kane, et al., 1988).

There is no clear relationship between serum concentrations of neuroleptics and clinical response (Van Putten, Marder, Wirshing, Aravagiri, & Chabert, 1991). Neuroleptic plasma levels can be affected by a number of pharmacokinetic variables and for the same dose of chlorpromazine 100-fold differences in plasma concentrations have been observed between individuals. Despite this plasma concentrations are said to account for less than 10% of the variation in clinical response (Lader, 1979).

2.3.2 Response of Individual Symptoms to Neuroleptic Drugs

Brown & Herz (1989) concluded that specific symptoms of schizophrenia are not reliably or powerfully associated with neuroleptic responsiveness and resistance. Crow in 1980 subdivided schizophrenic symptoms into two main types which differed in their response to neuroleptic drugs (Crow, 1980). Type I was characterised by positive symptoms particularly hallucinations, bizarre behaviour and thought disorder. These symptoms were of a more acute nature, responded well to neuroleptic treatment and intellectual impairment was absent. The putative pathology for this condition proposed by Crow was an increase in dopamine receptors. Type II was characterised by negative symptoms such as blunted affect, withdrawal, loss of drive and poverty of speech. In this case the response to neuroleptics was poor and intellectual impairment was sometimes present. The postulated mechanism for this type was cell loss and structural brain changes.

Although negative symptoms are widely regarded as being less responsive to neuroleptic drugs than positive symptoms (Lydiard & Laird, 1988), there are some studies which indicate that negative symptoms do respond to neuroleptic treatment (Goldberg, 1985). However some studies have shown that a dose reduction of neuroleptics brings about an improvement in blunted affect, emotional withdrawal and psychomotor retardation, suggesting that neuroleptic drugs may exacerbate negative symptoms (Kane, Rifkin & Woerner, 1986; Marder, Van Putten, Mintz, McKenzie, Lebell, Faltico, et al., 1984). One problem with comparing the results from different studies in this respect is that there is not uniformity in methods of assessment of negative

symptoms, and also in general design.

Mazure (1992) found that the symptoms which were significantly reduced after ten days of treatment of perphenazine were hallucinations, conceptual disorganisation and disorientation. This study investigated the relationship between serum concentration and response and found that improvement in two positive symptoms, hallucinations and conceptual disorganisation was related to perphenazine serum levels. Interestingly this study found that patients with a diagnosis of schizophrenia responded least well to perphenazine treatment, compared to other diagnostic groups such as manic depressive psychoses.

As well as differences in the response to psychotic symptoms according to symptom types, there are also differences according to an individual patients temporal course of symptomatology. For example Hill et al in 1992 found that patients with a recent onset of illness did not show a reduction in withdrawal-retardation scores on the Brief Psychiatric Rating Scale (BPRS). This contrasted with recurrent admission patients (who had at least a three year history of schizophrenia) who demonstrated a significant reduction in withdrawal-retardation scores (Hill, Keks, Jackson, Kulkarni, Hannah, Copolov, et al., 1992). In another study fifty chronic schizophrenic patients "with severe residual psychopathology" were followed up over a five year period (Beckmann, Fritze, & Franzek, 1992). It was found that over this five year period positive symptoms were unchanged in quality and severity in 60% of these patients and in 28% of these positive symptoms had persisted for more than twenty years despite neuroleptic treatment. Beckmann et al. concluded that for this group

the neuroleptic had only an unspecific effects on affectivity.

2.3.3 Patient Characteristics Associated with Good Response

A number of factors have been investigated for their predictive value of neuroleptic response, including; sociodemographic, disease related, neurocognitive and biochemical variables. The results from these studies are neither conclusive nor consistent but there are some variables which have been associated with better response. For example severity of positive symptoms at admission, reduced serum dopamine-ß-hydroxylase and good pre-admission social functioning have been associated with good response to neuroleptic drugs. Conversely family history of schizophrenia, impairment of working ability one year pre-admission and duration of previous admission have been found to correlate negatively with neuroleptic response (Bartko, Frecska, Horvath, Zador, & Arato, 1990; Klein, Rosen, & Oaks, 1973). Nimgaonkar Wessely, Tune, & Murray (1988) carried out a prospective study to investigate the contribution of biological factors such as ventricular enlargement, family history and obstetric complications in predicting neuroleptic response, but these failed to account for variability in response whereas early age of onset was predictive of poor response. This finding that more advanced age at first hospitalisation correlates with better response has been corroborated (Bartko, et al., 1990).

2.3.4 Psychological Factors Implicated in Response to Neuroleptics

Psychological variables may be implicated in patients' responses to

neuroleptics. Such variables may have a direct effect, in the sense that they may be implicated in symptoms and also responsive to medication, or they may have an indirect effect, in the sense that they may influence whether patients take their medications and thereby benefit from them. This latter issue, traditionally denoted by the term 'compliance', will be considered in Chapter 3.

There has been limited research into direct psychological mediators of drug response. However, evidence relevant to this question can be obtained from two sources. First, a number of researchers have attempted to compare medicated and non-medicated patients, or the same patients when drug-free and when receiving medication, in order to explore relationships between the clinical effects of neuroleptics and cognitive abnormalities which may in part be responsible for schizophrenic symptoms. In a review of the relevant literature, Spohn & Strauss (1989) found that chronic schizophrenic patients given neuroleptic medication became less disordered in their thinking, showed a reduction in attention deficits and became less distractible. However, no evidence was found that neuroleptics led to an improvement in reaction time. Integrating these kinds of findings, a number of researchers have suggested that neuroleptic medication results in improvements in controlled or effortful cognitive processes but has relatively little impact on more basic automatic or perceptual processes (Earl-Boyer, Serper, Davidson, & Harvey, 1991; Harvey & Pedley, 1989; Killian, Holzman, Davis, & Gibbons, 1984; Oltmanns, Ohayon, & Neale, 1979).

A second intriguing line of evidence has emerged from studies of the role of psychosocial factors in psychotic breakdowns. Considerable evidence,

collected over many years, indicates that there is a relationship between life stressors and variations in psychotic symptoms over time; there is less clear-cut evidence that psychotic patients have experienced more stressors in their lives than the general population or people suffering from other kinds of psychiatric disorders (Norman & Malla, 1993a; Norman & Malla, 1993b). These findings have usually been interpreted in terms of a diathesis-stress model, which was reviewed in Chapter 1.

Further evidence of a relationship between medication and sensitivity to stress was collected by Leff and his colleagues, who studied chronic stress associated with being exposed to a high expressed emotion family environment. Vaughn & Leff (1976) found that patients exposed to such an environment were more likely to relapse over a nine month follow-up period. Those living in high 'Expressed Emotion' (EE) environments were more likely to relapse if unmedicated, but no significant difference was observed between the relapse rates of medicated and unmedicated patients living in low EE environments. The implication of this observation was that the medication protected patients against chronic stress. In a subsequent two year follow-up of the same cohort of patients, Leff & Vaughan (1981) observed that the advantage of medication for those living in high EE environments had disappeared, whereas those living in low EE environments now benefited from drugs. Leff and Vaughn interpreted this finding as indicating that adverse life events would provoke a relapse even in patients living in a benign environment unless they received medication. However, Johnstone (1993b) has recently questioned Leff and Vaughn's two year follow-up findings on methodological grounds.

These observations, together with the results of the studies of the relationship between medication and cognitive abnormalities described above, support the suggestion by Schooler & Spohn (1992) that neuroleptics achieve their positive effects, at least in part, by redressing attentional abnormalities and thereby increasing patients' ability to cope with stressful events.

Evidence from early work by Heninger et al in 1965 suggested that individuals personality factors may account for some variability in neuroleptic response (Heninger, Dimascio, & Klerman, 1965). This was a small study of sixteen normal male volunteers and the authors found that they could predict drug response according to the personality type of volunteers. Thus type A subjects whose personalities reflected more physically active, extroverted and low anxiety characteristics responded in an adverse way to phenothiazines, being more irritable, apprehensive and unhappy and became significantly more indifferent to their environment. Type B volunteers were initially more introverted intellectuals with higher anxiety levels and they responded well to phenothiazines, reporting reduced anxiety and increased rapport. Unfortunately little interest has been shown in this early work but it may be of interest to future researchers in searching for factors involved in neuroleptic response.

2.4 Prescribing Regimens

2.4.1 Neuroleptic Dosage

The clinical dosage range of neuroleptic medication is wide for example

the British National Formulary states that the dose of oral chlorpromazine in the treatment of schizophrenia can vary from 75mg to 1000mg daily. Reviews of the trials of low dose neuroleptic have indicated that doses of below 300mg chlorpromazine or equivalent are no more effective than placebo in the treatment of schizophrenia (Davis & Garver, 1978a). For example Kane, Rifkin & Woerner (1983) found that relapse rates on lower doses of 1.25 to 5mg of fluphenazine decanoate every two weeks were higher at 56%, when compared to higher doses of between 12.5 to 50mg fluphenazine decanoate which produced a relapse rate of 7%. However the low dose patients had a better outcome in terms of social adjustment as well as lower dyskinesia scores. Dosage reduction studies have reported mixed results. Leblanc, Cormier, Gagne, & Vaillancourt (1994) found that a gradual reduction of dosage from a mean of 62mg a day or equivalent of haloperidol to a mean of 30mg in 32 outpatients resulted in a significant decrease in BPRS negative symptoms and a significant increase in symptoms of tardive dyskinesia (which is known to worsen on reduction of neuroleptic dosage).

Whilst there is consensus regarding the reduced efficacy of lower doses of neuroleptics there is more controversy when high or mega dose regimens are considered. Prien & Cole (1968) in a randomized trial of 838 chronic schizophrenics found that a sub-group of 25% who were below the age of forty and had been prescribed neuroleptic medication for less than ten years, responded better to 2000mg of chlorpromazine daily than to 300mg daily. Cookson, Muthu, George, & Dewey (1983) carried out a double blind crossover study in 30 male chronic schizophrenic in-patients who had shown a poor response to conventional doses. In this study Cookson et al. showed

advantages for a dose of 200mg flupenthixol two weekly compared with 40mg flupenthixol 2 weekly, in terms of symptom reduction. The same authors concluded that high dose neuroleptics are not associated with increased incidence of suicide, side effects and sudden death, and that quality of life is improved in those who respond to high doses. Aubree & Lader (1980) in a review of 14 controlled trials concluded that high doses of neuroleptics benefited a minority of psychotic patients possibly due to pharmacokinetic factors, but this was at the expense of increased extrapyramidal side effects. Mega-dose regimens have been tried particularly in the treatment of refractory psychosis. For example Quitkin, Rifkin, & Klein (1975) compared 1200mg of oral fluphenazine daily (equivalent to chlorpromazine 100000mg daily) to 30mg fluphenazine (equivalent to 2500mg chlorpromazine daily). Wijsenbeck, Steiner, & Goldberg (1974) compared 600mg trifluoperazine (equivalent to 21400mg chlorpromazine) with 60mg trifluoperazine (2140mg chlorpromazine). McClelland, Farquharson, Leyburn, Furness, & Schiff (1976) compared 250mg of depot fluphenazine weekly with 12.5mg weekly. None of these studies found any therapeutic advantage for the megadose regimen. The recommended dosage of neuroleptics and the doses prescribed for schizophrenic in and out patients has increased over the years. When haloperidol was introduced the maximum recommended dose was 15mg, and the current British National Formulary recommends a maximum of 100mg daily and rarely 200mg daily (September 1994). Van Putten, Marder, & Mintz (1990) carried out an interesting study comparing three doses of haloperidol; 5mg, 10mg or 20mg per day in 80 schizophrenic patients recently admitted as in-patients. Van Putten et al. found that the 20mg daily dose was superior to the lower doses in reducing symptoms in the first two weeks of the study but not thereafter. After this time

the 20mg daily group deteriorated on withdrawal-retardation scores measured using the Brief Psychiatric Rating Scale (BPRS) in comparison with the lower dosed groups. Furthermore, 35% of patients in the 20mg per day group insisted on leaving the hospital against medical advice as compared with only 4% of those patients receiving 5mg or 10mg daily. These authors concluded that a dose of 20mg haloperidol per day was associated with substantial psychotoxic effects by the second week of treatment. McEvoy, Hogarty, & Steingard (1991) also found no therapeutic advantage of higher haloperidol doses in terms of psychotic symptoms in a double blind trial in 106 schizophrenic patients. However this study demonstrated a greater decline in BPRS hostility scores which very nearly reached statistical significance ($p = 0.06$) in the higher dosage group. Higher doses were also associated with significantly more extrapyramidal side effects and significantly more dysphoria. A number of other studies have not demonstrated any benefit in increasing the daily dosage of neuroleptic above 600mg chlorpromazine or equivalent even in previously treatment resistant patients (Gardos, Cole, & Urzac, 1973; Hirsch, 1986; Kane, 1989).

The current consensus is that high doses of neuroleptics, particularly above BNF recommended doses, have no therapeutic advantage in the treatment of schizophrenia. This was highlighted in a recent document published by the Royal College of Psychiatrists "Consensus statement on the use of high dose antipsychotic medication" (1993), which included guidelines for the prescription of high doses (including regular monitoring of patients prescribed high doses) and recommended that high doses should only be used as a last resort. Bollini, Pampallona, Orza, Adams, & Chalmers (1994) recently

reported a meta-analysis of 22 published randomised controlled trials comparing neuroleptic doses, and concluded that doses above 375mg chlorpromazine daily or equivalent did not provide any clinical superiority in the maintenance treatment of schizophrenia, but were associated with a significant increase in adverse reactions.

2.4.2 Intermittent Versus Maintenance Regimens

There has been debate for a number of years concerning the advantages and disadvantages of intermittent versus continuous maintenance medication in the treatment of schizophrenia. This debate was initiated in the early 1980's when concern was growing about the long term risks of developing the potentially irreversible side effect of tardive dyskinesia. There was also concern that maintenance neuroleptic medication may worsen negative symptoms and impair social functioning. Huber, Gross, Schuttler, & Linz (1980) stated that for a large proportion of schizophrenic patients (40%) the most common outcome was a non-psychotic deficit state characterised by blunted affect and apathy, which remained unresponsive to treatment. As a result of these concerns it was hypothesised that intermittent rather than continuous maintenance medication would be of greatest benefit to the outcome of schizophrenic patients. The design of these studies has varied considerably and some of the studies have been poorly controlled. Some studies have included criteria for identifying prodromal symptoms, such as sleep disturbances, nervousness or depressed mood, which are thought to precede full blown psychotic symptoms. Once prodromal symptoms are identified, medication is restarted in order to prevent the emergence of psychotic symptoms.

One of the earliest pilot studies was carried out in a small number of patients by Herz, Szymanski, & Simon in 1982. In this study the dose of neuroleptic in nineteen patients was slowly reduced to zero over an eight week period. Patients attended group therapy and were closely monitored for prodromal signs. If prodromal signs occurred medication was reinstated until the patients remained stable for at least two weeks at which point it was withdrawn. Ten patients remained stable on the intermittent medication protocol over an average of eight months follow-up. Thus these authors indicated that further work in this area would be justified.

Further and more substantial work was carried out by Carpenter, Heinrichs, & Hanlon (1987) and this study compared continuous versus intermittent medication in a group of forty-two schizophrenic outpatients. This study was not blind, that is raters knew which experimental condition each patient was in. In the first year of the study, hospitalisation rates were found to be higher in the intermittent group. However the final outcome after two years in terms of social and work performance and symptomatology was the same for both groups. Unfortunately this study was not well controlled, as the intermittent group received a significant psychosocial intervention, which included contact with a therapist for forty five minutes per week throughout the study. The continuously medicated group saw a pharmacotherapist briefly for a short period of time every two weeks, which is not an adequate control condition. Therefore it is difficult to conclude from these results that intermittent and continuous medication produce the same outcome as the psychosocial intervention was a confounding factor. Jolley, Hirsch, Morrison, McRink, & Wilson (1990) carried out a more carefully controlled study by

comparing continuous versus intermittent medication in a double blind study carried out in 54 schizophrenic outpatients. In this study patients received either placebo or active drug in the form of a depot injection and all patients received active oral medication for the treatment of prodromal symptoms. This study found that 62% of the intermittent compared to 16% of the continuously medicated group relapsed over a two year follow up and this difference was statistically significant. The intermittent group experienced less extrapyramidal side effects (measured using a modified Simpson and Angus scale, 1970) at two years than the continuously medicated group and this difference also was statistically significant. There was no difference in overall social functioning (measured using the Social Adjustment Scale II) between the two groups throughout the study, although significantly lower scores were present in the intermittent group at baseline which may have compromised the results. These authors concluded that continuous medication was superior to intermittent medication in the maintenance treatment of schizophrenia.

Herz, Glazer, Mostert, Sheard, Szymanski, Hafez, et al. (1991) also carried out a two year double blind placebo controlled study 101 patients. Neuroleptic medication was withdrawn gradually over an eight week period ending with two weeks drug free and then patients were randomised to receive either active or placebo medication. All patients attended weekly group therapy and a monthly open family group meeting. Patients were dropped from this study if they had more than 3 prodromal episodes in one year or if they had an episode which lasted for more than 9 weeks. The proportion of patients dropped from the continuously medicated group was 14%, whilst the percentage dropout rate was 46% for the intermittent group. At two years 16% of the continuously

medicated group versus 30% of the intermittent group had relapsed although this difference was not statistically significant. This study differed from Jolley et al's research because although the intermittent group received significantly less medication than the continuously medicated group, there were no significant differences in side effects which were measured using the Abnormal Involuntary Movements Scale or AIMS (American Psychiatric Association, 1980b). One criticism of both of these studies is that the range of side effects measured was very narrow, concentrating on the extrapyramidal side effects. The Herz study also found that patients who had been prescribed oral medication prior to the study were more likely to relapse in the early stages than patients who had previously been prescribed depot medication. Although this difference was not statistically significant, the authors suggested that a two month withdrawal period may not have been a sufficient washout period for the depot preparation.

As a result of these studies the current consensus is that continuous maintenance medication is preferable, due to the higher risk of relapse when intermittent medication is prescribed for schizophrenic patients (Gaebel, 1994). However the alternative conclusion from these studies may be that the preferable treatment option is to prescribe intermittent treatment regimens alongside intensive psychosocial interventions as this may increase patient involvement and reduce adverse reactions. This option is often not carried out in clinical practice probably due to the increased need for training and personnel resources which would result from it's implementation. This is unfortunate as it has been shown that whilst neuroleptic medication improves relapse rates from approximately 70% to approximately 40%, the use of

psychosocial interventions can further reduce relapse rates to below 20% (Hogarty, 1993).

2.4.3 Oral Versus Depot Medication

Initially oral preparations of neuroleptic medication were the only dosage form available but in the 1960's depot medication was introduced. Depot medication is a suspension of neuroleptic medication in an oily base which is administered by deep intramuscular injection at intervals of 1 to 4 weeks. The drug is then released slowly into the body over a prolonged period. The introduction of depot neuroleptics was heralded as a major advance in the treatment of schizophrenia outside hospital (Daniel, 1968; Rasmussen, 1970). The major evidence for decreased relapse rates with depot medication stems from an article by Gottfries & Green (1974) which showed that relapse rates decreased dramatically in a group of 36 schizophrenic patients after being switched from oral to depot neuroleptic medication. Other proposed advantages of depot neuroleptics include the elimination of the first pass effect (metabolism of drugs in the liver subsequent to absorption from the gut), regular contact with mental health professional (usually community psychiatric nurse), stable plasma levels, purported to lead to better therapeutic effects and fewer side effects (Gerlach, 1994). Hirsch, Gaind, Rohde, Stevens, & Wing (1973) carried out a double blind placebo controlled trial of fluphenazine decanoate, controlling for non-specific effects of clinic attendance and demonstrated a superiority of depot medication to oral medication in reducing relapse rates. Although these preparations are widely believed to be associated with improved compliance and outcome for schizophrenic patients, this advantage

has not always been replicated in clinical trials. In two studies the relapse rate over a one year follow-up period, was similar at 30% for both orally and intra-muscularly administered fluphenazine (Rifkin, Quitkin, Rabiner, & Klein, 1977; Schooler, Lerme, Severo, Brauzen, DiMascio, Klerman, et al., 1980). Neuroleptic drugs can also be administered by other routes including intramuscular aqueous injection for the acute (often emergency) treatment of psychotic symptoms, liquid preparations and as suppositories.

2.5 Side Effects

The positive effects on psychotic symptoms have been described, but unfortunately the neuroleptics, similar to all pharmacological agents, produce a number of adverse effects. Although all neuroleptics can produce most of these side effects, some drugs are more likely to produce particular groups of side effects than others (See Table 2.2 for estimated side effect profiles of the most widely used compounds). For example, the butyrophenones such as haloperidol are more likely to produce extrapyramidal side effects than other neuroleptics, and thioridazine is associated with a high rate of sexual side effects compared with other drugs due to its high alpha adrenergic affinity. For this reason it should be possible to minimise side effects by carefully tailoring a drug to the individual.

In clinical practice, however, there are a number of reasons why it may be difficult to establish whether or not a symptom is an adverse effect of medication. In some cases it may be possible that the symptom is part the underlying disorder. Moreover, some side effects (for example, constipation) are

Drug	EPSE	Anti-Cholinergic	Cardiac	Hypo-tension	Sedation
Chlorpromazine	**	***	**	***	***
Thioridazine	**	***	*	***	**
Trifluoperazine	***	?	*	*	*
Sulpiride	*	*	?	?	*
Haloperidol	***	*	*	*	*
Flupenthixol	**	***	?	?	*
Fluphenazine	***	**	*	*	**
Clozapine	*	***	***	*	***

Table 2.2 Estimated relative side effect profile for commonly used neuroleptic drugs. The number of stars (*) indicates relative potency of drugs. There is a lack of well controlled studies so this table is intended only as a guide.
? indicates lack of data.

similar to the kinds of everyday complaints widely reported by relatively healthy non-medicated subjects. A further complication is that many patients are prescribed more than one type of medication, making it difficult to establish a causal relationship between a particular drug and a particular adverse response.

2.5.1 Neurological Effects

Neuroleptic drugs produce a number of neurological effects, the most common of which are of the extrapyramidal type. With the exception of the acute dystonias (prolonged muscle spasms), which are more common in men, women are most susceptible these kinds of adverse reactions. There are four main adverse reactions in this category:

(a) Parkinsonian side effects

Parkinsonian side effects include changes in gait, tremor, rigidity, hypersalivation, akinesia (slowing of movements), dysphagia (difficulty swallowing) and characteristic facies (a dazed or expressionless appearance which is often wrongly attributed to the underlying condition). It is not possible to differentiate between drug-induced Parkinsonism and classical idiopathic Parkinsonism. Parkinsonian effects are usually evident after 5 to 80 days of neuroleptic treatment and are reversible with the administration of anticholinergic drugs such as procyclidine. Various estimates have been given for the prevalence of drug-induced Parkinsonism, mostly ranging between 15 and 25 percent of patients (Ayd, 1961; Kennedy, Hershon, & McGuire, 1971).

(b) Acute dystonic reactions

Acute dystonic reactions are characterised by dramatic muscular spasms (or sustained tonic contractions of muscles or muscle groups), usually affecting the head and neck. Examples include oculogyric crisis in which muscles of the eye contract causing the eye to remain fixed in an upward stare, and spasmodic tortillosis in which muscles of the neck contract to cause a prolonged unnatural posture. These reactions are extremely distressing to those who experience them. They usually occur within the first five days of neuroleptic treatment, are more common in males and are quickly reversed by administration of intramuscular or intravenous anticholinergic drugs such as procyclidine. Younger individuals tend to be more susceptible to acute dystonias and the prevalence of this kind of reaction in neuroleptic treated patients has been estimated at about 10 percent (Swett, 1975).

(c) Akathisia

The term akathisia is derived from the Greek "unable to sit". Patients suffering this side effect experience an inner subjective restlessness which is often but not always accompanied by motor restlessness. In some cases, patients will constantly stand up and sit down in order to relieve inner discomfort. In severe cases they may shift continually from foot to foot or run from side to side. This adverse behavioural effect can be extremely distressing for a patient but it can also be mistaken for a worsening of psychotic symptoms, resulting in an inappropriate increase in the neuroleptic dosage. The prevalence rate for this type of side effect amongst treated patients has been estimated at

approximately 20 per cent (Ayd, 1961; Braude, Barnes, & Gore, 1983) although some authors have suggested that as many as 75 percent of patients may be affected (Van Putten, May, & Marder, 1984).

(d) Tardive Dyskinesia

Tardive dyskinesia is a late developing movement disorder which is often irreversible (Jeste & Wyatt, 1979). It is characterised by involuntary oro-buccal movements such as tongue protrusion, fly catching tongue, lip-smacking movements and lateral jaw movements. The aetiology and treatment of tardive dyskinesia remain equivocal. Widely differing estimates have been made for the proportion of neuroleptic-treated patients who eventually suffer from tardive dyskinesia, ranging from 0.5 percent to 65 percent (Simpson, Pi, & Stramek, 1982). The onset of the disorder is associated with increasing age, female gender and neuroleptic dosage (Kane & Smith, 1982; Muscettola, Pampallona, Barbato, Casiello, & Bollini, 1993). There is no proven treatment and withdrawing neuroleptics may exacerbate the condition. Tardive dyskinesia causes considerable concern for health professionals although not all patients feel a high level of distress as a result of this side effect (Rosen, Mukherjee, & Olarte, 1982).

2.5.2 Effects on Convulsive Threshold

In addition to the well known neurological side effects, neuroleptics often produce other kinds of adverse reactions. They may lower the convulsive threshold and thereby precipitate seizures, both in patients with a previous

history of seizures and in those previously seizure-free. This is most likely tooccur in patients given high doses of low potency neuroleptics, or following rapid dose changes (Toone & Fenton, 1977).

2.5.3 Anticholinergic Effects

As all neuroleptic drugs block muscarinic receptors in the CNS anticholinergic side effects are quite common, including dry mouth, constipation, blurred vision and urinary retention. These reactions are a particular problem in patients with pre-existing physical disorders such as glaucoma or prostatic hypertrophy. Some drugs such as thioridazine and chlorpromazine are more likely to cause anticholinergic effects due to their intrinsic selectivity for these receptors. Paradoxically, clozapine has a high affinity for muscarinic receptors but is associated with nocturnal hypersalivation. Overall, the prevalence of these kinds of side effects has been estimated at about 40 percent amongst treated patients (Lingjaerde, Ahlfors, Dech, Dencker, & Elgen, 1987).

2.5.4 Cardiovascular Effects

The most common drug-induced cardiovascular effect of neuroleptics is postural hypotension, which is related to a drug's capacity to antagonise alpha adrenergic receptors. Other cardiac effects include nonspecific ECG abnormalities, cardiac conduction defects and arrhythmias. There is an increase in sudden unexpected death due cardiac arrest in patients taking neuroleptic medication compared to matched non-medicated controls (Thorogood, Cowen,Mann, Murphy, & Vessey, 1992).

2.5.5 Hormonal Effects

Neuroleptics also induce hormonal and metabolic effects, mainly resulting in adverse consequences for sexual function and body weight. The sexual effects are primarily due to alpha adrenoceptor blockade and include orgastic dysfunction and reduced libido in both sexes and erectile dysfunction, ejaculatory dysfunction and priapism (permanent erection) in males (Segraves, 1988; Sullivan & Lukoff, 1990). The sparse research which exists overemphasises the adverse sexual effects for males. This could be a reflection of the fact that the majority of research has been carried out by male investigators.

Due to antagonism of dopamine receptors in the pituitary, neuroleptics elevate prolactin levels, often resulting in amenorrhoea (absence of menstruation in females), gynaecomastia (swollen and tender chest, which may occur in both males and females) and galactorrhoea (milk production, also in both sexes). Weight gain is also a common side effect of neuroleptic medication. Low potency neuroleptics such as chlorpromazine and thioridazine have a greater association with weight gain than higher potency drugs, and the gain in weight can be as much as 22 kg (50 lbs) (Gordon & Grotte, 1964). The mechanism of this side effect is not understood but it is thought that neuroleptics stimulate carbohydrate craving (Robinson, McHugh, & Follstein, 1975).

2.5.6 Haematological Effects

The most feared haematological consequence of neuroleptic medication, particularly the phenothiazines, is agranulocytosis (reduction in the white blood cell count) which has a 30 percent mortality rate (Edwards, 1986). It is reversible on discontinuation of the drug but due to its rarity and the commonality of its early symptoms (such as sore throat) it is often not recognised until it is well advanced. Agranulocytosis usually occurs within the first three months of treatment but may occur later. The estimated incidence rate varies from 1 in 3,000 to 1 in 250,000 patients (Meyler, 1992). However the incidence rises to 1-2 in 100 for clozapine (Shopshin & Feiner, 1983) which is the reason for strict monitoring of white blood cells in patients prescribed this drug.

2.5.7 Hepatic Effects

Neuroleptic drugs are predominantly metabolised in the liver and it is therefore not surprising that hepatic adverse effects have been reported. Hepatotoxicity was associated with chlorpromazine when it was first prescribed but fortunately has become a more rare reaction. Jaundice, which is particularly associated with the phenothiazines, may occur usually within the first two to four weeks of treatment and is thought to be an allergic reaction. Minor abnormalities as revealed by liver function tests have also been reported (Dickes, Schenker, & Deutsch, 1957).

2.5.8 Allergic Reactions

Neuroleptic drugs have been implicated in causing a number of skin reactions, including erythematous reaction (a red rash), morbilliform reaction (a measles-type rash), urticaria (itchy skin), exfoliative dermatitis (in which the skin flakes off) and photosensitivity reactions (which may require patients to use a sunblock to avoid sun burn even in winter months). Phenothiazines such as chlorpromazine are the most likely drugs to cause these reactions. After the administration of large doses of some neuroleptics, such as chlorpromazine and thioridazine over many years, a purple-blue pigmentation may accumulate in the skin and eyes (lenticular and corneal deposits and pigmentary retinopathy), in the latter case leading to visual impairment. These effects are usually reversible on withdrawal of the drug. In some cases a hypersensitivity syndrome is observed which includes bronchospasm (contraction of the airways) gastrointestinal symptoms, urticaria and cholestatic jaundice; again the phenothiazines have been particularly implicated in this kind of reaction (Edwards, 1986).

2.5.9 Miscellaneous Effects

The neuroleptics may affect mineral and fluid balance with water retention and oedema occurring rarely. Polyuria (excessive urination) and polydipsia (excessive drinking) are associated with the neuroleptics and are possibly caused by drug-induced dry mouth and/or direct stimulation of the hypothalamic thirst centre (Lawson, Karson, & Bigelow, 1985).

Neuroleptic malignant syndrome is a serious consequence of neuroleptic medication and is characterised by muscular rigidity, fever, fluctuating consciousness, hyperthermia, dyskinesia and autonomic dysfunction. It's presence can be mistaken for serious bacterial infection leading to inappropriate treatment with antibiotics. The condition is confirmed by the detection of raised serum creatinine phosphokinase and leucocytosis. Approximately 0.5 to 1% of patients experience this kind of reaction and the associated fatality rate is about 20 percent (Caroff, 1980). High potency drugs such as haloperidol are more likely to be implicated. Once the condition has been diagnosed the drug must be stopped and intensive monitoring of essential functions must be carried out, usually in an intensive care unit. Drugs used to treat this condition include dantrolene sodium (used for malignant hyperthermia) and bromocriptine (a dopamine agonist). The condition can persist for five to ten days after discontinuation of neuroleptics although this period may be prolonged (at least several weeks) if a depot preparation has been administered.

Another adverse effect of the neuroleptics which attracts considerable controversy is supersensitivity psychosis. This concept is based on the observation that some schizophrenic patients show a worsening of psychosis on withdrawal of neuroleptics and is thought to be mediated through dopamine receptor supersensitivity, for example via an increase in the number or affinity of dopamine receptors (Chouinard & Jones, 1980). However the evidence for the development of a supersensitivity psychosis in long term neuroleptic treatment has been questioned (Kirkpatrick, Alpha, & Buchanan, 1992).

2.6 Neuroleptic Induced Deficit Syndrome

The neuroleptic induced deficit syndrome (NIDS) is a term which is used to describe the state of emotional indifference and lethargy which is a consequence of consuming neuroleptic medication. The sedative action of the neuroleptics has been known since their introduction. This sedative effect can be a useful attribute of neuroleptic drugs, particularly where psychotic symptoms are associated with psychomotor excitation. However the need for such a sedative action is usually short-term clinically, and in maintenance treatment such an effect can be detrimental to well-being, quality of life and work output (Lewander, 1994). By reducing motivation and volition neuroleptic medication may also lessen the efficacy of other treatments such as psychotherapy, behavioural and cognitive therapy and may reduce the volition to seek work or reduce performance. Thus in a study by Crow, MacMillan, Johnson, & Johnstone (1986) the subjects who took neuroleptic medication achieved significantly less positive life events than those who did not take medication.

It has been acknowledged that is difficult to differentiate between the negative symptoms of schizophrenia and the NIDS (Lewander, 1994; Schooler, 1994). One possible way of discriminating between symptomatology and drug induced effects is to vary the dose of neuroleptic used. Thus if the effect were drug induced a dose reduction would result in improved volition and decreased dysphoria, whereas if the effect was a symptom of the underlying condition a dose reduction would result in a worsening of those symptoms. Unfortunately this is more complex than it may seem, as negative symptoms have been cited as

unresponsive to neuroleptic medication (Crow, 1980) although other authors contend that negative symptoms are at least partially responsive (Goldberg, 1985; Kane & Mayerhoff, 1989; Meltzer, Sommers, & Luchins, 1986). It would be useful to carry out further studies which use validated tools to evaluate negative symptoms as well as tools to evaluate neuroleptic induced dysphoria, before and after consumption of neuroleptics in previously neuroleptic naive individuals. Varying doses could then be used in order to investigate the contribution of neuroleptics to the deficit syndrome.

Some authors have commented on the lack of research carried out to investigate the NIDS and have called for more systematic and objective research to be carried out (Lewander, 1994). The syndrome has been known since the introduction of chlorpromazine to psychiatry and has been also referred to as neuroleptic dysphoria (Emerich & Sanberg, 1991), akinetic depression (Van Putten & May, 1978b) and the subjective aspects of akathisia (Van Putten & May, 1975). It is probable that the reason for the lack of objective research and practitioners reluctance to seriously address the issue of the NIDS is the range of terms used to define the condition and the overlap with general psychological symptoms. This leads to a lack of objective assessment and this in turn makes causality difficult to assess. Further confusion results and many practitioners assume lack of volition and dysphoria to be a consequence of schizophrenia rather than a cause of the drugs prescribed to treat it. Unfortunately there is not a generally accepted definition of the neuroleptic induced deficit syndrome and it is not widely recognised as a clinical problem in the United Kingdom.

The clinical significance of the NIDS cannot be underestimated in terms of treatment outcome. The NIDS has been implicated as a major reason for non-compliance with neuroleptics (Van Putten & May, 1978a; Weiden, Shaw, & Mann, 1986) and as discussed in Chapter 3, non-compliance with neuroleptic medication has a significant negative impact on clinical outcome.

2.7 Treatment of Extrapyramidal Side Effects with Anticholinergic Drugs

Initially, parkinsonian side effects of neuroleptic drugs, which are indistinguishable from symptoms of non iatrogenic parkinsons disease, were treated with the drugs traditionally used to treat parkinsonism. The first drug to be used was L-dopa, which is the precursor to dopamine, and has it's effect by correcting the dopamine-cholinergic balance in the nigro-striatal pathway which is responsible for motor control. Unfortunately L-dopa was found to have a detrimental effect on patient's mental state (Yaryura-Tobias, Diamond & Meris, 1970). Due to the possible exacerbation of delusions and hallucinations by L-dopa, which can also occur in people who have never previously suffered from those symptoms, it is not routinely used in clinical treatment of extrapyramidal side effects today. Anticholinergic drugs such as procyclidine and benzhexol are widely used in the treatment of extrapyramidal side effects, although surprisingly there is not an abundance of objective evidence to support their use. One of the earliest double-blind placebo controlled trials was carried out by Strang (1965) and found that procyclidine was more effective than placebo in the treatment of parkinsonism. A study by Mindham, Lamb, & Bradley (1977) demonstrated that procyclidine but not piribedil was more effective than placebo in the treatment of phenothiazine induced parkinsonism.

A number of other studies have shown anticholinergic drugs to be effective treatment of neuroleptic induced extrapyramidal effects (Bezchlibnyk-Butler & Remington, 1994). However trials to assess the efficacy of agents in the treatment of extrapyramidal side effects are associated with a number of methodological difficulties. For example there are inherent differences in the extrapyramidal potency of neuroleptics, which may mean that different placebo controlled trials are necessary for each different neuroleptic. In a number of studies it is assumed that volunteers are consuming the neuroleptic agent prescribed for them and the fact that they may not is often not controlled for. This assumption is also held for the antiparkinsonian drug which further compounds the interpretation of results. Whilst drug induced parkinsonism and dystonias generally show a favourable response to anticholinergic medication (Ayd, 1961; Goff, Arana, Greenblatt, Dupont, Ornsteen, Harmatz, et al., 1991a), research has shown that akathisia may respond more favourably to lipophilic beta blockers such as propranolol (Lipinski, Zubenko, & Cohen, 1983). Another drug which has shown to be useful in the treatment of extrapyramidal side effects is amantadine which is a dopamine agonist (Ananth, Sangani, & Noonan, 1975).

There has been considerable debate over the prophylactic use of anticholinergic medication for neuroleptic induced extrapyramidal reactions and there is no current consensus. A number of clinicians endorse the use of prophylactic antiparkinsonian drugs in order to prevent the emergence of extrapyramidal side effects or sub-clinical extrapyramidal effects which may be associated with premature discontinuation of medication (Manos, Levrentiadis, & Gkiouzepas, 1986; Rifkin, Quitkin, Kane, Struve, & Klein, 1978; Saran, 1986).

Some clinicians are wary about the use of prophylactic antiparkinsonian drugs due to the risk of additive anticholinergic effects, and the adverse effects on memory and cognition particularly in the elderly (Klett & Caffey, 1972). Another problem associated with anticholinergic medication is their misuse mainly for their euphorigenic and hallucinogenic effects (Ayd, 1985), and a number of physicians are wary of prescribing anticholinergics for this reason.

2.8 Recent Developments and the future

A number of new atypical neuroleptics have recently been released onto the market including remoxipride (now withdrawn) and risperidone and numerous others are in various stages of development and trials including savoxepine, raclopride, olanzapine and zotepine. These drugs are hailed as a breakthrough in neuroleptic treatment for various reasons including that they are more effective in the treatment of negative symptoms and that they have less side effects. The fact that they have less side effects than the traditional neuroleptics has led some authors to suggest that this may effect better compliance with treatment. However the relationship between side effects and compliance is not clear and this theory has been questioned (Hale, 1993). The advent of these new drugs has brought into question the theory that clinical efficacy of neuroleptic drugs is due to blockade of dopamine D_2 receptors. Thus drug development strategies no longer concentrate on D_2 blockade in the search for new drugs and a number of compounds with differing pharmacological properties are now being investigated such as $5HT_3$ and D_4 receptor antagonists, selective dopamine agonists and partial agonists and

sigma-site and excitatory amino acid antagonists (Lieberman, 1993). The concept of atypical neuroleptics with diverse psychopharmacology has produced a wave of excitement in the psychiatric journals in recent years. This has largely stemmed from the fact that clozapine, which has relatively weak dopaminergic activity, is more effective in the treatment of refractory patients than chlorpromazine and is associated with fewer extrapyramidal side effects (Kane, et al., 1988). However clozapine is associated with a higher incidence (1-2%) of the potentially fatal haematological side effect agranulocytosis which limit its use and necessitates regular blood monitoring. Generally the newer drugs are more expensive than traditional neuroleptics and as their long term effects will not be known until many more years of use, these drugs are used only in a minority of cases, mainly drug resistant. This is prudent as rare but potentially fatal side effects, such as blood dyscrasias which led to the recent withdrawal of remoxipride, may not be evident in early trials and clinical use. Consequently it may be some time before we can assess the real impact of these newer agents on the long term outcome of schizophrenia and their contribution to elucidating the aetiology of psychotic symptoms.

CHAPTER 3

Compliance with Neuroleptic Therapy

3.1 Introduction

The term compliance has been criticised by a number of authors who have stated that the term assumes a paternalistic philosophy and an unequal relationship between the health professional and the patient (Stimson, 1974). Other terms have been suggested as more appropriate such as 'adherence' or 'consensual regimen' in attempts to emphasise the autonomy of the patient (Piatkowska & Farnill, 1992). However, it is not clear how changes in terminology alone can alter the way the behaviour of taking medication is construed, or how such changes will encourage prescribers to be less paternalistic. Therefore the term compliance will be used in this thesis, but this should not be taken to imply that the individual's right to choose whether to take medication is not important, or that the array of situational, environmental and social factors which may influence an individual's decision to take or not to take neuroleptic medication have been overlooked.

There has been a great deal of interest in compliance with neuroleptic drugs and schizophrenic patients have been described as poor at adhering to drug treatment. This is reflected in the number of studies addressing the problem over the last twenty or more years and by this problem being addressed in government publications (Department of Health/ Royal College of Nursing, 1994). This section will describe the results of previous researchers'

findings in this area.

3.2 Patients' Experience of Neuroleptic Medication

There are few detailed objective assessments of patients' subjective experiences of neuroleptic medication. This is a surprising and disappointing deficiency in the literature as an understanding of the subjective experiences of people taking neuroleptic medication may provide important insights into medication taking behaviour. Van Putten and his colleagues have carried out much of the most interesting work in this area.

Van Putten, Mutalipassi, & Malkin (1974) described a systematic study of adverse behavioural reactions to phenothiazines and found that nine out of eighty patients experienced an exacerbation of psychosis associated with subtle akathisia. The exacerbations observed sometimes mimicked the original psychosis which, Van Putten observed, were sometimes inappropriately treated with by an increase in neuroleptic dosage. The exacerbations described responded to anticholinergic medication which seems to support the hypothesis that they were associated with extrapyramidal side effects.

In 1974 Van Putten first described the dysphoric response to neuroleptic medication and found this to be closely associated with extrapyramidal side effects and drug refusal. The dysphoric response is an adverse subjective response in which the effects of the drugs are experienced as a diffuse uncomfortable sensation. For example individuals may describe a dysphoric response as "slowing them down", "taking away motivation", "makes me

uptight" or even likening the effects as similar to "a bad acid trip". Van Putten, May, Marder, & Wittman (1981) found that dysphoric reaction shortly after administration of a neuroleptic was a predictor of poor compliance and poor clinical outcome.

A Canadian researcher, Hogan, has complemented Van Putten's work in a number of studies (Hogan & Awad, 1992; Hogan, Awad, & Eastwood, 1985; Hogan, Awad, & Eastwood, 1983), for example by developing a scale predictive of drug compliance, the Drug Attitude Inventory, which correlates highly with the Van Putten dysphoria scale (Hogan, et al., 1983). This scale was found to accurately discriminate between compliers and noncompliers with neuroleptic medication in 89% of cases. Hogan et al. found that the maximum variability in responses to the questionnaire was accounted for by items reflecting how patients felt on medication (e.g. 'my thoughts are clearer while on medication'), rather than what they knew or believed about medication. In contrast to Van Putten et al., Hogan found that early emergence of extrapyramidal side effects was not related to subjective response, but dysphoric patients had a greater incidence of extrapyramidal side effects than did nondysphoric responders by the end of treatment (Hogan & Awad, 1992).

Other researchers have explored attitudes towards neuroleptic medication, often using a survey type approach using open-ended and closed question styles. For example, Davidhizar, Austin, & McBride (1986) carried out a study of fifty schizophrenic patients in an acute-care psychiatric unit in Indianapolis and found that attitudes varied widely and that both strongly positive and strongly negative attitudes towards taking medication could be

held at the same time. The greatest proportion of beliefs identified in this study were negative totalling 53.5%. This study also found that there was a modest correlation between insight and attitude toward medication, and these results were replicated in a larger study of 100 patients (Davidhizar, 1987). In a survey of British psychiatric patients, Rogers, Pilgrim, & Lacey (1993) observed that, of the patients they questioned who had experienced neuroleptic therapy, 56.8 percent felt the medication to be helpful but 27.7 percent rated the medication as either 'harmful' or 'very harmful'.

In a more complex study, Finn, Bailey, Scultz, & Faber (1990) attempted to measure the subjective utility ratings of patients and significant others for neuroleptics in the treatment of schizophrenia. In this study no significant difference was observed between the distress caused by the symptoms of schizophrenia and the distress caused by side effects of neuroleptics as rated both by schizophrenic patients and by a group of psychiatrists. However the psychiatrists saw side effects as significantly less bothersome than symptoms when taking into account costs to society. An interesting finding was that, although psychiatrists were generally accurate at judging the overall distress caused to patients by symptoms and side effects, they misjudged the distress associated with particular side effects. For example the distress caused to patients by akathisia, dystonia and orthostatic hypotension was overestimated by the psychiatrists, whereas the distress resulting from constipation, painful urination and weight gain were underestimated.

The subjective response of individuals to neuroleptic medication may not be confined to those with a diagnosis of schizophrenia. A limited number of

case reports have been reported of the effects of neuroleptics in healthy subjects. For example Belmaker & Wald (1977), two psychiatrists, report the effects of being administered an intravenous injection of 5mg of haloperidol as part of a study they were carrying out.

They report the following effects;

> "The effect was marked and very similar in both of us: within ten minutes a marked slowing of thinking and movement developed, along with profound inner restlessness. Neither subject could continue work, and each left work for 36 hours. Each subject complained of a paralysis of volition, a lack of physical and psychic energy. The subjects felt unable to read, telephone or perform household tasks of their own will, but could perform these tasks if demanded to do so. There was no sleepiness or sedation; on the contrary, both subjects complained of severe anxiety".

Although this case study is a subjective report of the experiences of a small number of subjects, it seems that some of the effects of neuroleptics are not restricted to those with a diagnosis of schizophrenia. The lack of volition described by these psychiatrist has received scant attention when considering this effect in schizophrenic patients, and may sometimes be diagnosed as a symptom of the underlying condition.

3.3 Definition of Compliance

Compliance has been defined as;

> "the extent to which a person's behaviour, in terms of taking medications, following diets, or executing lifestyle changes, coincides with medical or health advice"

(Haynes, Taylor, & Sackett, 1979).

Noncompliance can include not taking enough medication, taking too much medication, not observing the correct interval between doses, not taking treatment for the prescribed time period or taking additional non-prescribed medications (Ley, 1992). Porter (1969) defined compliance as at least 80% of a prescribed medication being taken.

The concept of noncompliance is not new and it was even mentioned by Hippocrates in 200 B.C., who warned of patients who would lie to doctors about the taking of medications (Ley, 1992). In recent times the problem has attracted increased interest. For example the number of scientific publications addressing the problem has risen from a handful in the 1950's to thousands per year in the 1980's. Although the problem has received substantial attention, with some authors purporting noncompliance as the most significant problem facing medical practice (Eraker, Kirscht, & Becker, 1984), the standard of research in this area has often not been high.

3.4 Consequences of Noncompliance with Neuroleptic Therapy

Compliance with neuroleptic therapy in people with a diagnosis of schizophrenia has frequently been described as poor (Babiker, 1986; Pan & Tantum, 1989; Pool & Elder, 1986). Kane (1985) cites a rate of compliance of between 30 and 50 percent. A number of studies have found noncompliance rates of around 20% of schizophrenic in-patients and 50% of schizophrenic out-patients (Goldberg, Schooler, Hogarty, & Roper, 1977; Johnson, 1977;

Young, Zonana, & Shepler, 1986). Although it is often presumed that compliance in psychiatric patients is worse than in other patient groups the literature suggests that the extent of noncompliance is similar in schizophrenia in comparison to other chronic conditions such as hypertension or diabetes (Ley, 1992; Sackett & Snow, 1979). It has been shown that noncompliant patients are more likely to require involuntary commitment and to remain in hospital for a longer period of time than medication-compliant schizophrenic patients (McEvoy, Howe, & Hogarty, 1984). Although compliant patients relapse, their symptomatology has a more rapid onset and shows a more rapid recovery than is the case for their noncompliant contemporaries (McEvoy, et al., 1984).

Discontinuing neuroleptic medication carries an increased risk of relapse (Kissling, 1994; Prien & Klett, 1972) , and there is a well established association between noncompliance with neuroleptic medication and frequent rehospitalisation (Green, 1988). Noncompliance has been cited as the single most important cause of return of psychotic symptoms and readmission to hospital (Pool & Elder, 1986). It might therefore be argued that, if compliance with neuroleptics could be improved, there would be a reduction in both distress caused to patients and their families, and in the financial costs to services by prevention or shortening of hospital admissions.

3.5 Measurement of Neuroleptic Compliance

There have been a number of attempts to identify valid and reliable means of measuring compliance not only to neuroleptic treatment but also a

number of other pharmacological treatments. The techniques evolved include pill counts and urinary, plasma and salivary estimates of drug concentration. Pill counts involve open or surreptitious counting of tablets dispensed to patients. It is possible to calculate how many tablets or capsules a patient should have taken within a certain time period and therefore to quantify the number of tablets not taken or the excess number of tablets taken. This technique has been used in a number of studies despite inadequate validation. One of the most obvious flaws of the method is that the technique involves precisely what it suggests; counting the *number of tablets* in the medicine container. Thus if tablets are removed by the volunteer taking part in the study and discarded, the compliance rate subsequently measured will be inaccurate. Also the recipient of medication is usually aware of the tablet counts and may therefore alter the number of tablets present. The absence of a dosage form from a container is not evidence of consumption.

Some studies have found poor correlations between different indices of compliance (Boczkowski, Zeichner, & Desanto, 1985). A study by Pullar, Kumar, Tindall, & Feely (1989), in which compliance estimation by pill-count was compared with a pharmacological indicator technique, found that pill counts over-estimate compliance, sometimes to a considerable extent. Given the limitation of the pill count approach and the time consuming methodology involved it seems that it would be inadvisable to use this technique. However, as there is no "gold standard" available for estimating compliance it is difficult to assess alternative methods.

Other indirect measures of compliance include the impression of the

physician, patient interviews and therapeutic outcome, although all of these methods have also been shown to be unreliable (Caron & Roth, 1968; Mushlin & Appel, 1977). The use of a pharmacological indicator such as a low dose of phenobarbital or riboflavine included in the formulation is a useful technique. Such indicators have a long half life and can therefore indicate compliance over a longer time span (weeks rather than days). There are obvious practical problems with this technique including the formulation of neuroleptic medication combined with the chemical marker and the collection and analysis of blood or urine samples.

More accurate methods are available to measure neuroleptic compliance such as plasma and urinary estimates of the concentration of the drug. The techniques which have been used include biochemical and radioreceptor assays of the drug itself, its metabolites or substances affected by neuroleptic administration either in plasma or urine. The Forrest FPN test detects the presence of phenothiazines in urine based on a visual colour reaction between a ferric ion and the neuroleptic (Forrest, Forrest, & Mason, 1958). Unfortunately although a relatively simple and inexpensive test, this test is nonspecific, poorly quantitative, can yield false positive results and has been found to overestimate compliance with long half-life medications (Babiker, 1986). It was developed for detecting phenothiazine drugs and it is not suitable for detecting other chemically classified neuroleptics, such as the butyrophenones, the thioxanthines and the dibenzoxazepines. More specific, precisely quantifiable methods are available such as high performance liquid chromatography, and radioreceptor assay, but these techniques tend to be expensive, too specific for most purposes and insufficiently sensitive (Krska, Sampath, Shah, & Soni, 1986; Le Roux, Gaillot, & Bieder, 1982). These direct measures of neuroleptic

compliance can vary markedly depending on inter-individual pharmacokinetic variations such as absorption, distribution, metabolism and excretion of the drugs concerned. Direct measures of compliance whilst being more accurate are also more intrusive.

Mechanical devices have been developed to measure compliance with a variety of medications. Moulding (1962) invented a device which automatically recorded the time a medication container was opened. This device has been used in a number of studies, mainly by Moulding and colleagues in investigations of the medication-taking behaviour of patients with tuberculosis. This technique has also been used to monitor use of eye-drops in patients on long term treatment for glaucoma (Norell & Granstrom, 1980). Mechanical techniques tend to be expensive in large studies and, although there is an accurate recording of the time a medication container is opened, there is no record of whether a medication is actually consumed at that time. This type of method could also be objected to on ethical grounds due to invasion of privacy.

Another technique which has been used to estimate neuroleptic compliance involves the measurement of plasma prolactin which is increased by neuroleptic blockade of dopamine receptors in the tubero-infundibular centre (McCreadie, Mackie, Wiles, Jorgensen, Hansen, & Menzies, 1984; Meltzer & Fang, 1976). Unfortunately there is great inter-individual variation in the baseline and post neuroleptic levels of this hormone and prolactin levels are also affected by a number of other neurochemicals such as histamine, 5HT, oestrogens, and peptides (Young, et al., 1986). Natural variations in prolactin

levels are known to occur over time which makes interpretation of results difficult. All of these neurochemicals can be affected by pathological processes and other drug treatments such as antihypertensives and antiemetics.

There is one fundamental problem with all of the techniques reviewed. Any attempt to quantify compliance can be easily perceived by a participant in a study. Even if an individual is not told the reason for bringing in medication containers or for supplying a blood or urine sample (which would be ethically unsound in any case), they would be able to guess the reason. This knowledge in itself may affect the very behaviour which is being measured. Evidence from previous studies has indicated that medication-taking behaviour can be affected markedly by attempting to measure it, regardless of volunteers being informed of the measurement (Pullar, et al., 1989; Wilson & Johnson, 1980).

3.6 Factors Associated with Noncompliance with Neuroleptic Medication

3.6.1 Patient related factors

A number of researchers have investigated demographic factors associated with noncompliance. Noncompliant patients in comparison with compliant patients tend to be younger (Davis, Estess, Simonton & Gonda, 1977; Raynes & Patch, 1971), are equally represented in both sexes (Baekeland & Lundwall, 1975), and are more likely to come from a poor socioeconomic background and to be socially isolated (Altman, Brown & Sletten, 1972; Seltzer, Roncari & Garfinkel, 1980; Winkelman, 1964).

In a large study carried out in the USA, Hoge, Appelbaum, Lawlor, Beck, Litman, Greer, et al. (1990) observed that noncompliance with neuroleptics was associated with negative attitudes towards hospitalization and treatment, frequent seclusion and restraint, lengthy hospitalization, and lack of health-care insurance (presumably indicative of poor quality psychiatric care). Certain other personality factors have been associated with noncompliance including impulsivity and disregard for rules and regulations (Altman, Brown, & Sletten, 1972). Soskis & Bowers (1969) found that attitudes which were positive towards the illness such as "In a way having a breakdown helped me grow up" were associated with a lower rate of re-hospitalisation. It is difficult to make generalisations from these observations, although they are interesting, since the methodologies used vary widely and findings have not always been replicated.

A number of psychological symptoms have been linked to noncompliance including memory deficits (Fleischhacker, Meise, Gunther, & Kurz, 1994), persecutory delusions (Wilson & Enoch, 1967), grandiosity (Bartko, Herczeg, & Zador, 1988; Van Putten, Crumpton, & Yale, 1976), depression and negative symptoms such as motivational deficits (Carney & Sheffield, 1976; Pan & Tantum, 1989; Renton, Affleck, Carstairs, & Forrest, 1963). These findings have not been replicated by all researchers and it is difficult to assess causality since a person not taking neuroleptic medication is more likely to be experiencing psychotic symptoms. A one-off cross-sectional study would not adequately address this problem, and this technique has been employed in a number of studies.

A relationship between lack of insight or denial of illness and noncompliance has also been observed in a number of studies (Bartko, et al., 1988; Lin, Spiga, & Fortsch, 1979; Marder, Mebane, Chien, Winslade, Swann, & Van Putten, 1983; Nelson, Gold, Hutchinson, & Benezra, 1975). Hoge found that 21 percent of a large group of schizophrenic patients discontinued medication due to "denial of mental illness". However, this relationship has not been found by all investigators who have studied this issue. McEvoy, Freter, Everett, Geller, Appelbaum, Apperson et al. (1989b) and Buchanan (1992) observed that the relationship between insight and compliance is more complex than has previously been thought. Buchanan found, in a prospective study of 61 patients, that compliance did not correlate with with a measure of insight, particularly with questions such as "Do you think you have been unwell during this admission?", and "Why were you in hospital?", which Buchanan viewed as "close to the core of the modern concept of insight in psychosis". In this study questions which did correlate with compliance included "Did treatment help?" and "Will you take treatment after your discharge?". All of these studies depend on the definition of insight, a concept which is difficult to classify, and can be subjective.

3.6.2 Physician related factors

It seems likely that the quality of the communications between patients and prescribers has an impact on compliance with medication. Diamond (1985) suggested that it is important for clinicians to understand and respect the patients' subjective viewpoint. In particular Diamond recommends that it is important for prescribers to respect symbolic aspects of medication which may

influence patients attributions regarding treatment. For example, when a medication is prescribed it may be taken by the patient as evidence that the physician is a caring individual, or it may be interpreted as a threat to the patient's need for self-determination. Diamond promotes a philosophy in which autonomy of the patient and the right to refuse medication are emphasised. Although an interesting and ethically sound viewpoint, the compliance-promoting strategies which Diamond describes have not been put to any rigorous scientific enquiry, making it difficult to make any meaningful conclusions.

There is direct evidence of an association between compliance and the quality of the relationship between clinicians and patients (Frank & Gunderson, 1990). Although largely overlooked, a number of physician factors have been related to patient noncompliance. Interpersonal skills such as listening, empathy, and eye contact are positively related to compliance with medication (Meichenbaum & Turk, 1987). Provision of information about the expected beneficial and adverse effects of medication is likely to increase the patient-physician alliance, although a number of educational interventions have not been shown to improve compliance (Brown, Wright, & Christensen, 1987; Linden & Chaskell, 1981; Soskis, 1978). Irwin, Weitzel, & Morgan (1971) observed that compliance rates were higher when prescribers believed that medication had an essential role in the treatment of psychosis, as opposed to when prescribers felt ambivalent about the benefits of medication. This finding was replicated by Barofsky & Connelly (1983) who found that the therapist liking the patient and believing in medication was linked to improved compliance. More recently, in a study of psychodynamic therapy with

schizophrenic patients which failed to find any evidence of a superior outcome for patients receiving this form of treatment (Frank & Gunderson, 1990), many patients were observed to develop a poor alliance with their therapists, as measured by standardized rating scales. However, a good therapeutic alliance was found to predict compliance with medication and a better clinical outcome with less medication over a follow-up period of two years. Babiker (1986) has suggested that unresponsiveness to patients' complaints about side effects may also be related to noncompliance in schizophrenic patients. Nelson, et al. (1975) found that the patient's assessment of the physician's competence accounted for some of the variance of compliance measures.

In a study carried out by Hoge et al., it was found that psychiatrists did not agree with patients on the reasons for discontinuing neuroleptic medication. Thus 35% of patients attributed noncompliance with medication to side effects whilst only 7% of psychiatrists implicated side effects. Psychiatrists were more likely to blame interpersonal issues between patients and clinicians (11% of cases) and psychotic or idiosyncratic factors (49% of cases). The psychiatrists and their noncompliant patients disagreed about the patients' reasons for noncompliance in the majority of cases.

3.6.3 Medication-related factors

Although the side effects of neuroleptic medication are frequently cited as a cause of noncompliance, there are very few studies which have systematically investigated the contribution of side effects to noncompliance. Paradoxically some studies have shown that the presence of neuroleptic side

effects was associated with better compliance with neuroleptics (McEvoy, Apperson, Appelbaum, Ortlip, Brecosky, Hammill et al. 1989a; Willcox, Gillan, & Hare, 1965). Other studies have found that side effects are not a common reason for refusal of medication (Appelbaum & Gutheil, 1980; Fleischhacker, et al., 1994). In the large study by Hoge, et al. (1990) 35% of patients who had discontinued neuroleptic medication cited side effects as the main reason for stopping. Buchanan (1992) found that akathisia, drowsiness, tremor and dystonia were not found to be significantly associated with noncompliance. In contrast the absence of akinesia was associated with better compliance. Other studies have shown an association between noncompliance and side effects, particularly extrapyramidal side effects, weight gain and sexual dysfunction (Nelson, et al., 1975; Van Putten, 1974; Van Putten, et al., 1984). Thus it seems likely that whilst side effects are a problem for some patients and may in selected cases lead to drug refusal, neuroleptic side effects are not a universal reason for default.

Other aspects of the effects of neuroleptic medication may be associated with potential noncompliance including the slow onset of action, the delayed time to relapse on discontinuing medication and complexity of the drug regimen (Piatkowska & Farnill, 1992). It is well known that duration of the treatment regimen is associated with compliance, in that compliance decreases with increased duration of treatment (Haynes, 1976). This is pertinent in the drug treatment of schizophrenia since treatment is often prescribed for long time periods.

Treatments which prevent relapse as opposed to acute treatments are

also associated with a lower level of compliance and a delay in the relapse of symptoms on discontinuing medication can contribute to lower levels of compliance (Haynes, 1976). These considerations are important when considering compliance with neuroleptic treatment since a proportion of individuals who take the medication do not perceive any benefits and the mean time to relapse on discontinuing medication is between six and nine months (Hogarty, Ulrich, Mussare, & Aristigueta, 1976; Johnson, 1984; Wistedt, 1981). This makes it difficult for the patient to associate discontinuing medication with re-emergence of symptoms. A further factor which is often overlooked is that not all patients respond to neuroleptic medication and a sizeable proportion continue experiencing psychotic symptoms despite adequate compliance. Hence Hoge et al. (1990) found that 12% of a large sample of schizophrenic patients discontinued treatment due to "avowed ineffectiveness of medication". Nelson, et al. (1975) also found that the patient's assessment of the effectiveness of drug therapy accounted for some of the variance in compliance measures.

3.6.4 Predictors of noncompliance

A number of investigators have attempted to identify specific predictors of noncompliance. As described earlier in this chapter, Van Putten, et al. (1981) found that dysphoric reaction (an adverse subjective response in which the individual feels severely uncomfortable and attributes this to the medication) shortly after administration of a neuroleptic was a predictor of poor compliance and poor clinical outcome. There was some evidence that dysphoric patients tended to be less symptomatic and showed less impairment on the Continuous

Performance Test (CPT), a measure of sustained attention widely used in schizophrenia research. Given that CPT performance is often abnormal in psychotic patients, and that CPT performance has been observed to improve in such patients following treatment by a neuroleptic (Spohn & Strauss, 1989), the implication of this observation is that neuroleptics may only be appropriate for patients suffering from this specific attentional deficit. Clearly, this hypothesis deserves further attention from researchers.

3.7 Coercion in Treatment

Recently there has been considerable debate about the potential value of Community Treatment Orders and supervision registers. Patients' attitudes towards coercive treatment vary substantially from very positive to very negative, and a negative response to coercion is sometimes associated with poor clinical response (Hiday, 1992). Given that a sizeable minority of UK voluntary psychiatric patients feel that they have been coerced into hospital admission (their legal status notwithstanding) and that this perception is associated with negative attitudes towards psychiatric services and staff (Rogers, et al., 1993), a collaborative, coercion-free alliance between patients and prescribers of psychiatric drugs may be preferable to forced treatment.

3.8 Interventions designed to increase compliance with neuroleptic medication

A number of strategies have been attempted in order to influence the outcome of psychotic disorders by manipulating variables known to affect

compliance with neuroleptic therapy. The techniques employed have made use of varied methods and have varied success rates. One technique which is widely used by researchers is that of providing information and education regarding medication in an attempt to increase medication compliance. Lack of knowledge about the purpose of medication has been correlated with noncompliance in non-psychiatric patients (Hulka, Cassel, Kupper, & Burdette, 1976). Kelly & Scott (1990) found that education of patients and their families significantly improved medication compliance. Eckman & Liberman (1990) developed a short training scheme for mental health professionals designed to enable them to teach compliance-related skills to patients. Seltzer, Roncari, & Garfinkel (1980) found that an educational intervention increased compliance and reduced fear of side effects and addiction. However Brown, et al. (1987), in a small study, found that instruction about neuroleptic medication did not affect compliance but increased knowledge about medication, with verbal and written information resulting in a greater increase than verbal information alone. In a controlled trial, Boczkowski, et al. (1985) found that simple behavioural techniques (for example, self-monitoring of pill taking; tailoring pill taking to personal routines and habits) were superior to educational techniques when attempting to improve neuroleptic compliance amongst schizophrenic outpatients.

Some studies have used a client centred approach. For example Olarte & Masnik (1981) used a group therapy approach emphasising the caring attitude of the therapist in order to increase medication compliance. Corrigan, Liberman, & Engel (1990) suggested a number of strategies to enhance a collaborative relationship between the patient and the prescriber. They advocated changing

from an approach where it is assumed that noncompliance is something intrinsic within the patient, which the clinician is powerless to change, to one in which the patient and the physician collaborate to negotiate a treatment regimen which is suitable for the patient. Greenberg, Fine, Cohen, Larson, Michaelson-Baily, Rubinton, et al. (1988) found that it was useful to use a comprehensive approach in which patients were given information about schizophrenia and its treatment (including information on environmental stress), collaboration between patient family and staff was encouraged, and individual strengths and weaknesses were identified in order to teach relevant coping strategies.

3.9 Limitations of Studies Reviewed

The results from the studies reviewed, although interesting, are limited by a number of methodological weaknesses. There is wide range of definitions of compliance and the instruments used to measure compliance are often inadequate and poorly validated. Sample sizes tend to be small and lack statistical power. There is tendency to rely on cross-sectional designs and significant results tend to be small which may reduce their clinical relevance. Previous research has been based on many *a priori* assumptions about which variables influence neuroleptic-taking in the absence of solid data. Many of the papers reviewed use constructs which are difficult to define operationally such as denial, dependence and hostility. Studies tend to focus on medical aspects of treatment in relation to compliance and neglect wider pyschosocial aspects of medication taking behaviour, which are known to affect compliance. Most of the reported studies consider medication taking behaviour as a dichotomous compliant or noncompliant attribute, whereas it is known that compliance is

dynamic and erratic (Dirks & Kinsman, 1982).

The literature largely assumes that neuroleptic medication always has a beneficial effect on outcome and that failure to comply with neuroleptic medication is due to belligerence. This approach is paternalistic and overlooks the fact that some patients do not respond to neuroleptic medication (Brown & Herz, 1989) and that some patients may actually worsen (Bowers & Swigar, 1988). Compliance is only appropriate if an optimum dose of medication tailored to an individual's needs is prescribed and carefully monitored. It is possible that enhanced compliance with an inappropriate medication regime will increase adverse effects and produce little therapeutic benefit in some patients.

There is also a tendency in the literature to overemphasise negative personality characteristics of patients rather than considering the influence of the clinician when noncompliance occurs (Piatkowska & Farnill, 1992). This is an oversight given the fact that the relationship between the prescriber and patient is a factor which influences compliance, and also the fact that clinicians themselves vary widely in their attitudes to neuroleptic treatment and relapse prevention. Kissling (1994) has pointed out that prescribers often fail to monitor and reinforce patients' reliability in medication management, and that marked differences between prescribers in their recommendations for length of treatment make patients insecure. Kissling showed that prescribers underestimate the risk of relapse in first episode and multi-episode patients, and suggested that, as well as addressing the compliance of patients to their medication, the problem of prescribers complying with suitable methods of

monitoring neuroleptic medication should also be addressed.

It has been argued that a patient-centred approach to understanding compliance would be beneficial (Conrad, 1985). This approach emphasises the therapeutic costs and benefits of drugs and the patient's concern with self-regulation. A number of authors have endorsed the suggestion that compliance with neuroleptics can be enhanced by the development of a truly collaborative relationship between clinician and patient (Corrigan, Liberman & Engel, 1990; Eisenthal, Emery, Lazare & Udin, 1979; Frank & Gunderson, 1990; Piatkowsa & Farnill, 1992). Further well controlled research is required to investigate attitudes to neuroleptic medication, and the effect of these attitudes on compliance with treatment.

CHAPTER 4

Aims and Outlines of Studies Undertaken

Previous chapters have reviewed research which has been carried out to investigate the effects of drug treatments for patients diagnosed as suffering from schizophrenia. This review has highlighted a number of methodological problems which has impeded the progress of research in this area. Researchers must confront problems of diagnosis and classification, reflecting the fact that schizophrenia is a diverse and heterogenous condition. The main form of drug treatment for schizophrenia is neuroleptic medication and there are a wide range of chemical classifications and drugs within this group. Despite these difficulties a number of conclusions can be drawn. In particular, it was shown that not all patients experience benefits from neuroleptics which outweigh the costs associated with this kind of treatment, and most patients experience at least some of a possible wide range of side effects (Edwards, 1986).

Intervention studies aimed at improving neuroleptic compliance have focused on education. This approach overlooks a number of inconsistencies in the literature and is based on the assumption that people do not take neuroleptic medication because they do not understand it. There is also a tendency to view compliance as a static trait and to designate people as either compliant or noncompliant with medication, and it is likely that the situation is far more complex than this. The review of the literature indicates the importance of carrying out research which focuses on subjective responses to

medication and treatment compliance. There has been a lack of studies which investigate the patient's viewpoint regarding medication. The general aim of this thesis is to begin to redress this balance.

The first study which will be reported in Chapter 5 is an empirical investigation of schizophrenic patients' subjective attitudes towards neuroleptic medication designed from a social constructionist perspective. A social constructionist analysis acknowledges social forces and assumes that people are not just passive recipients of handed-down knowledge but are actively engaged in its construction (Stainton-Rogers, 1991). Patients' accounts of their treatment were therefore explored in a way which minimised the influence of the investigator's a priori assumptions. The methodology chosen for this purpose was a semi-qualitative technique known as Q-methodology (McKeown & Thomas, 1988; Stephenson, 1935), which allows patients to construct their own distinctive viewpoints about their experiences in a particular domain (in this case neuroleptic treatment).

The review of the literature has indicated the importance of neuroleptic side effects as components of patient's experience of treatment, and these are the focus of the second study, which is reported in Chapter 6. Despite the long period of time for which neuroleptic medications have been prescribed, there has until now been no validated scale available which allows patients to self-report their own side effects. A questionnaire was therefore designed which allowed patients to self-rate neuroleptic side effects. Although it was felt that the data collected from such a questionnaire would add to current understanding of patients' experiences of side effects, it was also felt that the

questionnaire might prove useful in future research. The scale was therefore validated using standard psychometric procedures. Patient's distress caused by side effects and their attribution of these effects to neuroleptic medication were also studied.

Previous research has indicated that there might sometimes be discrepancies between patients' experiences of side effects and the prescribers' assessments of these effects. Therefore a postal survey was carried out of psychiatrists, senior registrars and registrars in Merseyside and North Wales in which their opinions about the prevalence, distress and likelihood of informing patients about the side effects of neuroleptic medication were elicited. Data from this study are described in detail in Chapter 7 which also describes a comparison of the data collected from psychiatrists with that obtained from patients in Chapter 6.

The final and most complicated study in the thesis was intended to fill a gap identified in previous research. Clearly, patients' experiences of and attitudes towards neuroleptic medication are not static but evolve over time as treatment progresses. In Chapter 8, therefore, a longitudinal study of patients' experiences is reported, in which parameters thought to contribute to neuroleptic compliance were measured. This study was carried out in two groups; one consisting of patients who had been prescribed neuroleptic medication for at least three years, and another consisting of people who were experiencing psychotic symptoms and were being prescribed neuroleptic medication for the first time. The parameters measured included positive and negative symptoms, dosage of neuroleptic medication, side effects of

neuroleptic medication, knowledge of neuroleptic medication, attitudes towards neuroleptic medication, and neuroleptic dysphoria. These variables were measured at initial contact with the investigator and then after one and six months. Other variables measured included length of time spent on psychiatric inpatient wards and attendance at outpatient appointments. The relationship between these variables at different points in time was assessed using various statistical procedures and regression analyses were carried out in order to investigate the contribution of the parameters to the variance in final attitude to treatment.

The final chapter concludes the thesis and gives an overview of the work carried out and it's relevance to recently published government documents as well as indicating possible new areas for research. The aim of the thesis was ambitious since the area of study is complex. Compliance with and attitudes towards neuroleptic medication are poorly understood, response of psychotic symptoms to neuroleptics is unpredictable and schizophrenia is a heterogenous disorder. A combination of quantitative and qualitative methods was used as it was felt that a broad approach would be most likely to yield useful results.

CHAPTER 5

Schizophrenic patients' subjective perspectives on neuroleptic medication: A social-constructionist investigation using Q-methodology

5.1 Introduction

The attitudes which are held by schizophrenic patients towards their neuroleptic medication are complex for a number of reasons, as discussed in Chapters 2 and 3. Finn, et al. (1990) found that the distress experienced by patients as a result of side effects was very similar to that experienced as a consequence of symptoms of schizophrenia suggesting that the decision whether or not to take medication was very fine one. Crow, et al. (1986) found that although patients receiving neuroleptics were less likely to relapse than patients receiving placebo medication, they also made significantly less life achievements than those receiving placebo. Although findings such as these indicate that patients' subjective experiences of and attitudes towards neuroleptic medication may be of considerable clinical importance (Awad & Hogan, 1994), researchers have paid very little attention to these experiences and attitudes, preferring to focus instead on clinical outcomes such as symptoms and hospital admission rates. Awad & Hogan (1994) have argued that there is a need for innovative methods for researching patients' subjective responses to neuroleptic therapy. In this study, a social constructionist approach was used to explore different dialogues or subjective attitudes that psychotic patients take towards their neuroleptic treatment. Social constructionist approaches assume that individuals, far from being passive

recipients of information, actively construct knowledge about events and experiences which are important to them (Sackett & Snow, 1979; Stainton Rogers, 1991). On this view, the attitudes which patients take towards their treatment should not be seen as one- or even multi-dimensional constructs which can be objectively defined in advance by investigators. Rather, each patient can be seen as constructing a point of view which may differ, both in structure and degree, from the points of view of other patients.

As previous studies which have investigated attitudes to neuroleptic medication have often been carried out with small numbers of patients using traditional attitude scaling techniques, it was decided to use a novel approach and one which focused on the patients' ideas and attitudes rather than those of the investigator. A method which did not require a priori assumptions was chosen in order to elucidate as wide a range of attitudes as possible from people who had personal experience of taking neuroleptic medication. For this reason the technique chosen for exploring patients' subjective attitudes towards neuroleptics was Q-methodology (Sackett & Snow, 1979; Stephenson, 1935). This approach has been used to empirically investigate subjective judgements in a variety of domains including; carers' beliefs about appropriate social and therapeutic rules for psychiatric inpatients (Morrison, 1987), subjective political beliefs (Brown, 1980), beliefs about infant-mother attachment (Pederson, Moran, Sitko, Campbell, Ghesquire, & Acton, 1990), and lay perceptions of health and illness (Stainton Rogers, 1991).

Q-methodology involves a method of ranking items from a range printed on cards along a continuum, and this produces a Q-sort for each participant.

Statements about a subject are rank-ordered or sorted along a continuum according to the level of agreement or disagreement. The number of items included in Q-sort usually varies between forty and one hundred and these cards are usually sorted into a quasi-normal distribution. Factor analysis is then used to extract prototypical viewpoints which represent the dialogues commonly employed by individuals when talking about the subject area (in this case neuroleptic medication). The technique contrasts with more traditional methods for assessing attitudes, for example Likert scaling, in that the participant considers all items at once in relation to each other, reflecting real-life situations where decisions are made taking into account a broad range of factors. The approach is social constructionist in the sense that items are not given externally defined objective meanings; respondents are given the freedom to create their own subjective structure when producing the Q-sort so that attitudes can be sampled without an *a priori* structure of beliefs about neuroleptics or compliance being imposed by the researcher. An important difference between Q analysis and traditional R methodology (traditional factor analytical approaches of assessing attitude) is that correlations between persons are studied, producing person clusters or factors rather than correlations between tests scales items or variables.

Consistent with many other studies employing Q-methodology (McKeown & Thomas, 1988), an attempt was made to minimise bias in the selection of items for the Q-sorts by selecting statements obtained from interviews with a small group of participants who had experience with neuroleptic treatment, either as clinicians or patients. The members of this group were selected in order to achieve breadth and diversity in terms of their

experience of neuroleptic drugs.

5.2 Method

5.2.1 Participants

Nine participants were interviewed in the initial phase of the study in order to collect a range of attitude statements about neuroleptics suitable for inclusion in the Q-sort. Four of these participants had a DSM-III-R (American Psychiatric Association, 1987) diagnosis of schizophrenia as determined from case note data, three were community psychiatric nurses and two were consultant psychiatrists. The patients were selected randomly from outpatient clinics where they were interviewed, the community psychiatric nurses were recruited from a service review meeting, and the two psychiatrists were recruited from hospitals in the Mersey region. These participants' opinions about neuroleptics were not known prior to the interviews.

Fifty psychiatric patients participated in and completed the main part of the study. The inclusion criteria were: a DSM-III-R diagnosis of schizophrenia as determined by their consultant psychiatrist and by case note data; at least a one-year history of neuroleptic drug therapy; and aged between 20 and 70 years. Participants were selected randomly from local day centres, outpatient clinics and psychiatric in-patient wards. This recruitment strategy was employed in order to obtain attitude statements which reflected distinct and contrasting experiences and thereby to give a fair representation of a broad range of attitudes. In addition to the fifty patients whose data is reported here,

three patients who commenced the study did not complete Q-sorts. Thirty four of the patients who completed the study were male and 16 were female. The mean age of these participants was 45.1 years with a range of 23 to 69 years. Their mean IQ estimated using the National Adult Reading Test (Nelson, 1982) was 103.9 with a range of 94 to 124. Their mean duration of neuroleptic treatment was 15.5 years with a range of 1 to 30 years.

5.2.2 Item Selection

The semi-structured interviews carried out in the initial phase of the study each lasted approximately one hour and covered the following broad topics: personal experiences with neuroleptics, efficacy of neuroleptics, advantages of neuroleptics, disadvantages of neuroleptics, dosage adjustment decisions and differences between neuroleptic drugs. Interviews were audiotape-recorded and subsequently transcribed. Specific statements about neuroleptic drugs were then highlighted in the transcripts. Initially 127 such statements were identified but, on inspection, many of these were similar and could be represented by a single summary statement. Other statements were rejected because they were too complicated or lengthy or because they were clearly specific to an individual rather than expressive of a general attitude. This process of item reduction was carried out by three investigators working together (two clinical psychologists and the author) and resulted in the selection of 45 statements for inclusion in the final Q-sort. These statements were then typed on to cards (4cm x 9cm) and numbered randomly.

5.2.3 Administration of Q-Sorts

In order to explore patients' subjective opinions about neuroleptics, participants were asked to perform a structured Q-sort by placing the items into piles labelled on a scale from +5 (most agree), through 0 (unsure, don't understand or undecided) to -5 (most disagree) as described in Kerlinger (1986) and McKeown & Thomas (1988) and shown in Table 5.1.. Cards were numbered from +5 to -5 and placed along the top of a large table or work-top as a guide for the placement of statements. The number of cards placed in each pile was determined by a forced quasi-normal distribution: participants were required to place 2 cards in both the +5 and -5 piles, 3 cards in the +4 and - 4 piles, 4 cards in the +3 and -3 piles, 5 cards in the +2, +1, -1 and -2 piles, and 7 cards in the 0 pile. In order to facilitate this process, participants first sorted the cards into three piles labelled "agree", "disagree" and "undecided". They then further sorted the cards according to the extent of their agreement or disagreement in order to produce a final sort. Participants were allowed to change the position of cards if they wished to do so. The position of each statement was then recorded on a response sheet by making a copy of the numbers on the back of each card.

Data were analyzed using the PCQ programme for Q-technique, version 2.0 (Stricklin, 1990) which allows a centroid factor analysis to be carried out on the data. Factors were selected if one or more of the participants had a factor loading of 0.45 or greater and were then rotated to simple structure using the varimax criterion. This process was repeated to select factors with a factor loading of 0.40. It is worth repeating that methods of Q-analysis differ from

DISTRIBUTION PLAN FOR STATEMENTS IN Q-SORT

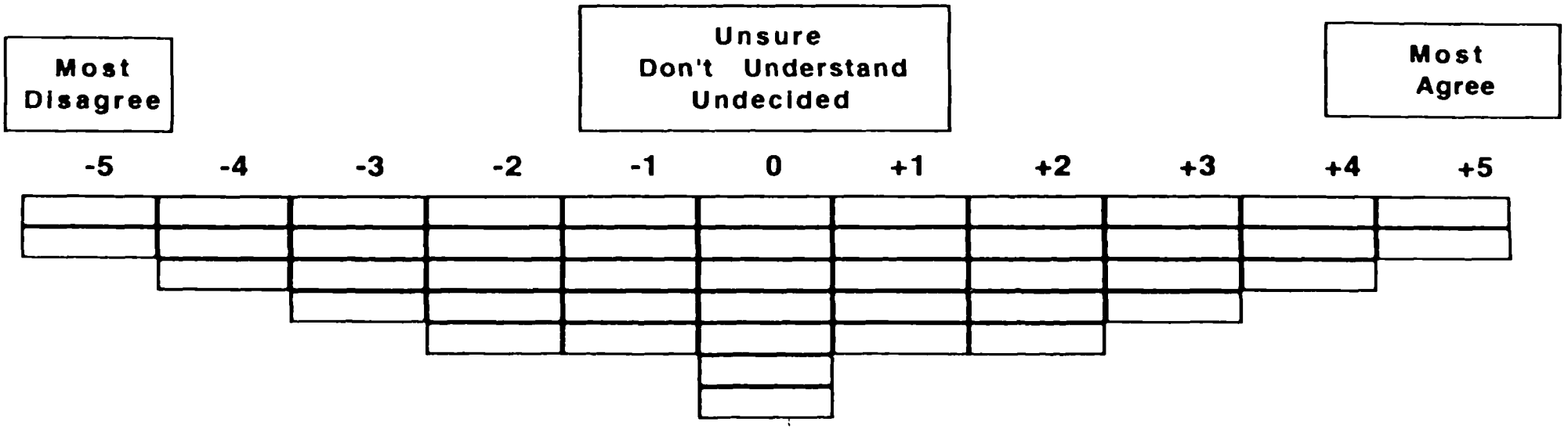


Table 5.1 To show distribution plan for placement of statements in Q-sort. Each block represents one statement, so that for example 7 statement are placed at the 0 position.

conventional factor analytic approaches in that individuals rather than items are the unit of analysis; ie. the correlation matrix is constructed to show relationships between the individuals. Brown (1971) and McKeown & Thomas (1988) have pointed out that the results of Q investigations are little influenced by the actual method of factor analysis employed and centroid analysis followed by varimax rotation have become standard in this area.

5.3 Results

5.3.1 Interview data

Before examining the results of the Q-sort it will be useful to consider some of the comments elicited from patients and professionals during the initial interviews. In fact, all of those interviewed expressed both positive and negative attitudes towards the medication. However, considerable differences in perspectives became evident when the professionals and the patients were asked to consider the effectiveness of neuroleptics, reasons for noncompliance, and issues of control.

The positive effects of neuroleptics were perceived differently by the people interviewed. For example, one patient stated, "I feel calmer and more tranquil, more normal really, more comfortable with myself when I take the medication." Another said, "I don't think it has a great effect on me, to tell the truth, but I still come here (to the depot clinic). I can meet people, can't I?", a comment which is interesting in the light of the observation of Hoge, et al. (1990) that patients sometimes refuse medication because it is perceived as

ineffective. For another patient, the drugs were helpful because of their effects on anxiety and agitation rather than positive symptoms: "My symptoms are still there but they just don't bother me as much when I take the medication".

One of the psychiatrists denied that the only benefits of the drugs were always in domain of symptomatology, stating, "It's amazing how many people's personality seems to change from being a real rat-bag to being a really nice person when they're actually treated, even though some of them don't have florid psychotic symptoms. They are just very behaviourally disordered and unpleasant. And yet, when they are on the phenothiazines or whatever that is they're a different person, very nice."

Some of the health professionals expressed reservations about their use of neuroleptics within their personal framework, two independently commenting to the effect that, "I .... would be very frightened if somebody was suggesting giving such severe drugs to a child of mine." Statements such as these sometimes contrasted with the answers given when the health professionals were asked why they thought that psychiatric patients were often reluctant to take medication, which often implicated negative characteristics of the patients such as lack of insight or lack of understanding. This difference between personal and professional perspectives on compliance was also evident when the health care professionals were asked to consider the side effects of neuroleptics. For example, one of the psychiatrists asserted that the dyskinesias, akathisia, and sedation were the most frequently complained about side effects but, when asked which side effects he would be most worried about if he had to take neuroleptics, replied with a smile, "With me it

would be weight gain". This statement is interesting in the light of the findings of Finn, et al. (1990) that psychiatrists sometimes inaccurately estimated the relative distress caused by particular side effects, particularly neuroleptic-induced weight gain. A CPN noted that, "Some patients, you know, say to me that the actual side effects aren't as disabling to them as they appear to me by looking at them.." One patient asserted that, "The strongest thing that I've ever took is Anadin," and added that he experienced no side effects at all, despite showing a slight dyskinesia of the facial muscles throughout the interview. For another, the main disadvantage of the medication was the apparent effect it had on her social life: "I've no social life. I don't go anywhere, like. I don't go out at night.... The doctor said, you can't drink with the tablets. I know some of them (other patients) did.... I don't go anywhere. I'm always stuck in the house."

Issues of control were evident in many of the statements made by the professionals. For example, one of the health professionals commented that, "Some people are frightened of being given something that is going to control them" and another said, "When they take tablets they are actually swallowing them. When they're having injections I think perhaps it takes away their control". A related theme which was also addressed by both health professionals and patients was apathy and lack of volition following neuroleptic medication. According to one of the psychiatrists, "There's a sense that it (medication) takes something away from them (the patients). It's surprising how people take some distressing side effects. It's as though the drug is holding them in a way they don't have the power to complain so much." One patient was happy to leave control over medication entirely in the

hands of his psychiatrist, saying, "It's beyond me, like, so if someone puts me on injection, like my doctor, I just come down and, you know, accept the injection.... I mean, I leave it up to the medical world. Why should I get involved with it?" Another had stopped taking the medication, "Because of the effects on my sex drive and because of a feeling of timidity and inadequacy."

These quotations give an indication of the variety of responses made during the interviews. Even from this small number of interviewees, it is clear that each has a particular perspective which cannot be readily reduced to a simple positive or negative attitude towards neuroleptic medication.

5.3.2 Interpretation of Q-Sorts

When the results from the Q-sorts carried out by the fifty patients taking neuroleptic medication were analysed, four factors were identified, each being a prototypical sort reflecting clusters of participants who had ordered statements similarly. Each of these prototypical sorts therefore represents a particular viewpoint or discourse about neuroleptics which was shared, in large degree, by a small group of patients.

The number of participants loading significantly on each factor are shown in Table 5.2. Eighteen participants loaded significantly and exclusively on factor A, 16 positively (in agreement) and 2 negatively (in disagreement). Eight participants loaded positively only on factor B and seven loaded positively only on factor C. Only two participants loaded on factor D, one

Table 5.2: Number of participants loading at least 0.45 and at least 0.40 on each varimax rotated factor (A, B, C and D) extracted. Signs following factor labels indicate whether participants loaded positively or negatively. Ten participants produced sorts which did not load on any factor using the 0.45 criterion and 4 produced sorts which did not load on any factor using the 0.40 criterion.

Nonconfounded Sorts			Confounded Sorts		
Factor	N		Factors	N	
	0.45	0.40		0.45	0.40
A	16	16	A+ C+	3	5
A-	2	3	A+ D+	1	1
B+	8	9	B+ D+	1	1
C+	7	7	B+ C+	0	1
D+	1	1	A- B+	0	1
D-	1	1			

positively and one negatively. There were five confounded sorts from participants who loaded significantly on more than one factor (three positively on A and C, one positively on B and D, and one positively on A and D). Ten participants did not load significantly on any of the factors. Factor A accounted for 22 per cent of the variance, Factor B for 10 per cent of the variance, Factor C for 11 per cent of the variance, and Factor D for 5 per cent of the variance. The four-factor model therefore accounted for a total of 48 per cent of the variance in the data. Accepting a lower criterion of factor loadings of 0.40 or greater only 4 patients failed to load on at least one of the factors, as shown in Table 5.2.

The interpretation of the four factors is based on an examination of the place of the individual items within the prototypical sorts. The position of each statement for each of the factors is shown in Table 5.3.

Factor A: Unquestioning, uncomplaining, dependent

The twenty participants who loaded positively on Factor A expressed dependence on neuroleptic medication, agreeing strongly with the following statements:

"I can't do without my medication" (+5)
"If I didn't take my medication I'd end up back in hospital" (+4), and
"I'm worried about what will happen if they stop my medication" (+4).

Table 5.3: Items distinguishing each factor from the other factors. Numbers shown indicate the position of each item, ranging from - 5 (most disagree), through 0 (unsure, don't understand or undecided) to + 5 (most agree), within each factor. Each of the items listed had a position on the criterion factor at least three positions different than its position on all other factors.

Factors	A	B	C	D
Factor A: Unquestioning, uncomplaining, dependent				
This medication drains my energy	**-4**	+1	+1	+1
The medication doesn't cure the illness it just controls the symptoms	**0**	+5	+4	+3
Factor B: Autonomous, sceptical				
Neuroleptics aren't good for everyone	0	**+4**	0	+1
I don't have any side effects from my medication	+3	**0**	-5	-3
Neuroleptics make me see reality better	+1	**-4**	+2	0
If I got any serious side effects I'd stop taking my medication	0	**+4**	0	+1
Neuroleptics aren't as good as they're made out to be	-2	**+2**	-1	-4
Neuroleptics make me less tense	+2	**-3**	+3	+1
Factor C: Balanced appraisers				
People wouldn't like me if they saw me without medication	-1	-2	**+3**	-1
This medication is harmless to me	+2	+2	**-2**	+4
I come to get my medication to meet people	0	0	**-4**	0
I don't know why I take my medication	-1	0	**-4**	0
Neuroleptics give me control over my life	+2	-4	**-1**	+3
I don't think my medication is totally suited to me	-2	+1	**-5**	-1
I don't like taking any medication	-3	+5	**+1**	-2
Factor D: Autonomous responders				
My family don't like me being on this medication	-1	-1	-2	**+2**
I can't do without my medication	+5	-1	+4	**-4**
Neuroleptics make me happier	+2	-5	+1	**+5**
It is hell taking this medication	-5	-2	-3	**+1**
The neuroleptics make me timid and inadequate	-1	0	-2	**-5**
I see taking medication as an invasion of privacy	-2	-1	0	**+3**
I would never change my medication of my own accord	+4	+1	+2	**-2**
If I didn't take my medication I'd end up back in hospital	+4	+2	+5	**-5**
If a doctor prescribes something I think I should stick to it	+5	+3	0	**-4**
I'm worried about what will happen if they stop my medication	+4	+3	+5	**-1**
Neuroleptics make the brain work better	+1	-5	0	**+4**
Neuroleptics make me think clearer	+1	-4	-1	**+5**

A list of all items included in the Q-sort can be found in Appendix 9

These participants also expressed a strong belief in the authority of the doctor, agreeing that they would never change their medication of their own accord (+4). They were also unconcerned about the negative effects of medication, as indicated by their ordering of the following statements:

"It is hell taking this medication" (-5)

"Neuroleptics are just chemical strait jackets" (-5).

"The medication drains my energy" (-4), and

"I don't have any side effects from my medication" (+3).

Items which distinguished this factor from the other four factors are given in Table 5.3. Of particular note is the fact that all factors with the exception of Factor A entailed agreement with the statement, "The medication doesn't cure the illness, it just controls the symptoms". Participants loading on Factor A might therefore be described as unquestioning, uncomplaining, and dependent. Conversely, participants who load negatively on the factor might be described as questioning, complaining and independent.

Factor B: Autonomous, sceptical

The nine participants who loaded positively on Factor B expressed a negative attitude towards neuroleptics and did not express a strong belief in benefits of the medication. They agreed strongly with the statements:

"I don't like taking any medication" (+5)

"Neuroleptics aren't good for everyone" (+4)

"People should have the minimum dose to keep their symptoms under control" (+4), and
"Medication doesn't cure the illness it just controls the symptoms" (+5).

This group indicated a concern with autonomy by their ordering of the statements:

"If I started getting any serious side effects I would stop taking my medication"(+4), and
"I don't think I should get involved in decisions about my treatment" (-3).

They disagreed with statements indicating that they might experience any benefits from neuroleptics such as:

"Neuroleptics make me happier" (-5)
"Neuroleptics give me control over my life" (-4)
"Neuroleptics make me think clearer" (-4), and
"Neuroleptics make me see reality better" (-4).

Interestingly, participants who loaded on this factor had a neutral attitude towards items pertaining to side effects (eg. "I don't have any side effects from my medication"; "The side effects of neuroleptics are worse than the symptoms"; and "Side effects put me off taking medication; all scored 0), indicating that the experience of side effects was not a major determinant of

their general attitude towards the drugs. They did express strong agreement with the statement "If I started getting any serious side effects I'd stop taking my medication" (+4), but in the context of their general attitude this appeared to be due to a concern with autonomy rather than concern with the presence of side effects at the time of testing. The items which distinguished between this factor and the other factors, shown in Table 5.3, are consistent with the above findings and suggest that participants who load highly on the factor might be thought of as autonomous and sceptical. No participants loaded negatively on this factor.

Factor C: Balanced appraisal

In total, ten participants loaded positively on Factor C. These participants disagreed more strongly than other participants with the statement "I don't have any side effects from my medication" (-5), suggesting that the presence of side effects may be an important consideration for them. They nonetheless agreed strongly with the statements:

"I can't do without my medication" (+4)

"If I did not take my medication I'd end up back in hospital" (+5), and

"I'm worried about what would happen if they stop my medication" (+5)

Participants who loaded on this factor also disagreed strongly with the statement, "I think all neuroleptics are the same so it doesn't matter which one I'm on" (-4) suggesting that they may have experienced a range of

neuroleptics. The statements which distinguish this factor from the other factors, shown in Table 5.3, indicate that the participants scoring highly on the factor have a positive attitude towards neuroleptics which reflects a balanced appraisal of the positive and negative consequences of taking the drugs.

Factor D: Autonomous, responding

Only three participants loaded positively and only one participant negatively on the final Factor D. Those who loaded positively on this factor perceived real benefits from taking neuroleptic medication, for example that the neuroleptics made them happier (+5) and allowed them to think more clearly (+5). Despite this, they expressed low dependence on the medication by strongly disagreeing with the statements,

"If I didn't take my medication I'd end up back in hospital" (-5), and
"I can't do without my medication" (-4).

They asserted their relative autonomy by disagreeing with the statement, "If a doctor prescribes something I think I should stick to it" (-4). The statements which discriminated between this factor and the other factors, shown in Table 5.3, confirm that these participants experience some benefits from neuroleptics, believe nonetheless that they do not need them, and are sceptical about medical advice. These participants might therefore be described as autonomous responders to neuroleptics.

The one participant who loaded negatively on this factor exhibited a

mirror image of these attitudes, perceiving no benefit from the neuroleptics in terms of happiness (-5), clarity of thought (-5) or decrease in symptomatology (-4). However, this participant believed that he could not do without his medication (+4) and that, without it, he would end up in hospital (+5). When asked after testing if he could account for the apparent discrepancy between these attitudes, he explained that taking neuroleptics had not resulted in a reduction in his tension, auditory hallucinations or paranoia, but had induced a reduction in the aggressive behaviour which had previously precipitated his admission into hospital.

5.4 Discussion

The use of Q-methodology in this study provided a unique insight into patients' subjective experiences of neuroleptic medication, an area which has previously received little attention. However the technique is controversial and has been criticised for a number of reasons. For example Q-studies usually employ relatively small samples. However Q-studies (including the one reported in this Chapter) usually take pains to sample from a broad range of attitudes. It is important to be cautious when generalising from the results of Q-studies to wider populations. For this reason it is often helpful to follow up findings from Q-studies using traditional attitude scaling techniques.

Q-methodology has also been criticised on statistical grounds. The most serious objection to Q-methodology is that because statements are placed along a forced distribution, the placement of a certain item along the continuum affects the placement of other cards and this violates the independence

assumption which is essential for most statistical tests. There is debate as to whether this violation is sufficient to invalidate the use of correlational analyses in Q (Kerlinger, 1986). The forced choice feature of Q-methodology has also been criticised on the grounds that it involves an unnatural forced procedure. However this constraint argument applies to all psychometric procedures and does not seem sufficient to negate the validity of the sorting technique.

Both the interview and Q data from this study indicate the complexity of patients' appraisals of their neuroleptics. Specifically, the data show that it would be an oversimplification to classify patients as either for or against taking neuroleptic medication. It is more likely that patients construct a variety of discourses, each of which expresses different interrelationships between those issues which are perceived to be important, for example the apparent benefits and costs of medication, interactions with prescribers, and issues of autonomy. It was shown that individuals could agree with aspects of more than one viewpoint which further invalidates the dichotomy of attitudes theory.

The prototypical Q-sorts generated by the participants in the study were in many ways similar to lay perspectives on long term medical treatment identified in previous qualitative studies, particularly those by Fallsberg (1992) and Stainton-Rogers (1991). Fallsberg (1992) carried out a qualitative study to investigate attitudes of patients with asthma, hypertension and pain towards their medication, using content analysis. Five clusters of attitudes were identified, three of which bear some similarity to those reported here. One category of attitudes, which was clearly similar to that identified in Factor A of the current study, was described as 'unreflected compliance' because patients

believed that compliance with medication was an imperative and that advice from health care professionals must be adhered to. Another category in the Fallsberg study was described as 'reflected compliance', because people in that group chose to take their medication as a result of careful consideration of the costs and benefits of treatment. This category shows similarities to Factor C identified in the present study, as people loading positively on this factor have made a balanced appraisal of the positive and negative effects of the medication. Another category in the Fallsberg study described people who expressed a generalized negative attitude towards taking medication; this is clearly similar to Factor B identified in the present study. In Stainton-Roger's, study (1991), Q-methodology was used to explore 83 participants' subjective attitudes towards responsibility for health and illness. The participants were from diverse backgrounds and had experience of various illnesses to give wide breadth to the range of attitudes constructed. One of the factors revealed in that study was described by Stainton-Rogers as 'body as machine' because of the patient's preoccupation with the positive benefits of modern biomedicine and medical expertise, such that compliance with medical expertise was seen as the only way of coping with illness. A second factor was described as 'robust individualism' because patients expressing this viewpoint were found to be less concerned with the impact of illness and its treatment than with their own autonomy. Stainton-Rogers argues that both of these perspectives are pervasive, culturally-sedimented discourses about illness, and they are certainly strikingly similar to those attitudes towards neuroleptic therapy expressed by volunteers loading on factors A and B identified in the present study.

Hogan, et al. (1983) used conventional factor analytic methodology to

study schizophrenic patients' attitudes towards neuroleptics. It is interesting to note that three quarters of the total variance in the study by Hogan, et al. (1983) was accounted for by subjective experiences of medication, which contributed to all the attitude clusters identified in the present study with the exception of the first. Concerns about autonomy, which were also prominent in the present findings, are represented by two factors in Hogan et al.'s study.

The fact that results were obtained in this study which were comparable with those obtained by other authors working with different qualitative techniques and different patient groups suggests that there is some evidence of validity and generalisability of the present findings. However the observations made in the present study need to be qualified for several reasons. The focus of this study has been the elicitation of different viewpoints or perspectives, and the study should not therefore be seen as a 'survey' of patients' attitudes. It has been noted that in Q studies, it is more important that the statements used to generate Q-sorts reflect the range of attitudes and opinions available to the group of people studied, than that the participants in the study are a fair representation of a wider population of individuals (Stainton-Rogers, 1991). Although the largest group of patients in this study held the perspective which was defined as unquestioning, uncomplaining and dependent, it is possible that the other perspectives would have been more important to other samples of psychiatric patients. It be should not be assumed that the perspectives taken by the participants in this study are static or correspond to stable traits. Social constructionist investigators have emphasised that individuals often switch from one viewpoint to another as dialogues unfold, for example when the individual is presented with a counter-argument or is asked to consider another

point of view (Gergen, 1985). It would be interesting to explore this with further research.

The observations reported in this Chapter have a number of clinical implications. In recent years, there has been considerable debate about the most appropriate regimens for delivering neuroleptic treatment, with various protagonists arguing the merits of oral versus depot, low-dose versus high dose, and continuous versus intermittent medications (as described in Chapter 2). These results suggest that the patient's perspective may have important implications for these debates. It may be that the most effective prescribing strategy to ensure patient satisfaction will be that which is consistent with their viewpoint. This could be particularly relevant in the case of the autonomous sceptics and the balanced appraisers. In the case of the autonomous sceptics it is tempting to argue that depot medication may be required to ensure compliance. However, such a response would fail to take into account the need for autonomy which is intrinsic to the beliefs of people loading on this factor. It is possible that an empowering approach which actively encourages the patient to self-regulate the effects of medication would be more effective in the long-term for this group. In the case of the balanced appraisers, it is the opportunity to weigh up the costs and benefits of medication in advance, with full recognition of the difficulty in striking the best balance between these, that is most likely to facilitate a lasting and positive relationship between the patient and the prescriber. Specific psychological techniques to facilitate such an appraisal have been found to have a powerful positive impact on motivation to undergo other kinds of difficult treatment (Miller, 1985; Miller, Benefield, & Tonigan, 1993).

The finding that health professional viewpoints conflict when considering medication from personal as opposed to professional perspectives is interesting. A greater understanding of this conflict may aid understanding of the patient-professional relationship, and may lead the way towards new strategies for increasing compliance. Diamond (1985) emphasised that clinicians should take into account the global subjective viewpoint of the individual, including symbolic aspects of the medication. Taking into account such perspectives is likely to have a positive impact on the therapeutic alliance between patient and prescriber which, as Frank & Gunderson (1990) have shown, may have an important impact on compliance with medication and the long-term outcome of a psychotic illness.

CHAPTER 6

Development and Validation of a Self-Rating Scale For Measuring Neuroleptic Side Effects The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)

6.1 Introduction

The side effects of neuroleptic drugs which are described in detail in chapter 2 are numerous and can be distressing. Clinicians who are able to efficiently monitor and treat side effects may enhance the therapeutic alliance and compliance. The development of efficient means of systematically assessing side effects would also be useful in clinical trials of new antipsychotic drugs.

A recent guide to good practice in the administration of depot medication jointly published by the Royal College of Nursing and the Department of Health (1994) advocated that monitoring of neuroleptic side effects should be carried out as matter of routine. Unfortunately, in clinical practice monitoring for side effects is often haphazard and unsystematic. This may reflect an ethos in psychiatry which has de-emphasised the patient's perspective, and also the absence of well-validated and easy to use instruments for this purpose.

Most scales which have been developed to measure neuroleptic side effects have focused on the extrapyramidal side effects, and have been designed for administration by trained raters, e.g. medical practitioners, who

make their ratings on the basis of the observed behaviour of patients. The Simpson and Angus scale, which has been used in many studies and clinical trials, consists of ten items designed to measure extrapyramidal side effects rated on a 5-point scale varying from 0 ("complete absence of the condition") to 4 ("condition in extreme form") (Simpson & Angus, 1970). Detailed scoring criteria are given for each of the items, some of which require physical manipulation and examination of the patient. For example rigidity is assessed by bending the patient's elbow joints and rating the resistance to movement on a five point scale. The assessment also includes "the head dropping test" in which the patient lies down on a well padded table and his/her head is raised by the examiner and allowed to drop. If the head falls resoundingly a rating of zero is given, and if the neck muscles are rigid and the head does not reach the table a maximum score of 4 is given.The reliability and validity of the scale have been assessed in a number of studies.

Mindham (1976) has described a similar, five-item scale also designed to assess drug-induced extrapyramidal reactions, based on Simspon and Angus' original scale. Ratings are given on a 0 to 3 scale. Although formal reliability and validity data are not reported, changes in scores on this assessment were reported following the start of neuroleptic treatment, peaking approximately three weeks after treatment had begun. Mindham also the advocated the use of simple psychomotor tests such as the 'grooved peg board test' (which requires subjects to place grooved pegs into grooved holes whilst being timed) noting that patterns of changes in performance on such tests over time are often similar to those observed on his scale.

The American Psychiatric Association developed the Abnormal Involuntary Movements Scale (AIMS) which is a validated means of assessing dyskinesias (American Psychiatric Association, 1980b; Munetz & Benjamine, 1988). The assessment consists of observation of the patient and an interview which is used to rate dyskinesias on a twelve item scale. Validation of the scale has been carried out in a number of studies, including an elderly population (Sweet, DeSensi, & Zubenko, 1993).

The three scales considered so far all focus on involuntary movements. Barnes (1989) has described a rating scale for assessing drug-induced akathisia consisting of three items: objective akathisia, subjective akathisia and global clinical assessment of akathisia. Patients are observed and then asked directly about subjective feelings of restlessness. Both objective and subjective akathisia are then rated on 4 point scales, and a separate distress score is recorded for subjective akathisia. The global assessment consists of a six-point scale, which varies between 0 ("absent") and 5 ("severe akathisia"). Inter-rater reliability for the individual items is reported to vary between a Cohen's kappa of 0.74 and 0.95.

The instruments which have so far been reported all assess a very limited range of the side effects experienced by patients, predominantly extrapyramidal side effects. The most comprehensive scale so far developed for the assessment of the adverse effects of neuroleptics is the UKU side effect rating scale (Lingjaerde, et al., 1987), developed by the Scandinavian Society of Psychopharmacology's Committee on Clinical Investigations (Udvalg for kliniske undersøgelser, hence UKU). This 48 item scale has been extensively

tested, has been shown to have good validity and reliability and has also been used in a longitudinal investigation of patients' side effects (Lingjaerde, et al., 1987). The main disadvantage of the scale is that it is intended for administration by a suitably qualified investigator (usually a psychiatrist) and the necessary interview can take 30 to 60 minutes or even longer. For this reason it would be impractical to use the UKU routinely in the clinical setting.

Considering the number of years neuroleptic medication has been available, it is surprising that a *self-rated* scale for assessing neuroleptic side effects has not been developed. A comprehensive self-administered side effect scale would obviously have a number of practical advantages in comparison with the UKU. Such a scale could be used routinely in clinical practice, except perhaps in the case of the most severely disturbed patients, and would be cost-effective if employed in clinical trials or other kinds of research studies. However, some authors have argued that psychotic patients may not be able to accurately rate themselves on psychometric scales. For example, in a review of social functioning measures for use in psychiatric settings, Platt (1986) argued that, although self-report inventories are an economic method of data collection with no threat to validity from interviewer bias, psychotic patients are likely to be too disturbed to understand the questions or report accurately on their social functioning.

Despite these reservations, evidence from previous research indicates that the majority of psychotic patients can be trained to self rate their own symptoms. For example, Birchwood, Smith, & Macmillan (1989) have described a method of training schizophrenic patients to monitor their own prodromal

signs in order to avoid or alleviate severity of relapse. A number of investigators have described methods by which patients may self-rate even florid psychotic symptomatology (Brett-Jones, Garety, & Hemsley, 1987) and these methods have been successfully employed in studies of cognitive-behaviour therapy for psychotic symptoms (Bentall, Haddock, & Slade, 1994; Chadwick & Lowe, 1990). It therefore seems feasible that the majority of psychotic patients would be able to self report neuroleptic side effects in a similar manner.

The aim of this study was therefore to design and evaluate a self-administered questionnaire for neuroleptic side effects. The items included in the scale were similar to those included on the UKU scale but were simplified and rewritten in plain English. In order to ascertain whether the patients who participated in the study were accurately reporting side effects or whether, on the contrary, they were reporting a high level of general symptomatology (perhaps because they are highly suggestible or experiencing a high degree of general distress) items which are not known to be neuroleptic side effects (e.g. hair loss, runny nose, chilblains) were included in the questionnaire. These items were termed "red herring" items. In order to assess the validity of the questionnaire, it was administered not only to patients being treated with neuroleptics but also to control subjects, who were not being prescribed any medication and had no history of any psychiatric disorder. Test-retest reliability of the questionnaire was assessed over a period of one week, and its concurrent validity against the UKU was also assessed.

As Finn, et al. (1990) have shown that patients' subjective estimates of

distress associated with particular side effects do not always concord with estimates made by mental health care professionals, patients were also asked to rate the extent of distress they experienced as a consequence of neuroleptic side effects. Patients were also asked to indicate whether they believed that the side effects they were experiencing were a consequence of the neuroleptic drugs they were being prescribed.

6.2 Method

Subjects

Fifty psychiatric patients were recruited from local day centres, neuroleptic depot administration clinics and outpatient departments. In addition to those recruited, five patients refused to take part. All patients included had received a diagnosis of schizophrenia from their consultant psychiatrists and all met the DSM-IIIR (American Psychiatric Association, 1987) criteria for schizophrenia as determined by case note data. All were currently receiving neuroleptic medication and 23 were concurrently receiving anticholinergic medication. None were being treated with any other form of medication.

Fifty normal control subjects were recruited from a variety of sources including continuing education classes, a local fire station, and from the administration and portering staff of Liverpool University. None of these subjects were receiving psychiatric treatment of any kind or were receiving any kind of medication. None had received formal education in any discipline relating to the practice of psychiatry.

Design of the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)

Items selected for the LUNSERS were mainly based on the physician-rated items included in the UKU Scale (Lingjaerde, et al., 1987). A copy of LUNSERS is included in Appendix 1. Forty-one items, covering psychological, neurological, autonomic, hormonal and other miscellaneous side effects, were constructed by rewording the appropriate UKU items so that they could be self-rated. Four UKU items, covering physical and psychological dependence, galactorrhoea, and fits were felt to be inappropriate for self-rating and no equivalent LUNSERS items were constructed. In the case of UKU items involving sexual dysfunction (erectile dysfunction, ejaculatory dysfunction, vaginal dryness and orgastic dysfunction) one global LUNSERS item ('difficulty achieving climax') was constructed in the hope of simplifying responding and in order to avoid items which had an exclusive sex bias.

In addition to the 41 side effect items, 10 red herring items were included, referring to symptoms which are not known neuroleptic side effects (e.g. chilblains, hair loss). The LUNSERS was constructed as a standard Likert scale with respondents being asked; "Please tick off how much you have experienced the following symptoms over the last month". Items were designed for self-rating on a 0-4 scale and were scored as follows: 'Not at all=0'; 'Very little=1'; 'A little=2'; 'Quite a lot=3'; 'Very much=4'.

Additional measures

A second questionnaire was designed to assess the extent to which

patients attributed their symptoms or side effects to medication and this is shown in Appendix 2. This questionnaire contained the symptoms listed on the LUNSERS but required respondents to indicate whether they believed each of the symptoms which they had previously endorsed on the LUNSERS was a neuroleptic side effect. The instructions at the top of this questionnaire stated' "Please tick off how much you think the following symptoms have been due to your neuroleptic medication during the last month". Three choices were available for each item: 'Due to medication'; 'Not due to medication'; 'Don't know'.

A further scale based on the LUNSERS was designed to assess the distress patients experienced as a consequence of particular side effects and this is shown in Appendix 3. Subjects were required to rate the amount of distress caused by each LUNSERS symptom on a 0 to 4 scale (choices: 'Not at all'; 'Very little'; 'A little'; 'Quite a lot'; 'Very much'). The instructions at the top of this questionnaire stated, "Please tick off how much you have been distressed by the following symptoms during the last month".

Procedure

Patients were invited to take part in the research on a voluntary basis but were excluded if they could not read or if they were prescribed medication additional to neuroleptics excepting antimuscarinic medication. After signing a consent form they were asked to complete a LUNSERS questionnaire after being told that the questionnaire included general symptoms and possible side effects of medication. On most occasions this occurred in the patient's own

home. Patients were then asked to complete the second questionnaire designed to measure the extent to which they attributed side effects to their medication. One week later the patients were again visited and were asked to complete the LUNSERS for a second time and to rate the amount of distress associated with each symptom using the distress scale. Subjects were then administered the UKU rating scale. In order to yield a crude indication of the reliability of the authors's UKU ratings, a consultant psychiatrist independently rated ten of the patients, also using the UKU scale. These ratings were all carried out within 24 hours of each other. The two ratings were generally in good agreement; across the ten subjects, the raters exactly agreed about the scores assigned for 81 % of items.

6.3 Results

Of the patients who took part in this study, 29 were male and 21 were female. They had a mean age of 46 years (range 23-65 years) and had been receiving neuroleptics for a mean of 16 years (range 2-38 years). The number of patients receiving particular neuroleptics are given in Table 6.1. Twenty-eight patients were receiving only one neuroleptic, with all the remaining patients receiving two neuroleptics. Chlorpromazine equivalent doses for the neuroleptics prescribed for patients were calculated using standard procedures (Davis, 1974; Foster, 1989). These ranged between 50 mg daily to 1600 mg daily with a mean of 427.5 mg daily. Of the fifty control subjects who took part in the study, 29 were male and 21 were female. The mean age of the control subjects was 40 years (range 17-73 years). The difference between the ages of the patients and the ages of the normal controls was significant ($t = 2.5$, $p < .05$, 98 df).

Table 6.1: To show range of neuroleptic drugs prescribed to 50 schizophrenic patients taking part in the study.

Patients on oral Medication only

Drug	Number Receiving Medication
Trifluoperazine	1
Haloperidol	1
Remoxipride	1
Clozapine	1

Patients on Depot Medication only

Drug	Number Receiving Medication
Flupenthixol	12
Fluphenazine	8
Pipothiazine	1
Haloperidol	1
Zuclopenthixol	2

Patients on Oral and Depot Medication

Drugs	Number Receiving Medication
Flupenthixol + Thioridazine	3
Flupenthixol + Sulpiride	1
Flupenthixol + Chlorpromazine	4
Flupenthixol + Remoxipride	1
Flupenthixol + Trifluoperazine	1
Fluphenazine + Thioridazine	1
Fluphenazine + Haloperidol	1
Fluphenazine + Chlorpromazine	3
Fluphenazine + Trifluoperazine	1
Pipothiazine + Thioridazine	2
Zuclopenthixol + Chlorpromazine	2
Fluspirilene + Haloperidol	1
Fluspirilene + Chlorpromazine	1

The results for the study will be considered in two sections, first, with regard to the reliability and validity of the LUNSERS and, second, with regard to patients' experiences of neuroleptic side effects as reflected in their scores on the LUNSERS and accompanying measures.

Reliability

Cronbach's alpha coefficient was calculated for the LUNSERS using patient data only and was found to be 0.889 on first testing and 0.886 on second testing. Test-retest reliability was assessed by calculating Pearson correlation coefficients between LUNSERS scores of patients recorded on the first occasion and those recorded one week later. Correlations were calculated for known side effect items individually and for total known side effect scores excluding red herring items. The mean correlation between individual items was 0.579 (range = 0.264 - 0.834). All correlations were significant at least at $p < 0.05$ and correlations for 34 of the 41 items were significant at $p < 0.001$. Correlations lower than 0.4 were obtained for 'reduced sex drive' ($r = 0.264$), gynaecomastia ('swollen/tender chest'; $r = 0.324$), and 'losing weight' ($r = 0.347$), 'difficulty achieving orgasm/climax' ($r = 0.352$) and 'drooling mouth' ($r = 0.363$). There was a highly significant correlation between the total known side effect scores on the LUNSERS measured one week apart ($r=0.811$, $p < 0.001$). However, there was a modest decrease in these scores from a mean of 45.08 to 36.80 over the same period, which was statistically significant ($t = 3.71$, $p < 0.001$, 49 df).

Concurrent validity

The concurrent validity of the LUNSERS was assessed by comparing patients' scores on second testing with the LUNSERS against their UKU scores obtained at the same time. These correlations were slightly higher than those observed between LUNSERS scores on first and second testing, with a mean correlation for individual items from the LUNSERS compared to corresponding items from the UKU scale of $r = 0.605$ (range = 0.115 - 0.884). The two lowest correlations were obtained for 'sleeping too much' ($r = 0.115$), and 'difficulty in getting to sleep' ($r = 0.116$), which were compared with the UKU items 'increased duration of sleep' and 'reduced duration of sleep'. Correlations lower than 0.4 were also observed for 'muscle spasms' ($r = 0.34$), and 'periods less frequent' ($r = 0.388$). All correlations were significant at $p < 0.05$ with the exception of the two items referring to sleep difficulties and 35 out of the 41 correlations were significant at $p < 0.001$. The correlation between total scores on the LUNSERS and total scores on the UKU scale was 0.828 ($p < 0.001$).

An indication of the degree of agreement between the LUNSERS and the UKU was calculated using the method described by Bland & Altman (1986). Figure 6.1 shows the relationship between the mean of the UKU and LUNSERS scores for total side effects and the difference between the scores for the two measures. For the purpose of this analysis, LUNSERS scores were rescaled to take into account the different theoretical maximum scores due to the different methods by which the items were scored on the two measures. It can be seen that the mean discrepancy between the two measures was 21.32 (SD = 11.5), indicating that, on average, subjects reported higher levels of side

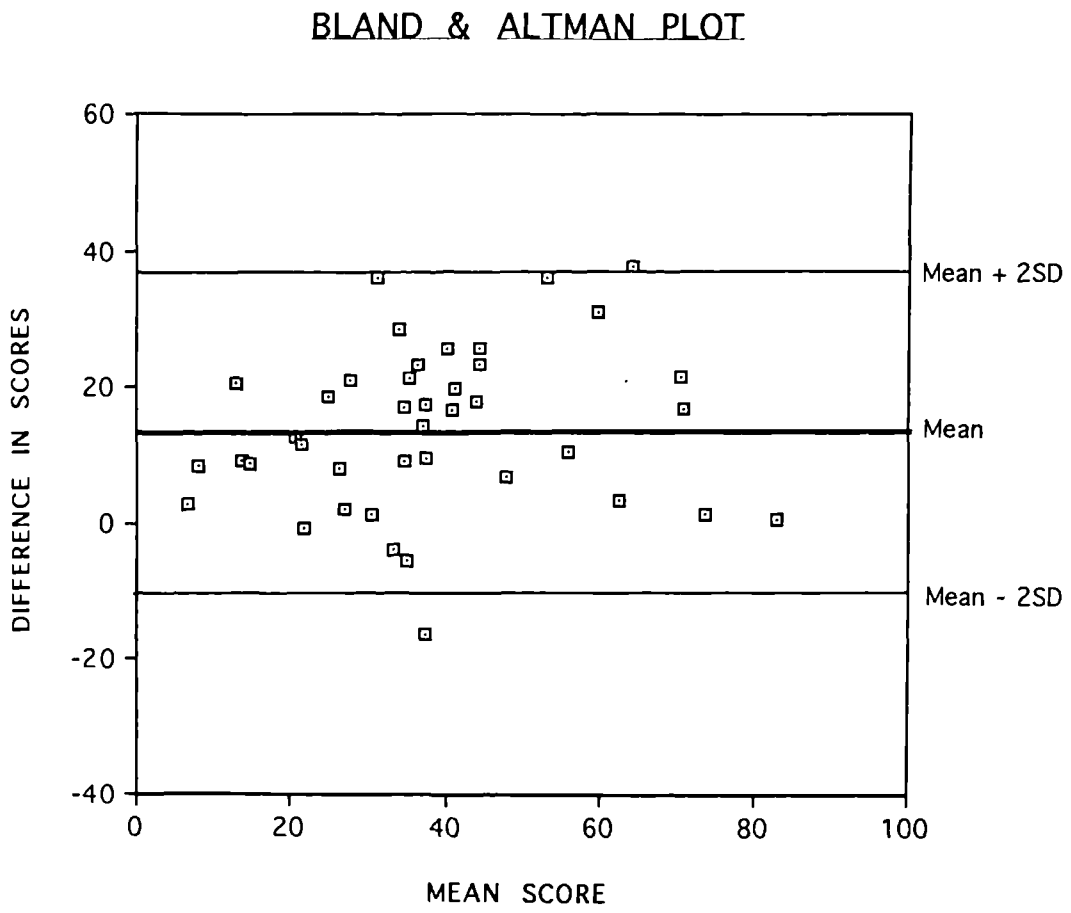


Figure 6.1: Bland and Altman plot for LUNSERS data, which shows relationship between mean of UKU and LUNSERS scores (x axis) for side effects against the difference between the scores on the two measures (y axis). The mean of the difference scores indicates that patients more readily report side effects on the LUNSERS than on the UKU.

effects on the LUNSERS than on the UKU.

These findings indicate that, overall, there is good concurrent validity between LUNSERS and the UKU. However, the LUNSERS scores pertaining to sleep difficulties did not agree well with those obtained by means of the UKU. This may, in part, reflect the fact that, on the UKU, these symptoms are scored objectively in terms of hours of sleep lost or gained rather than subjectively as on the LUNSERS.

Side effects and neuroleptic dosage

In order to further assess the validity of the LUNSERS, the relationship between patients' neuroleptic dosage, as measured in chlorpromazine equivalents estimated using standard techniques (Davis, 1974; Foster, 1989), and LUNSERS total side effects scores was examined. Pearson's r for this relationship was 0.31 ($p < 0.02$).

Comparison of medicated and non-medicated subjects

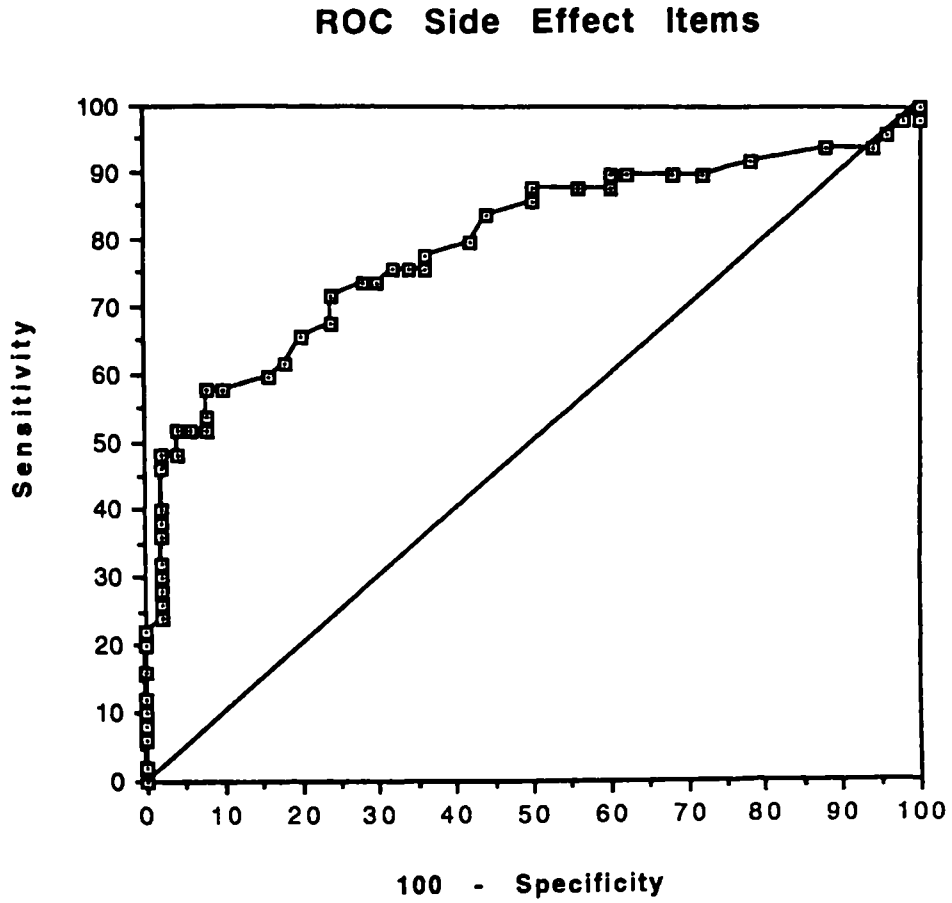
A third method of addressing the validity of the LUNSERS concerned comparisons between the medicated patients and the non-medicated control subjects. Mean total known side effect scores and mean total red herring item scores for test and control groups for these two measures are given in Table 6.2.

Table 6.2: Total side effect scores and red herring scores for schizophrenic patients receiving neuroleptics and unmedicated normal control subjects.

	Mean Score for test group	Mean score for control group
Known Side effects	45.1 ± 3.7	18.5 ± 1.9
Red herring items	5.1 ± 5.3	4.4 ± 4.1

Significant differences were observed for known side effects ($t = 6.30$, $p < 0.001$, 98 df) but not for red herring scores ($t = 0.80$, $p = 0.424$, 98 df). Differences between medicated and non-medicated subjects were less apparent when individual items were taken into account. Mann Whitney U tests between item scores for medicated and non-medicated subjects were significant ($p < 0.05$) for 26 out of 41 items. Generally, small differences between the groups were observed for items which concerned side effects which were rare (e.g. rash) or, in the case of sensitivity to the sun, which were troublesome only in the summer months (most of the subjects were tested at other times of the year).

A second method of assessing the validity of the LUNSERS by comparing data from the medicated and non-medicated subjects is shown in Figure 6.2, which gives Receiver-Operator Characteristic (ROC) curves (Swets & Pickett, 1982) for side effect scores and red herring scores. These curves, which indicate the extent to which the scores discriminate between medicated



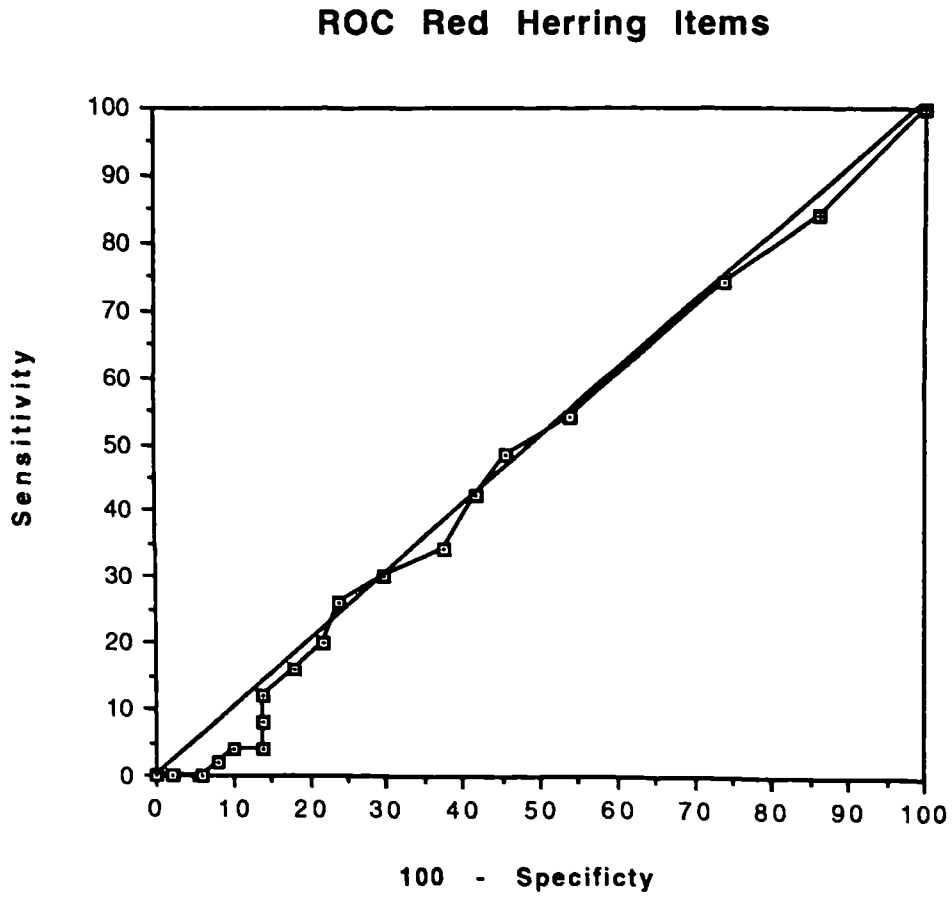


Figure 6.2: Receiver Operator Characteristic (ROC) curves for known neuroleptic side effects and for red herring items as self-rated by fifty schizophrenic patients. Sensitivity is plotted against 100 - specificity and curves indicate discrimination between test and control groups for known side effects (due to skew of curve to the left) but not for red herring symptoms.

and non-medicated subjects, are constructed by plotting sensitivity against 100 - specificity. By inspecting the curve it is possible to see how changing the cut-off point for LUNSERS side effect scores changes the ratio of medicated patients correctly assigned to their group to non-medicated subjects incorrectly assigned to the medicated group.

In the case of the red herring items, all scores lie close to the diagonal, indicating that the scores from these items do not discriminate between the two groups. In the case of the known side effect scores, however, the ROC curve is bowed upwards and to the left above the diagonal indicating that these scores do effectively discriminate between the two groups. As lower cut off points are accepted more non-medicated subjects are incorrectly assigned. Obviously, choice of cut-off on the LUNSERS must depend on the purpose for which the scale is being employed. However, our data indicates that, at a cut-off of 42 approximately 50 percent of medicated patients would be correctly classified and very few non-medicated individuals would be incorrectly classified. At a cut-off of 26, nearly 70 percent of patients would be correctly classified but approximately 25 percent of non-medicated individuals would be incorrectly assigned to the medicated group.

It should be noted that this ROC analysis provides a conservative indication of the performance of the LUNSERS. The LUNSERS has been designed to indicate the extent of side effects experienced by medicated patients and, in practice, it is unlikely that the scale would be used to determine whether individuals are medicated or not.

Prevalence rates for neuroleptic side effects, associated distress and attributions

The percentage of patients endorsing each of the known side effects recorded on the LUNSERS, together with the mean distress scores of those people who experienced each side effect and the percentage of individuals who attributed each symptom as a consequence of neuroleptic medication are given in Table 6.3. It is important to note that, when calculating these distress scores, only the data from those reporting a particular side effect were included. The most commonly reported side effects were tiredness, dry mouth, difficulty remembering things, tension and depression, all well-recognised adverse effects of neuroleptic medication (Edwards, 1986). It is apparent from Table 6.3 that the most common side effects were not necessarily those which caused most distress to patients. In fact, the highest levels of distress were reported for lack of emotions, period problems, tension, depression, difficulty in passing water, putting on weight, drooling mouth and tiredness.

The percentage of patients suffering from each side effect who attributed the effects to neuroleptics is also given in Table 6.3. Six out of the ten red herring symptoms fell into the group of ten symptoms which were least readily attributed to neuroleptics. However, dark urine, flushing of the face and hair loss were all attributed to neuroleptics by more than 30 percent of patients. At the other extreme, dry mouth, tiredness and shakiness were attributed to neuroleptics by only 54 percent of patients and other common side effects such as restlessness, muscle stiffness, blurred vision and difficulties in concentrating were attributed to medication by less than half of the sample.

Side Effect	Mean prevalence	Mean Distress	Attribution
Tiredness	78	2.3	54
Dry mouth	74	1.4	54
Memory probs	70	2.0	29
Tension	68	2.5	15
Depression	68	2.5	27
Restlessness	66	2.0	46
Blurred vision	66	1.9	27
Conc. probs	66	2.3	30
Inc. dreaming	66	1.5	21
Diff getting to sleep	64	2.2	28
Polyuria	58	1.6	28
Shakiness	56	1.9	54
Sensitivity to sun	56	1.5	68
Dyskinesias	54	1.7	52
Muscle stiffness	54	2.2	37
Headaches	54	2.1	22
Inc. sweating	52	1.4	23
Weight gain	50	2.4	64
Slow movements	50	1.6	52
Diff staying awake	48	1.9	54
Lack of emotions	48	2.3	50
Dizziness	48	1.6	38
Period problems	48	2.7	56
Sleeping too much	46	1.5	70
Constipation	44	1.3	23
Palpitations	40	1.8	30
Feeling sick	38	1.8	37
Muscle spasms	36	1.9	44
Reduced sex drive	34	1.5	41
Amenorrhoea	33	1.1	57
Inc sex drive	32	1.2	6
Losing weight	28	1.3	21
Rash	24	1.1	42
Itchy skin	22	1.8	45
Anorgasmia	20	2.2	40
Diarrhoea	20	2.3	20
Drooling mouth	20	2.4	70
Skin marks	18	1.4	45
Diff passing water	16	2.5	37
Gynaecomastia	8	1.7	50

Table 6.3: Prevalence of side effects in the sample of 50 schizophrenic patients, distress associated with side effects in those patients who report them (0 ='Not at all'; 1 = 'Very little'; 2 = 'A little'; 3 = 'Quite a lot'; 4= 'Very much') and percentage of patients experiencing side effects who attribute them to medication.

6.4 Discussion

This chapter has outlined the development and validation of a scale designed to measure neuroleptic side effects. Generally, the scale was found to be acceptable to both patients and non-medicated normal subjects, with most patients completing the scale within a period of five to twenty minutes. A few patients required some of the items to be explained to them. However, experience following this validation study has indicated that the scale can usually be completed even by acutely disturbed patients, can be administered easily by members of various health care disciplines (psychiatrists, psychologists, nurses and nursing assistants) without specialist training and, in many cases, can be completed by patients without supervision (i.e. patients can take the questionnaire away in order to complete it and return it later).

The internal consistency of the scale as measured by Cronbach's coefficient was high, indicating that the scale measured a coherent set of related experiences. The test-retest reliability data reported indicates that patients' responses are stable over relatively short periods of time (days). This result was to be expected because neuroleptic side effects, especially in patients who have been receiving their medication over some time, do not vary dramatically from day to day. However, the fact that patients' responses on the LUNSERS tended to be stable gives some indication that they are consistent in their reporting of side effects, a necessary condition for the validity of the scale. One caveat to this observation concerns the modest decrease in LUNSERS scores over the period between testings. It is unlikely that this change reflects absolute changes in neuroleptic side effects. Nor does the data indicate that the

reduction in scores can be accounted for by changes in the prevalence of side effects reported. Rather, patients seemed to give slightly lower estimates of the severity of their side effects on second testing and these lower estimates translate into lower total known side effect scores. Whether the apparent decrease in LUNSERS scores between testings would continue over a greater number of testings can only be established by further investigations.

The scale was not designed to assess the aetiology of particular symptoms and it is possible that patients' responses sometimes reflected aspects of their psychotic disorder, or perhaps even concurrent physical disorders which were causally unrelated to medication. In clinical practice it is difficult to assess symptom causality with a high degree of confidence although an effect is more likely to be drug induced: (a) if it differs from symptoms of the underlying disorder; (b) if it is consistent with the known side-effect profile of a particular drug; (c) if no other drugs are being given or withdrawn at the time of onset of the effect; (d) if there is a close temporal association between the effects and the plasma levels of the drug; and (e) if the effect disappears on withdrawing the drug and reoccurs on its reintroduction. In the present study, withdrawal of neuroleptic medication was not attempted for both ethical and practical reasons. However if the LUNSERS was used routinely before and during clinical use of neuroleptics, it would be easier to assess the likelihood of the reported effects occurring as a response to neuroleptic medication.

These reservations notwithstanding, four lines of evidence attest to the validity of the scale. First, responses to the questionnaire correlated with scores on the UKU, both for total symptomatology and for individual items. The only

exception to this was two items covering sleep difficulties. Second, there was an association between total known side effect scores on the LUNSERS and neuroleptic dosage. The fact that this association was modest was to be expected because the patients participating in this study were receiving a wide range of medications which varied in the side effects associated with them. It is difficult to accurately calculate neuroleptic equivalence for a range of drugs which have varied psychopharmacological action (e.g. in their affinity for a range of receptors) and this equivalence does not account for inter-individual variation in sensitivity of patients to side effects. The validity of converting neuroleptic dosages to equivalents has been criticised as crude (Kane, 1989). Third, the known side effect items on the LUNSERS discriminated effectively between medicated and non-medicated individuals. Fourth, patients receiving neuroleptics, although differing from normal controls in their reporting of known neuroleptic side effects, did not return high scores for the 'red herring' items. This latter finding is particularly important as it indicates that, despite fears that psychotic patients may not be able to accurately self-rate symptomatology (Platt, 1986), or that side effects may be elicited simply by asking patients about them (Newcomer & Anderson, 1974), patients responses on the LUNSERS are highly specific and do not reflect a general bias towards reporting symptoms.

Despite these observations, the patients in the present study showed greater willingness to report known neuroleptic side effects on the LUNSERS in comparison with the UKU. However, this finding does not necessarily indicate that LUNSERS data is less valid than data collected using the UKU. Responses to self-rated questionnaires may sometimes be more accurate than

data collected via face to face interviews with a stranger, particularly when questions concern embarrassing symptoms and attitudes (Hochstim, 1967; Siemiatycki, 1979) although this is not always the case (Cutler, Wallace, & Haines, 1988).

The relative prevalence of different side effects on the LUNSERS corresponded reasonably with the relative prevalence of side effects elicited by Lingjaerde, et al. (1987) using the UKU. In that study, as in the present study, tiredness, dry mouth, memory difficulties, tension and depression were all highly reported symptoms, leading Lingjaerde, et al. (1987), to note that psychic side effects are at least as common as neurological side effects. There was also a considerable amount of agreement between the two studies on low frequency side effects, with gynaecomastia, difficulty passing water and skin complaints being relatively rarely reported.

The distress associated with particular side effects was not related to the prevalence of the side effects, the greatest distress being reported for lack of emotions, period problems, tension, depression, difficulty in passing water, putting on weight, drooling mouth and tiredness. It is notable that neurological side effects, such as dyskinesias, although usually of considerable concern to psychiatrists (Finn, et al., 1990), were associated with only moderate levels of distress. Patients' attributions about side effects may indicate that a lack of knowledge about the adverse effects associated with their medication. Consistent with this observation, Rogers, et al. (1993) found that few of the patients they surveyed had been informed about side effects by the doctors and nurses who had prescribed and administered their medication. In part, this

may be a consequence of clinician's fear that informing patients about side effects will reduce compliance. There is scant empirical evidence to indicate that informing patients about side effects impairs adherence to neuroleptic regimens. Indeed, Seltzer, et al. (1980), despite finding that fear of side effects was associated with noncompliance, observed that educating patients about the side effects of neuroleptics reduced fear without compromising compliance. In a number of studies investigating the effects of informing depressed patients about the side effects of tricyclic antidepressants, it was found that patients who received this information did not differ from controls in terms of the number of drop-outs or clinical outcome (Myers & Calvert, 1976; Myers & Calvert, 1978). More recently, Kleinman, Schacter, & Koritar (1989) found that informing patients about the risk of tardive dyskinesia had no impact on compliance rates.

The results reported in this Chapter indicate that the LUNSERS may be a useful tool for a variety of purposes. The observation of a modest decline in LUNSERS scores between testings suggests that some caution may be warranted if the LUNSERS is employed in longitudinal investigations. However the reduction of scores on a second testing of psychiatric symptoms is a well known artefact, even when using instruments such as the Present State Examination (PSE) and is not affected by the duration of time between the first and second assessments (Jorm, Duncan-Jones, & Scott, 1989). Despite this qualification, the LUNSERS might be used as a brief and cost effective measure of side effects in pharmacological research, clinical trials and studies of adherence to neuroleptic regimens.

CHAPTER 7

A survey of Psychiatrists' and Registrars' Attitudes towards Neuroleptic Side Effects

7.1 Introduction

Previous studies have indicated that psychiatrists' perceptions of neuroleptic side effects may not always coincide with those of their patients who consume neuroleptic medication. As discussed in Chapter 2 Finn, et al. (1990) and colleagues observed a discrepancy between the distress associated with side effects as perceived by psychiatrists and the distress actually experienced by individuals taking neuroleptic medication. In chapter 5 of this thesis the "personal/professional conflict" was described as observed from the semi-structured interviews, suggesting that prescribers may perceive side effects differently when considering them from a personal viewpoint ("Weight gain would bother me most") as opposed to a professional viewpoint.

There have been some surveys of prescribing of psychotropic drugs such as that by Beardsley, Gardocki, Larson, & Hidalgo (1988) which have compared the prescribing of psychotropic drugs by primary care physicians and psychiatrists. However there have been very few studies of prescribers' attitudes towards prescribing. One Danish qualitative study investigated general practitioners' attitudes to prescription of psychotropic medications and this highlighted marked differences between prescribers. For example some prescribers were mostly concerned about the autonomy of the patient, whilst

others were most concerned about the need to act paternally (Holm & Husted, 1991). Another study in Israel which investigated the prescribing practices of psychiatrists for schizophrenic patients found a wide variation in the range and dosage of neuroleptics used (Heresco-Levy, 1993). To date little attention has been addressed to the issue of prescribers' attitudes towards the drugs they prescribe. A detailed literature search failed to reveal any studies which focus on possible discrepancies between prescribers' and patients' attitudes towards neuroleptics, other than the study by Finn, et al. (1990) previously referred to. The current study will attempt to address this deficiency.

As data had already been collected using the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS, see chapter 6), it was possible to survey psychiatrists' and psychiatric medical staffs' impressions of neuroleptic side effects and to compare the results with those already obtained from patients. A questionnaire was therefore constructed comprising the side effect items included in the LUNSERS, and which asked medical staff to estimate the incidence and severity of side effects and also to state how likely they would be to inform patients about the possibility of developing each side effect.

7.2 Method

The questionnaire employed in this study was based on side effect items included in the LUNSERS. For each side effect, respondents were asked to estimate the percentage prevalence amongst patients prescribed neuroleptics, the percentage prevalence as a side effect (i.e. taking into account the fact that

some patients may experience a particular symptom but not as a direct consequence of taking medication), the level of distress likely to be experienced by someone suffering from the side effect, and the likelihood of informing a patient about the possibility of experiencing the side effect. (In fact, one LUNSERS item - 'pins and needles' - was not included in the questionnaire due to an error. The final questionnaire therefore had 40 items as opposed to the 41 known side effect items on the LUNSERS). Initially four psychiatrists (not in the Mersey or North West region) were asked to complete the questionnaire and to give comments on the format and the comprehension. As a result of this initial pilot, a further item was added in order to distinguish between general prevalence of a symptom and the prevalence of actual side effects.

In order to collect data on psychiatrists' estimations of the prevalence of neuroleptic side effects the first item was phrased: "What in your clinical opinion is the overall percentage prevalence of dry mouth amongst patients who are prescribed neuroleptic medication?". As well as this respondents were also asked "What in your clinical opinion is the percentage of patients prescribed neuroleptic medication who experience this symptom directly as a consequence of their medication (i.e. in whom this symptom is a side effect)?". For each of these items the response asked for was an estimated percentage. Respondents were also asked to rate the level of distress associated with each side effect by the question: "What level of distress, in your opinion, do patients typically experience when they are affected by this neuroleptic side effect?", and asked to circle their response on a Likert scale: rated from "Not at all", "Very little", "Quite a lot" and "A lot" (scored from 0 to 4 similar to the

patient-rated distress questionnaire). Respondents were also asked to circle their response to the question: "How likely would you be to inform a patient prescribed neuroleptic medication about the possibility of experiencing this side effect?" on a scale from "definitely", "probably", "not sure", "probably not" and "definitely not", scored from 0 for definitely to 4 for definitely not.

Names and addresses of all consultant psychiatrists (69 in total), senior registrars (14 in total) and registrars (23 in total) in psychiatry in the Mersey Region were obtained from Regional Personnel Officers. The questionnaires (Appendix 4) were sent by post to all identified psychiatric medical staff with a covering letter, which amounted to one hundred and six medical staff. One month later another copy of the questionnaire along with a further covering letter was sent to all those who had not returned the questionnaire. Subsequent to this, an attempt was made to contact doctors who had not returned questionnaires by telephone.

Sixteen further respondents were recruited at a clinical meeting in North Wales and these consisted of 9 consultant psychiatrists, 2 senior registrars and 5 registrars in psychiatry who were asked to complete the questionnaire at a clinical meeting, and all agreed to do so. (Their willingness to cooperate may have reflected the fact that the study was strongly supported by a local consultant.)

7.3 Results

7.3.1 Response rate.

Five blank questionnaires were returned as the person concerned was

either on long term leave or was no longer in post. One respondent felt he could not fill in the questionnaire as he did not treat schizophrenic patients. Four individuals responded in writing that they were unwilling to complete the questionnaire for various reasons (one individual returned the questionnaire with "You must be joking" written across it in pencil). The initial response rate was 25 returned after the first mailing, 32 (in total) after the second mailing and only a further two after the telephone contact. Thus the final response rate was 34 out of a possible maximum of 100, ie 34%. The composition of responses was: 18 consultants, 4 senior registrars and 10 registrars and two respondents who did not report their grade of staff.

The total of all questionnaires returned was 50 (with a response rate of 43%, or 50 out of 116, for the two samples combined) and it is this cohort whose results were analysed and reported in the remainder of this chapter. In order to reduce repetition in the remainder of this chapter, the medical staff will be referred to as "psychiatrists" although some of the staff were at more junior grades as reported above.

7.3.2 Analyses of Results

Summary data of the means of psychiatrists' estimations of prevalence of side effects, distress associated with side effects and likelihood of informing patients of possible side effects were compared with patients self-reports of prevalence, distress and attribution of side effects to medication (these results are described in detail in Chapter 6). The main comparison was in the form of Spearman correlations between the reports of patients for prevalence, distress

associated with and attribution of side effects and estimation of the same variables as reported by psychiatric medical staff.

7.3.3 Summary data

The summary data are presented in Table 7.1. The most striking observation on initial inspection of the data was the wide variation in estimations made by medical personnel. For example the estimation of the overall prevalence of hypokinesia varied from 0% to 80%, the average level of distress which respondents estimate that patients would report varied from 0 (not at all) to 4 (very much) and the likelihood of informing patients about developing this side effect varied from 0 (definitely) to 4 (definitely not). This pattern was observed for most of the side effects included in the questionnaire. A subgroup of five psychiatrists did not attempt to make estimations for the sexual side effects included.

7.3.3.1 Prevalence of Side Effects

The mean rating of psychiatrists for overall prevalence of side effects was lower than the observed incidence of patients' self-rated side effects for all but two of the side effects (reduced libido and drooling mouth, each of which were rated 1% higher by psychiatrists than patients' mean ratings) included in the questionnaire. The psychiatrists were within 10% of the mean prevalence as rated by patients for weight gain, daytime sedation, anorgasmia, micturition difficulty and gynaecomastia. The mean ratings of the medical staff differed from those of the patients by more than 50% for memory problems, increased

Side Effect	Mean prevalence		Mean distress		Attribution	
	Patient	Psychiatrist	Patient	Psychiatrist	Patient	Psychiatrist
Tiredness	78	44	2 3	2 6	54	1.3
Dry mouth	74	43	1.4	2 1	54	1.5
Memory probs	70	15	2.0	1.8	29	3.1
Tension	68	27	2 5	2.3	15	2.8
Depression	68	27	2 5	2.5	27	2.3
Restlessness	66	34	2.0	3.1	46	1.0
Blurred vision	66	23	1.9	2.5	27	1.1
Conc. probs	66	39	2 3	2 5	30	2.3
Inc. dreaming	66	13	1 5	1.3	21	3.3
Diff getting to sleep	64	10	2 2	1.6	28	3.2
Polyuria	58	6	1 6	1 2	28	3.3
Shakiness	56	33	1 9	2.5	54	0.9
Sensitivity to sun	56	20	1.5	2.5	68	1.1
Dyskinesias	54	24	1 7	2 7	52	1 1
Muscle stiffness	54	35	2 2	2.8	37	0 7
Headaches	54	17	2 1	1 6	22	3.3
Inc sweating	52	13	1 4	1 9	23	2 9
Weight gain	50	40	2 4	2 8	64	1.4
Slow movements	50	26	1 6	2 2	52	1 7
Diff. staying awake	48	46	1 9	2 8	54	0 6
Lack of emotions	48	27	2 3	1 9	50	2.6
Dizziness	48	22	1 6	2 6	38	1 3
Period problems	48	8	2 7	1.7	56	3.4
Sleeping too much	46	26	1 5	1.5	70	2 1
Constipation	44	30	1 3	2.2	23	1.7
Palpitations	40	8	1 8	1 6	30	3.2
Feeling sick	38	8	1 8	1 7	37	3 1
Muscle spasms	36	18	1 9	3 3	44	1 1
Reduced sex drive	34	35	1 5	2 7	41	2.2
Amenorrhoea	33	15	1 1	2 3	57	2.2
Inc sex drive	32	3	1 2	0.6	6	3 7
Losing weight	28	7	1 3	1 0	21	3 6
Rash	24	8	1 1	2 4	42	2 4
Itchy skin	22	5	1 8	2 2	45	3 2
Anorgasmia	20	14	2 2	2.5	40	3 0
Diarrhoea	20	4	2 3	1 4	20	3 4
Drooling mouth	20	21	2 4	2 4	70	1 9
Skin marks	18	6	1 4	1 6	45	3 1
Diff passing water	16	10	2 5	2 3	37	2 3
Gynaecomastia	8	7	1 7	2 8	50	3 0

Table 7 1 Table to show in order, per cent prevalence of neuroleptic side effects as reported by patients (n 50), mean Psychiatrist's estimate of per cent prevalence of side effects (n=50), mean patient's rating of distress associated with neuroleptic side effects (Likert scaling from 0=not at all to 4=very much), mean Psychiatrist's estimate of distress (same scale), per cent attribution of side effects to neuroleptic medication (per cent of patients who experienced side effect who stated it was attributed to medication) and mean Psychiatrist s likelihood of informing patients about side effects (from 0 definitely to 4 definitely not)

dreaming, reduced duration of sleep and polyuria. For some side effects such as polyuria, psychiatrist's mean estimation of the prevalence of this side effect (6%) suggest that it is rare, whilst the mean self-rating of the patients (58%) suggest the opposite. Polyuria is a documented side effect of neuroleptic drugs probably associated with increased fluid consumption as a consequence of dry mouth (an anticholinergic side effect).

Psychiatrists' ratings for symptoms as side effects of neuroleptic medication rather than general prevalence was lower in all cases (except one photosensitivity, where general prevalence was estimated as the same as prevalence as a side effect) by between 1 and 19% (mean 5.2%). For the purposes of further analysis the general prevalence rate will be used since it was the general prevalence which was reported by patients using the LUNSERS in Chapter 6.

7.3.3.2 Distress associated with Side Effects

There was a notable variation in the level of distress estimated by psychiatrists with responses ranging from 0 (not at all) to 4 (very much) for more than half of the side effects included in the scale. Psychiatrists estimated the most distressing side effects to be: dystonias (mean estimation, 3.35), akathisia (mean 3.08) daytime sedation (mean 2.84), muscular rigidity (2.82) and weight gain (2.82). Psychiatrists estimated that the least distressing side effects were: increased libido (0.58), weight loss (0.98) and polyuria (1.18). The level of distress estimated by psychiatrists as compared to patients reports of distress was lower for 14 side effects and higher for 24 side effects, with two

side effects rated identically. The difference in means varied between 0.03 and 1.42. The greatest differences in psychiatrists estimations of distress were for: dystonias (psychiatrists mean rating greater by 1.42), rash (psychiatrists +1.29), reduced libido (psychiatrists +1.21) and amenorrhoea (psychiatrists +1.17). The greatest differences in underestimating distress caused to patients were for menorrhagia (psychiatrists mean rating less by 1.02), diarrhoea (-0.97), reduced duration of sleep (-0.65) and increased libido (-0.65). There was no overall trend of psychiatrists either over- or under-estimating the distress associated with neuroleptic side effects when comparing estimation with patients reports of distress.

7.3.3.3 Likelihood of informing patients of possibility of developing side effects

There was considerable variation between prescribers in the likelihood of informing patients of the possibility of developing side effects. The side effects which prescribers were most likely to inform patients about included muscular rigidity, daytime sedation and tremor (mean estimate between 0, definitely inform, and 1, probably inform, on the Likert scale). The side effects which prescribers were next most likely to inform patients about included; tiredness, dry mouth, akathisia, blurred vision, photosensitivity, dyskinesias, weight gain, akinesia, postural hypotension, constipation, dystonias and hypersalivation (mean estimate between 1, probably inform and 2, don't know). Prescribers were less likely to inform patients about the development of tension, depression, concentration difficulties, increased sweating, lack of emotions, increased duration of sleep, decreased libido, amenorrhoea, rash, difficult

micturition and gynaecomastia (mean estimate between 2 and 3, probably not inform). Prescribers were least likely to inform patients about the possibility of developing the following side effects: memory problems, increased dreaming, decreased duration of sleep, polyuria, headaches, menorrhagia, palpitations, nausea, increased libido, losing weight, pruritis, anorgasmia, diarrhoea and skin pigmentation (mean estimates between 3 and 4, definitely not inform).

7.3.4 Correlational Analyses

Table 7.2 shows Spearman correlations calculated between estimates of prevalence and distress derived from the patient data and the corresponding estimates from the psychiatrists. Note that it is the total prevalence estimates (ignoring whether or not the symptom is attributed to medication) of the psychiatrists which is included in the table. The patient data is the same as that reported in Chapter 6, so % prevalence is the percentage of patients reporting the presence of side effects at a score of 1 or above, distress is the mean reported distress for each side effects and % attribution is the percentage of patients reporting a side effect who state that it is due to medication.

It can be seen that psychiatrists estimates of prevalence correlate significantly with those of patients ($r = 0.5537$, $p < 0.001$). However, Figure 7.1, which shows a scattergram for these data, demonstrates that absolute estimates differ. Thus although both groups are generally rating the same side effects as having a lower or higher prevalence, there is a general trend for Psychiatrists to rate prevalence lower than patients in all cases. This data must be interpreted cautiously as it cannot be assumed that similar scale points for the two groups

Psychiatrists Prevalence Rating	r = 0.362 p = 0.022				
Psychiatrists Distress Rating	r = 0.428 p = 0.006	r = 0.630 p < 0.001			
Psychiatrists Likelihood to Inform	r = -0.537 p < 0 001	r = 0.783 p < 0.001	r = -0.812 p < 0.001		
Patients Prevalence Rating	r = -0.919 p = 0.573	r = 0.554 p < 0.001	r = 0.120 p = 0.459	r = -0.294 p = 0.065	
Patients Distress Rating	r – -0 167 p – 0 918	r = 0.154 p 0.343	r = 0.214 p = 0.185	r = -0.008 p = 0.996	r = 0.130 p = 0.423
	Patients Positive Attribution	Psychiatrists Prevalence Rating	Psychiatrists Distress Rating	Psychiatrists Likelihood to Inform	Patients Prevalence Rating

Table 7.2 To show Spearman correlation's between psychiatrists and patients mean ratings of prevalence and distress of 40 neuroleptic side effects, patients mean attribution of symptoms being caused by medication and mean likelihood of psychiatrists to inform patients about side effects.

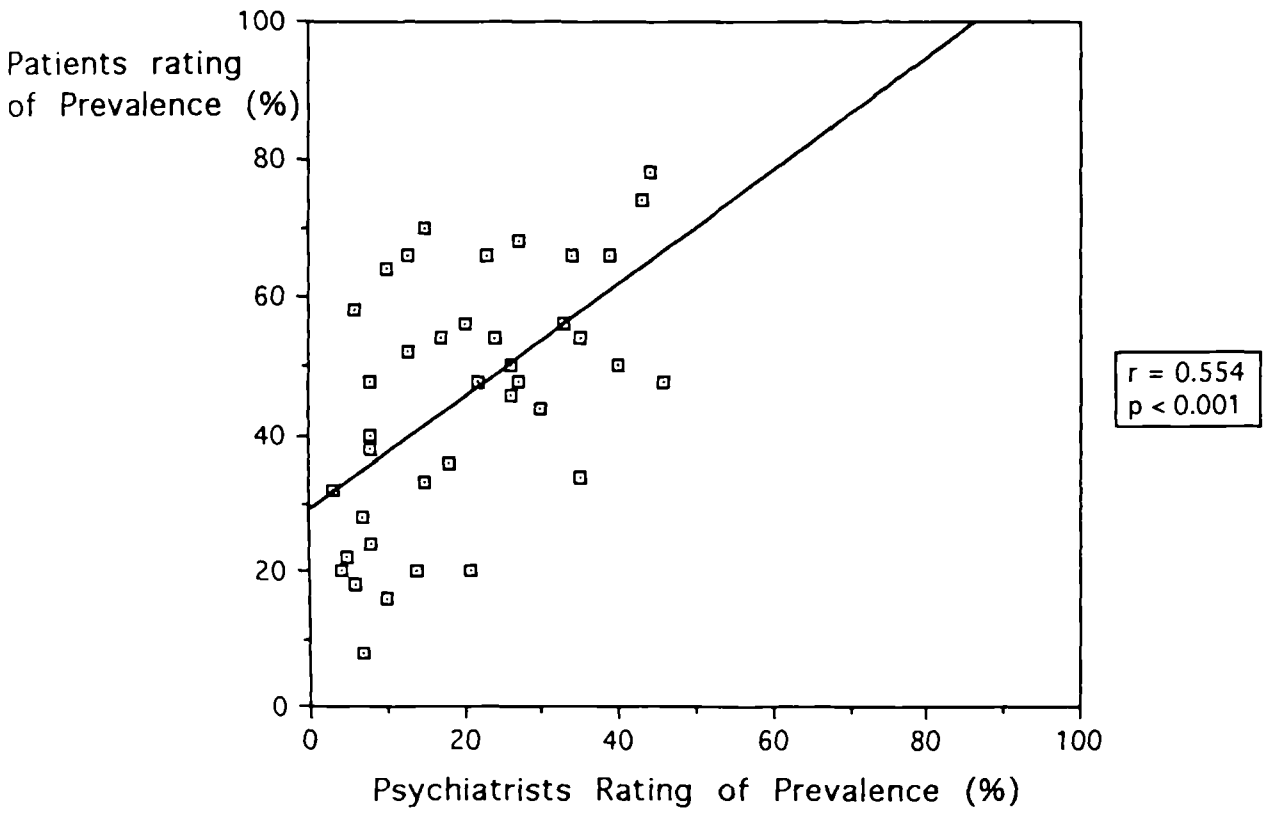


Figure 7.1 To show relationship between prevalence of neuroleptic side effects reported by patients and psychiatrists' mean estimates of prevalence of side effects. Prevalence is plotted for each of 40 neuroleptic side effects. A statistically significant correlation was observed between patients' and psychiatrists' ratings of prevalence ($r = 0.554$, $p < 0.001$).

have the same meanings. Also as reported in Chapter 6 responses on the LUNSERS, although significantly correlated with responses on the UKU, tended to be higher.

There was no statistically significant correlation between patients and psychiatrists' estimates of distress associated with neuroleptic side effects ($r = 0.214$, $p = 0.185$). That there is no relationship between the distress rated by psychiatrists and patients, can be seen clearly by the scattergram in Figure 7.2. This observation corroborates Finn et al.s' findings that psychiatrists are not always accurate at rating the distress caused to patients by side effects of their neuroleptic medication.

A statistically significant correlation was observed between psychiatrist's likelihood to inform patients of the risks of side effects and patients' attributions of side effects to medication. This correlation was negative ($r = -0.537$, $p < 0.001$) since the psychiatrist's scale was rated from 0 definitely inform to 4 definitely not inform. Hence those side effects which psychiatrists were more likely to inform patients about, were the same side effects that patients were more likely to attribute to medication.

Table 7.2 also shows statistically significant Spearman correlations between psychiatrists' estimates of prevalence, and psychiatrists' estimates of distress ($r = 0.630$, $p < 0 .001$), and also with their likelihood of informing patients about each of the 40 side effects ($r = -0.783$, $p < 0.001$). Thus psychiatrists generally estimate that side effects which are most prevalent are also most distressing, and they are more likely to inform patients about those side effects which they

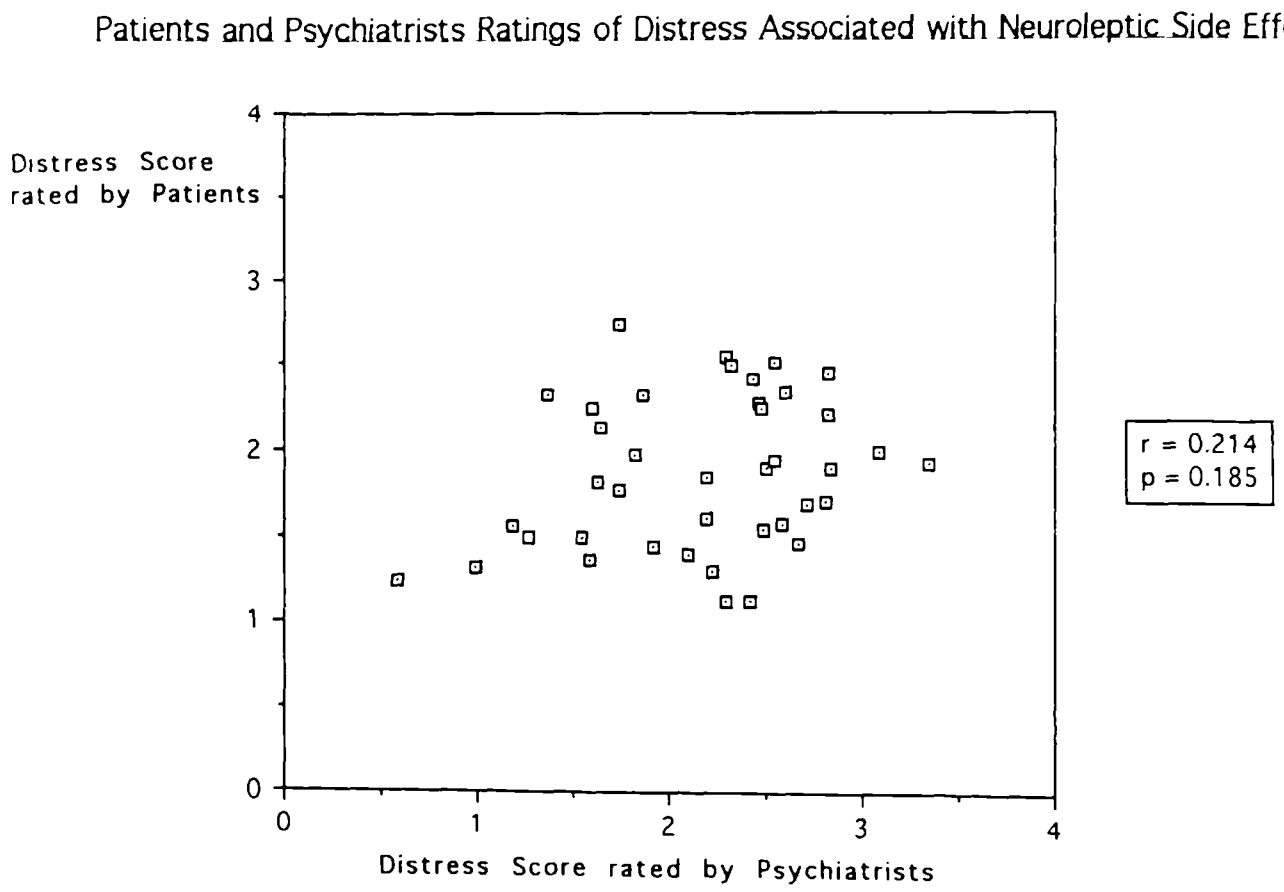


Figure 7.2 To show relationship between mean distress of neuroleptic side effects reported by patients and psychiatrists' mean estimates of distress of side effects. Mean distress is plotted for each of 40 neuroleptic side effects. No statistically significant correlation was observed between patients' and psychiatrists' ratings of distress (r = 0.214, p =0.185).

perceive as most common. The partial correlation between estimated prevalence and likelihood of informing ($r = -0.598$, $p < 0.001$) remains significant when controlling for distress. Similarly, the partial correlation between estimated distress and likelihood of informing also remains significant when controlling for prevalence ($r = -0.632$, $p < 0.001$). It therefore seems reasonable to conclude that psychiatrists' decisions about whether to inform patients about side effects are influenced by both the perceived distress associated with the side effects, and also their perceived prevalence, and that both of these influences are independent of one another.

Table 7.2 shows similar correlations between psychiatrists' estimates of their willingness to inform and patients' estimates of prevalence and their reports of distress. The relationship for prevalence just fails to reach significance; this is perhaps not surprising given that patients' estimates of prevalence correlate with those of the psychiatrists. However, there is no significant relationship between patients' reports of the distress and the likelihood that psychiatrists would inform patients about the particular side effects. This is also not surprising given that the psychiatrists were unable to make accurate estimates of the extent to which different side effects were distressing to patients.

7.4 Discussion

Psychiatrists showed a general understanding of the prevalence of neuroleptic side effects as demonstrated by their estimations of the most common side effects corresponding to the patients' actual reports of the

prevalence of side effects. However the general trend was that psychiatrists' ratings of prevalence were lower than those reported by patients. It was also demonstrated, perhaps not surprisingly, that the side effects which psychiatrists were most likely to inform patients of were also those which patients were more likely to attribute as side effects of the medication. However psychiatrists' and patients' ratings of distress showed no correlation. This has been found by other investigators and complements the findings in the Q-methodological study in Chapter 5, that there is sometimes a discrepancy between personal and professional perspectives regarding treatment with neuroleptic medication. Why this discrepancy occurs for the distress ratings and not for prevalence is unknown but there are important implications for the treatment of patients prescribed neuroleptic medication. It may be that training of mental health professionals does not include patients' perceptions of medication and this could explain the lack of awareness of the distress associated with side effects. Further research would have to be carried out in order to investigate this hypothesis. There was a tendency for psychiatrists to particularly overate the distress associated with extrapyramidal side effects and this probably reflects overinterest in these side effects at the expense of other adverse events both in medical training and the medical literature. If these issues were tackled in training it is possible that this would have a beneficial effect on the therapeutic alliance between prescriber and patient, the patient's clinical outcome and any impact neuroleptic side effects may have on quality of life.

For many side effects clinical interventions can be carried out to reduce discomfort experienced. For example if a patient is suffering from dry mouth, changing to a drug with less anticholinergic properties or prescribing a drug

such as salivix (which stimulates saliva production) can minimise or obliterate the adverse effect. It is known that some patients consume vast quantities of fluid in an attempt to dispel the unpleasant sensation of a dry mouth, and compound the problem with an additional stressor of polyuria, and this causes a vicious circle of dry mouth - increased fluid consumption - polyuria - polydipsia/dry mouth. On rare occasions, urinary obstruction (another anticholinergic side effect) can be complicated by water intoxication provoked by an excessive intake of fluids due to decreased salivary secretion (Edwards, 1986). If clinicians are unaware of the problem of polyuria (psychiatrist's mean rating of prevalence was 6% as opposed to patient's mean rating of 58% and other investigators findings of approximately 40% prevalence (Lingjaerde, et al., 1987) , they may not be advising patients in the best way to minimise the side effect and this may adversely affect the patient's quality of life. Thus the discrepancies observed may highlight possible improvements in training of clinicians which would directly benefit management of patients' side effects.

Similarly, psychiatrists' perceptions of the distress suffered as a consequence of neuroleptic medication influenced their decision to inform patients about those side effects. However it is clear that patients' and psychiatrists' perceptions of distress do not correlate and therefore psychiatrists may be using a limited knowledge base in their judgement.

Another finding of the study was that psychiatrists were less likely to inform patients about some of the more embarrassing side effects such as decreased libido, amenorrhoea, menorrhagia and anorgasmia. There was also a sub-group of five psychiatrists who did not attempt to estimate prevalence,

distress and likelihood of informing patients for these more embarrassing side effects. This again raises queries about communication between psychiatrists and patients. Psychiatrists were unwilling to make estimations on an anonymous questionnaire, this could mean that they are unwilling to discuss these side effects with patients, and patients themselves may also be unlikely to raise these issues. Estimations of sexual difficulties experienced as side effects of neuroleptic medication are high with some studies reporting 60% of people prescribed thioridazine experiencing this problem (Kotin, et al., 1976). Thus, this may be a hidden problem and further research would be useful in this area.

This study is limited by a number of factors which may have potentially biased the results. For example, the response rate was not very high (only 34% of Merseyside psychiatrists responded in spite strenuous attempts to improve the response rate), although similar to previously published survey studies. For example Meise, Kurz, & Fleischhacker (1994) attempted to survey 960 psychiatrists and neurologists and achieved a response rate of 46.5% with only 29.6% being returned complete and useful for analysis. However selective bias due to non-response cannot be excluded. The sampling methods were different in North Wales as opposed to the postal Merseyside survey and this may have biased the results. However it was not possible to analyse the Merseyside respondents data separately as the response rate was too low. Also the survey asked psychiatrists to *estimate* the prevalence, distress and likelihood of informing patients about neuroleptic side effects and this may not reflect what actually happens in practice. However the results indicate that further research into this area is merited.

There are two important issues which emerge from the findings of this study. Firstly, that psychiatrists do not have an in-depth understanding of the distress that patients suffer as a result of experiencing neuroleptic side effects, and secondly, that psychiatrists are informing patients about medication side effects based on an erroneous assumptions about the distress suffered. Each of these factors may lead to a lack of empathy for patients experiences and this may result in a less successful clinician-patient relationship. As it is known that the patient-clinician relationship has a role to play in patient compliance this could have serious implications in terms of noncompliance and its' consequences described in Chapter 3. It would seem that the perceptions of prescribers of the effects of neuroleptic medication and the consequences of those perceptions is an area worthy of further investigation.

CHAPTER 8

A Longitudinal Study of Variables Related to Neuroleptic Compliance: A Comparison of Chronically and Newly Prescribed Patients

8.1 Introduction

This chapter describes a longitudinal study of response and attitudes to neuroleptic therapy in patients with a diagnosis of schizophrenia. Two groups of patients were recruited into the study. One group had been taking neuroleptic medication for at least three years and the other was being prescribed neuroleptic medication for the first time. The variables measured in the study included: attitudes to medication, symptoms, side effects, neuroleptic dosage and knowledge of medication. These variables were measured at three time points: shortly after admission to an inpatient psychiatric ward, one month later, and then six months after the initial assessment. The unique aspects of the study were that it was carried out longitudinally and that it included a comparison of neuroleptic naive individuals with individuals who had a longer experience of the drugs. There were a number of reasons for carrying out the study in this way.

First, as a number of authors who have investigated attitudes to neuroleptic medication have noted, attitudes may vary over time, although few studies have investigated this. For example Davidhizar, et al. (1986) stated that no studies have been reported on patients' attitudes to neuroleptic medication

contrasting those who have only been on medication a short time with those who have had extensive experience with the medication. Also it has been found that the pattern of response of psychotic symptoms to neuroleptic medication is different in recent onset patients when compared to more long term patients. For example in a study of 39 patients with a DSM IIIR diagnosis of schizophrenia assessed using the Brief Psychiatric Rating Scale, it was found those with a recent onset of illness showed no reduction in withdrawal retardation scores in contrast to those with at least a three year duration of illness (Hill, et al., 1992). As attitudes may vary over time, their relationship with other variables may also change. For this reason, Hogan, et al. (1983) suggested that concurrent measurement of subjective response and side effects throughout a prolonged course of drug therapy may enhance understanding of the development of attitudes towards medication.

8.2 Method

8.2.1 Recruitment of Volunteers

Forty-six subjects were recruited into the study from inpatient wards in Merseyside. There were two groups of patients: (i) patients with a DSM IIIR diagnosis of schizophrenia and at least a three year history of treatment with neuroleptic drugs and (ii) patients experiencing a first admission for a psychotic disorder resulting in treatment with neuroleptics for the first time (although most of the latter group would be expected to fulfil the DSM IIIR criteria for schizophrenia, in some cases the initial diagnosis was uncertain). Subjects were given an information sheet and if they agreed to take part, they were asked to

sign a consent form. It was made clear that they were able to withdraw from the study at any time.

8.2.2. Research Tools administered

The following questionnaires and symptom schedule were administered initially, and at one and six months after the initial assessment;

Instrument	Measures
PANSS (Positive and Negative Syndrome Scale)	Psychotic symptoms
LUNSERS (Liverpool University Neuroleptic Side Effect Rating Scale)	Neuroleptic side effects
Neuroleptic Knowledge Questionnaire	Knowledge of neuroleptic medication
DAI (Drug Attitude Inventory)	Attitudes towards neuroleptic medication
Van Putten Dysphoria scale	Dysphoric reaction to neuroleptic medication

A more detailed description of each of these scales is provided in the following paragraphs, and copies of each of the scales is provided in the appendices.

8.2.2.1 PANSS

The Positive and Negative Syndrome Scale (PANSS) was developed by Kay, Fiszbein, & Opler in 1987. It is a 30-item rating instrument which was developed using a defined operationalised method to evaluate positive,

negative and general symptom dimensions of schizophrenia. A summary of the symptoms included in the scale is provided in Appendix 5. The assessment is based on a semi-structured clinical interview and other sources of information such as health professional's or family member's observations. The PANSS was based on the Brief Psychiatric Rating Scale (Overall & Gorham, 1962) and the Psychopathology Rating Schedule (Singh & Kay, 1975). This scale was an improvement on previously developed scales for a number of reasons. For example there is a specific focus on the evaluation of positive and negative symptoms of schizophrenia and a composite score is obtained which indicates the balance of positive and negative symptoms. Strict operational criteria and detailed definitions are included to enable accurate decisions on the severity of symptomatology which are rated on a seven point scale. The PANSS has also been assessed for sensitivity to drug changes (e.g. Feinberg, Kay, Elijovich, Fiszbein, & Opler, 1988) and it's validity in longitudinal studies has been demonstrated.

A number of studies have been carried out to assess the psychometric properties of the PANSS and the reliability and validity of the scale have been well tested. The PANSS has been shown to produce a normal distribution of scores, is internally consistent, and has demonstrated stability and reliability (Kay, Opler, & Lindenmayer, 1989).

The investigator was trained to administer the PANSS by the use of a training video and the PANSS rating manual. As an index of the ability of an individual to administer this instrument, inter-rater reliability is measured by comparing the results of the trainee with a trained psychiatrist. This is achieved

by the trainee rating video-taped interviews with psychotic patients. The video consists of five interviews with psychotic patients. The trainee watches each patient being interviewed by a psychiatrist and rates the psychotic symptoms exhibited. At the end of the interview the scores of the trained psychiatrist are compared to those of the trainee. In order to continue with the training an inter-rater reliability of at least 80% must be obtained for each of the positive, the negative and the general scores rated. Scores are only given for the first two patients presented and then there are a further three practice interviews. In order to assess the reliability of the scores rated for these patients the scores of the author were compared with the scores of another trainee who was also learning to use the PANSS in the Department of Clinical Psychology. The results of the comparisons of scores rated (shown as % within one point of other raters score) on the PANSS are as follows;

Interview	Positive	Negative	General
1	93%	87%	86%
2	90%	81%	90%
3	100%	90%	96%
4	86%	85%	97%
5	89%	80%	95%

In addition to this training, a practice run was carried out with two "real" patients before the onset of the study in order to further familiarise the author with the interview schedule.

8.2.2.2 LUNSERS (Liverpool University Neuroleptic Side Effect Rating Scale)

This scale was developed for patients to self-rate the side effects they experience as a result of taking neuroleptic medication and shown in Appendix 1. The development and validation of this scale is described fully in Chapter 6 of this thesis. The scale was used in this study in order to assess the contribution of side effects to attitudes to neuroleptic medication.

8.2.2.3 Neuroleptic Knowledge Questionnaire

This scale attempted to measure knowledge acquired by patients about their neuroleptic medication. The scale was based on an instrument designed to assess knowledge of depot medication, developed by Dr Malcolm Peet, Senior Lecturer in Psychiatry at Sheffield University, and colleagues. Prior to the onset of the study it was assumed that not all of the volunteers would be prescribed depot medication alone (in previous studies at least 10% of the sample were taking oral medication alone) and so the questionnaire was adapted so that it included knowledge of both oral and depot medication.

The scale consists of general questions about neuroleptic medication specific questions about the name, dosage and frequency of medication prescribed, and questions about information received regarding neuroleptic medication. The format of the questions was closed yes/no style for the majority of the items and open style for others. The full scale is shown in appendix 6.

For statistical analyses two separate knowledge scores were used: a general knowledge score and a specific knowledge score. The general knowledge score was calculated by totalling correct scores from four of the items; item 7 concerning the correct classification of the medication (i.e. neuroleptic allocated 1 mark), item 8 which asked respondents to indicate which of ten symptoms were side effects of medication (allocated 5 marks, 1 for each correct response), item 9 concerning tardive dyskinesia (allocated 1 mark) and item 10 concerning the reason for continuing medication. Negative marking was included to minimise the effects of a positive response bias, so that any incorrect response was scored -1. Thus the total maximum general knowledge score was +8. The specific knowledge score was calculated by considering responses to the name of the medication (proprietary or approved name was accepted; if completely correct 2 marks were awarded, if partially correct or if the correct name was given for one medication but not for another one mark was awarded), the dose of medication (one mark allocated if partially correct and two marks if completely correct) and frequency of dosage (one mark allocated if partially correct and two marks if completely correct). These scores were used in the statistical analyses described later in this chapter. The respondents' answers were compared with each patient's medication prescription in order to assess the accuracy of their responses. Results from all of the items are also described as a detailed analysis of patients knowledge of neuroleptic medication in section 8.3.

8.2.2.4 Drug Attitude Inventory

This scale was developed by a Canadian researcher Tom Hogan and his co-workers and is described in detail in previously published reports (Hogan & Awad, 1992; Hogan, et al., 1983). The scale was developed from an initial sample of 100 statements generated from patient's comments about neuroleptic medication by three psychiatrists over a period of several months. This set of statements was then administered to a group of 41 out-patient schizophrenic volunteers. The medication compliance of these volunteers was then estimated on a seven point scale by their therapist. Thirty items were found to discriminate between compliers and noncompliers based on therapists ratings. The response set bias was minimised by attempting to balance the number of items scored true or false by each prototypical group. The final version of the scale consisted of thirty statements to which patients responded "true" or "false", with the result of possible total scores in the range -30 to +30. Thus a person with the most positive attitude towards neuroleptic medication possible would achieve a score of +30. A copy of the scale is included in Appendix 7.

The final version of the questionnaire was then administered to one hundred and fifty schizophrenic out-patients. The internal consistency coefficient was found to be 0.93 and the test-retest reliability coefficient was found to be 0.82 when a randomly selected sample of subjects were re-tested four weeks after the initial testing. The authors also carried out factor analysis which identified seven robust factors. The first two factors "positive subjective feelings which the patients attribute to neuroleptic drugs" and the "negative pole of the dysphoric-syntonic continuum" accounted for 71.5% of the total

variance. The scale correctly classified 89% of the sample as either compliant or noncompliant as assessed by physician's rating. The scale has also been compared to biochemical measurement of neuroleptic compliance using thin layer chromatography to analyse levels of neuroleptic medication in urine samples and was found to correctly classify 74% of patients as compliant or noncompliant (Trenerry, 1983).

8.2.2.5 Van Putten Dysphoria scale

This scale was developed by Van Putten and is described in detail in a study which found that an early dysphoric response to chlorpromazine predicted drug refusal and a poor prognosis (Van Putten & May, 1978a). The scale consists of four questions asking the consumer's subjective opinions about the effects of the neuroleptic (see appendix 8) and the response to each question is graded on a continuum from -11 which is maximal disagreement and +11 which is maximal agreement. Thus scores on this scale can range from -44 through to +44. Van Putten and his colleagues described anyone with a positive score as a euphoric responder and anyone with a negative response a dystonic responder whilst a score of zero indicated a syntonic responder. In this study 60% had a euphoric and 40% a dystonic response. Typical descriptions of the effects of the neuroleptic by the dystonic responders included assertions that chlorpromazine made them "goofy", "lazy","mummified", "dull" "fuzzy "or " like a hangover without a headache". Descriptions of the euphoric responders included assertions that the drug made them "calmer", "tranquil", "relaxed", "less wound up" or "more together"

Further details recorded

In addition to the assessments listed above which were carried out at each time point, other details were recorded including attendance at out patient appointments and number of nights spent in hospital before and during the experimental period. Age and gender of volunteers was recorded and prescribed neuroleptic medication was noted at each time point. Chlorpromazine equivalent doses for each time-point were calculated using standard procedures (Davis, 1974; Foster, 1989).

8.3 Results

8.3.1 Subject Characteristics

A total of 46 subjects participated in the study. There were 19 refusals, 9 female and 10 male, and 2 further subjects (both male) who withdrew from the study during the initial assessment, following significant life events (death of a near relative in each case). For ethical reasons, no attempt was made to elicit a reason for refusal, but when individuals volunteered a reason it was usually that they were too distressed to take part, or that they were suspicious about the purpose of the study.

Twenty three of the volunteers were being prescribed neuroleptics for the first time (the Newly Medicated or NM group); of these 6 were female and 17 were male and the mean age of this group was 27 (S.D=9). The remaining 23 volunteers had received neuroleptic medication for at least three years (the Long-term or LT group); of these 3 were female and 20 were male and their

mean age was 40 (S.D.=11). At the one month follow-up, a further three volunteers (all male) decided that they no longer wanted to take part in the study, two were in the LT group and one had been prescribed neuroleptic medication for the first time. Again for ethical reasons subjects were not asked to give a reason for withdrawing from the study, but all three were clearly distressed at the time and one had developed severe paranoid delusions about the investigator. Sadly, one of the male volunteers who had been prescribed neuroleptics for the first time took his own life before the one month follow up.

At six months a further two patients (One in the LT group and one in the NM group, both male) could not be traced, despite repeated attempts to make contact. One male volunteer who had been prescribed neuroleptics for the first time refused to complete the questionnaires at six months as he was very angry at being readmitted to hospital. Of the long term group who completed the study, 13 lived alone and 7 lived with others. Of the Newly Medicated group 5 lived alone and 14 lived with others. The following table shows the number of people who completed assessments at each time point.

Table 8.1

Time/months	0	1	6
New group	23	21	19
Chronic group	23	21	20

The results obtained were analysed in a number of ways. Firstly correlations between the different measures were examined at each point in time in each group. Analyses of variance (repeated measures) were calculated

to assess differences between groups and changes in parameters over time. Finally, regression analyses were carried out in order to assess the predictive validity of the various attributes for attitudes towards neuroleptic medication at the six month follow up.

8.3.2 Correlations

Spearman correlations were carried out between the following variables: psychotic symptoms, side effects, dysphoria, drug attitudes and knowledge of medication for each group at each time point. The results of these analyses are shown in tables 8.2 to 8.4, in which correlations between variables are shown at each time point for each group. Many correlations were carried out on the data obtained from this study and therefore the risk of obtaining spurious results by chance is increased. For this reason it may be expedient to consider only those correlations which occurred on more than one occasion or those which were statistically significant at the $p < 0.001$ level. A number of theoretically interesting correlations were observed between the variables.

A statistically significant correlation was observed between scores on the Van Putten dysphoria scale and the Drug Attitude Inventory at each time point for each group, and this confirms the results of previous researchers that the scales are concordant (Hogan & Awad, 1992). The correlation coefficient was always at least $r = 0.485$ and was greater than 0.8 for three out of six of the correlations and the level of significance was $p < 0.001$ on five occasions and on one occasion was at the level of $p < 0.01$. This indicates that this correlation was stable and strong.

Newly Medicated group

LUNS SE							
DAI	r =0.620 p<0.001						
PPOS			r=-0.431 p=0.020				
PNEG		r=0.523 p=0.008					
PGEN		r=0 657 p<0 001			r=0.643 p<0.001		
SK					r=-0.373 p=0.040		
GK				r=0 370 p=0.042			
	VP	LUNS SE	DAI	PPOS	PNEG	PGEN	SK

Long Term group

LUNS SE							
DAI	r =0 485 p=0 009						
PPOS		r=0.467 p=0.012	r=-0.476 p=0 011				
PNEG							
PGEN							
SK			r=0 370 p=0 041	r=-0 390 p=0 033			
GK							
	VP	LUNS SE	DAI	PPOS	PNEG	PGEN	SK

Table 8 2 To show correlations between dysphoria meaured by the Van Putten Scale (VP), neuroleptic side effects (LUNS SE), drug attitude inventory scores (DAI), positive symptoms measured using the PANSS (PPOS), PANSS negative symptoms (PNEG), PANSS general psychopathology symptoms (PGEN), specific knowledge about neuroleptic medication (SK) and general knowledge about medication (GK) at the initial assessment for the newly medicated group (top table) and the long term group (bottom table)

On only one occasion of the possible six, side effects correlated negatively with scores on the Drug Attitude Inventory and this was in the Long Term group at six months ($r = -0.507$, $p < 0.05$). This means that for people having taken medication for at least three years the presence of side effects was associated with a negative attitude to medication at the six month follow up but not at the initial assessment or at one month follow up. This correlation was moderate at $r = 0.507$, but the level of significance was not high at $p < 0.05$. Due to the large number of correlations carried out, a spurious result cannot be ruled out and therefore this result must be interpreted with caution. Overall, the presence of side effects did not have a consistent effect on consumers' attitudes to medication, as assessed by correlational analyses.

In the case of both groups there was a significant negative correlation between positive symptoms and scores on the DAI, at the initial assessment and at one month follow-up but not at the 6 month follow-up as shown in Tables 8.2 to 8.4. At one month the level of statistical significance was high ($p < 0.01$ for the NM group, $p < 0.01$ for the LT group). This observation indicates that volunteers with a high score for positive symptoms as assessed using the PANSS were more likely to have a negative attitude towards their medication on these occasions. As this correlation occurred on four occasions it seems unlikely that it was a chance observation. Negative symptoms were not correlated with scores on the Drug Attitude Inventory (DAI) in any group at any time.

There was a small but statistically significant correlation between specific knowledge and drug attitudes at the initial testing for the Long Term group ($r =$

Newly Medicated group

LUNS SE							
DAI	r =0.832 p<0.001						
PPOS	r=-0.704 p<0.001		r=-0.521 p=0.009				
PNEG							
PGEN	r=-0.719 p<0.001	r=0.581 p=0.004	r=-0.590 p=0.003	r=0.609 p=0.002	r=0.408 p=0.037		
SK					r=-0.634 p<0.001	r=-0.429 p=0.030	
GK							
	VP	LUNS SE	DAI	PPOS	PNEG	PGEN	SK

Long Term group

LUNS SE							
DAI	r =0.812 p<0.001						
PPOS	r=-0 458 p=0 019		r=-0.595 p=0.002				
PNEG							
PGEN	r=-0.451 p=0.020			r=0.607 p=0.002	r=0.486 p=0.013		
SK							
GK							
	VP	LUNS SE	DAI	PPOS	PNEG	PGEN	SK

Table 8.3 To show correlations between dysphoria meaured by the Van Putten Scale (VP), neuroleptic side effects (LUNS SE), drug attitude inventory scores (DAI), positive symptoms measured using the PANSS (PPOS), PANSS negative symptoms (PNEG), PANSS general psychopathology symptoms (PGEN), specific knowledge about neuroleptic medication (SK) and general knowledge about medication (GK) at the one month follow up for the newly medicated group (top table) and the long term group (bottom table)

Newly Medicated group

LUNS SE							
DAI	r=0.785 p<0.001						
PPOS		r=0.599 p=0.009					
PNEG							
PGEN		r=0.718 p<0.001		r=0.737 p<0.001	r=0.472 p=0.041		
SK							
GK		r=0 568 p=0.014					
	VP	LUNS SE	DAI	PPOS	PNEG	PGEN	SK

Long Term group

LUNS SE							
DAI	r=0 826 p<0 001	r=-507 p=0.022					
PPOS							
PNEG							
PGEN	r=-0 505 p=0 023	r=0 534 p=0 015		r=0 614 p=0 004	r=0.486 p=0.030		
SK							
GK							
	VP	LUNS SE	DAI	PPOS	PNEG	PGEN	SK

Table 8 4 To show correlations between dysphoria meaured by the Van Putten Scale (VP), neuroleptic side effects (LUNS SE), drug attitude inventory scores (DAI), positive symptoms measured using the PANSS (PPOS), PANSS negative symptoms (PNEG), PANSS general psychopathology symptoms (PGEN), specific knowledge about neuroleptic medication (SK) and general knowledge about medication (GK) at the six month follow up for the newly medicated group (top table) and the long term group (bottom table)

0.370, $p < 0.05$). This correlation was not observed for the Newly Medicated group or at any other time point. Thus knowing the name dose and frequency of medication was not consistently associated with a positive attitude towards neuroleptic medication. General knowledge was not correlated with positive attitudes towards medication in either group at any time point.

In order to assess the relationship between DAI scores and the admission length and attendance at out-patient appointments, Spearman correlations were carried out between DAI scores at each time point and the number of nights spent in hospital during the study period. The results of these analyses are shown in Table 8.5. In the NM group the number of nights spent in hospital during the six month study period was not significantly correlated with DAI scores measured at any of the three time points. Attendance at out patient appointments correlated with initial DAI scores ($r = 0.467$, $p < 0.05$) and scores at six months ($r = 0.524$, $p < 0.05$) but not at the one month assessment. A statistically significant negative correlation was observed between the number of nights spent in hospital and DAI scores measured at the initial assessment in the LT group ($r = -0.512$, $p < 0.05$) but not at one month or six months. There was no correlation between DAI scores at any time point and number of nights spent in hospital for the LT group.

The results reported so far have focused on correlations with scores obtained using the DAI, as drug attitudes were the most important aspect of this study. However a number of other statistically significant correlations were obtained and these, which can also be seen in Tables 8.2 to 8.4., will now be briefly described.

Newly Medicated Group

Nights in hospital	r=0.029 p=0.905	r=-0.365 p=0.114	r=-0.086 p=0.735
Out patient attendance	r=0.467 p=0.044	r=0.355 p=0.136	r=0.524 p=0.031
	DAI 0 month	DAI 1 month	DAI 6 months

Long Term Group

Nights in hospital	r=-0.512 p 0.021	r=-0.354 p 0.125	r=-0.388 p=0.091
Out patient attendance	r=-0.269 p=0.281	r=-0.217 p=0.388	r -0.257 p=0.304
	DAI 0 month	DAI 1 month	DAI 6 months

Table 8.5 To show correlations between nights spent in hospital during the study period, attendance at out-patient appointments, and attitudes towards treatment (Drug Attitude Inventory scores) measured initially, at one month and at six months in the Newly Medicated group (top table) and in the Long Term group (bottom table

Scores for neuroleptic dysphoria as measured using the Van Putten scale showed a statistically significant negative correlation with PANSS general psychopathology scores for both groups at the one month assessment and for the LT group at the six month assessment. Thus those individuals with high general psychopathology scores (including anxiety, depression and lack of judgement and insight) were more likely to show a high dysphoric response to neuroleptic medication on these occasions.

LUNSERS scores correlated with positive symptoms on two of six possible occasions, in the Long Term group at the initial assessment ($r = 0.467$, $p < 0.05$), and in the Newly Medicated group at six months ($r = 0.599$, $p < 0.01$). Hence on these occasions the presence of positive symptoms was associated with the experience of neuroleptic side effects. In order to assess whether the increase in side effects was a consequence of higher doses being prescribed for people with greater positive symptomatology, partial correlations were carried out between positive symptoms and neuroleptic side effects controlling for chlorpromazine equivalent doses. For the LT group at initial assessment the partial correlation was 0.438 ($p = 0.061$) and so the correlation just failed to reach significance when controlling for neuroleptic dosage. However in the NM group at the six month follow up this correlation ($r = 0.606$) remained statistically significant ($p < 0.05$) even when controlling for neuroleptic dosage. LUNSERS scores also correlated with general psychopathology scores on the PANSS in both groups at 6 months (NM $r = 0.718$, $p < 0.001$; LT $r = 0.534$, $p < 0.05$) and in the NM group at the initial assessment ($r = 0.657$, $p < 0.001$) and at one month ($r = 0.581$, $p < 0.01$). Thus general psychopathology scores which included items such as depression,

anxiety and poor attention correlated with side effects scores. As this was consistent, relatively high and on three occasions at a high level of significance it is less likely to have been a chance finding.

There were a number of consistent significant correlations between symptoms scores on the PANSS sub-scales, for example between positive symptoms and general psychopathology which can be seen in Tables 8.2 to 8.4.. Specific knowledge scores correlated negatively with negative symptoms at the initial assessment ($r = -0.373$, $p < 0.05$) and at one month in the NM group ($r = -0.634$, $p < 0.001$) but not at six months. Again, this was observed on more than one occasion and was highly significant at one month so would be more likely to be a genuine effect than if it occurred on a single occasion. Specific knowledge also correlated negatively with positive symptoms in the LT group at the initial assessment ($r = -0.390$, $p < 0.05$) but this was not a consistent finding and was not highly significant so must be given less consideration than some of the other findings. A negative correlation was also observed between general psychopathology symptoms and specific knowledge for the NM group at the one month assessment. General knowledge correlated significantly with positive symptoms in the Newly Medicated group at the initial assessment ($r = 0.370$, $p < 0.05$) and also with side effects in the NM group at the six month assessment ($p = 0.568$, $p < 0.05$).

As a number of authors have indicated that there is a relationship between insight and compliance with medication (Bartko, Frecska,Horvath, Zador & Arato, 1988; Davidhizar, 1987; Lin, Spiga & Fortsch, 1979; Marder, Mebane, Chien , Winslade, Swann & Van Putten, 1983; Nelson, Gold,

Hutchinson & Benezra, 1975), correlations were carried out between scores on the PANSS insight item and DAI scores at each time point. There was a statistically significant negative correlation between the PANSS insight item and scores on the DAI for each group at 0 and 1 month and for the LT group at 6 months ($p < 0.01$ in each case). However there was no significant correlation between the PANSS insight item and DAI score at 6 months for the NM group.

8.3.3 Group Differences and Changes over time

The following section will describe changes over time in the attributes measured as part of the research. These changes, which were tested using two-way ANOVAs (group x time with time as a repeated-measure variable), are shown in Figures 8.1 to 8.5.

Symptoms of Schizophrenia

In both groups there was a decrease in total PANSS scores one month after the initial assessment and a further decrease was observed after six months as shown in Figure 8.1. The mean scores for the LT group appeared higher. A two way ANOVA (group x time) was carried out on the data. There was a significant effect for time, $F(2,62) = 26.00$, $p < 0.001$. Post-hoc Tukey tests showed a significant difference between scores at the initial assessment and at the one month assessment, and between the initial assessment and the assessment at six months ($p < 0.01$ in both cases) but not between assessments at one and six months. The effect for group just failed to reach significance, $F(1,31) = 3.57$, $p = 0.067$, and the interaction between group and time was not

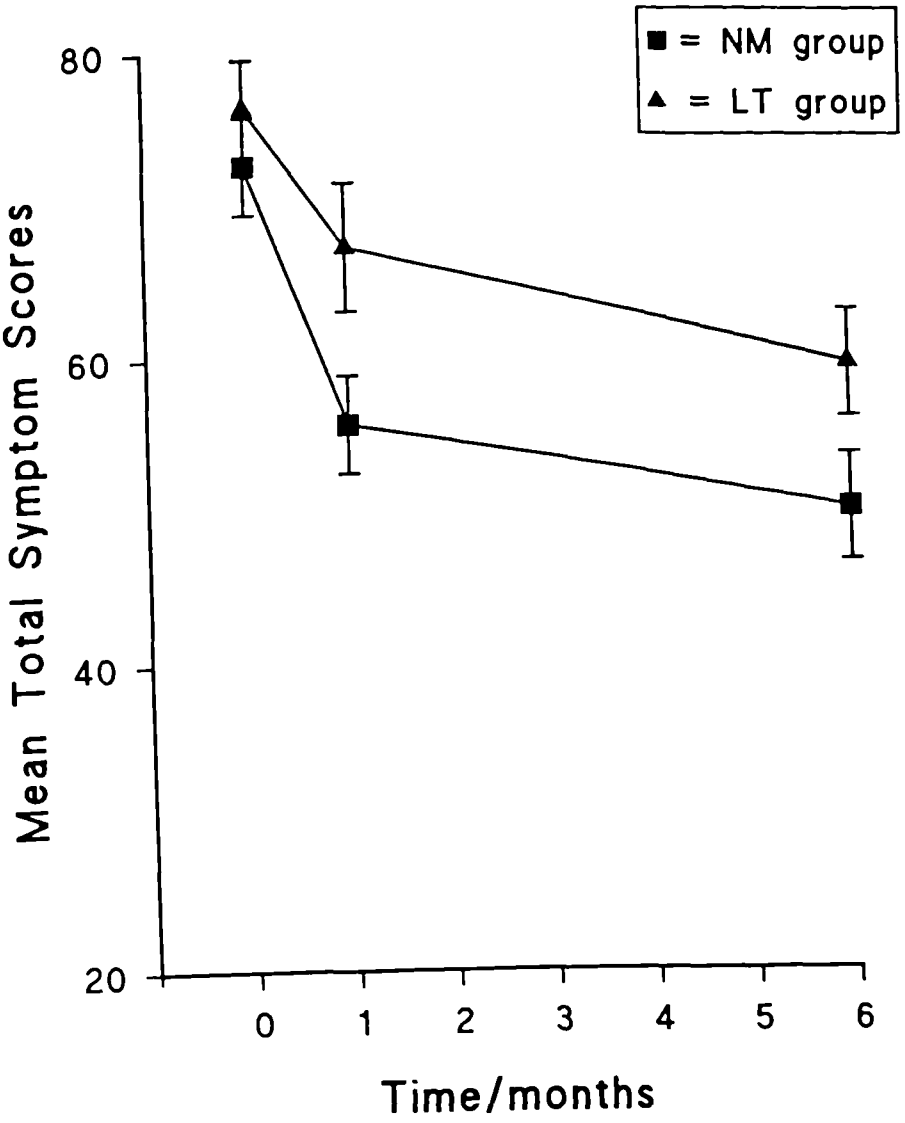


Figure 8.1 To show changes in mean total symptom scores as measured using the Positive and Negative Syndrome Scale over the six month study period. Mean values are shown for the Newly Medicated (NM) group and the Long Term (LT) group ± standard error of the mean.

significant, $F(2,62) = 0.80$, $p = 0.454$. This indicates that total symptom scores decreased in both groups, with no difference in response between groups.

Both groups also showed a reduction in positive symptoms over the six month period as shown in Figure 8.2. A two way ANOVA showed a significant effect for time $F(2,72) = 39.47$, $p < 0.001$, and post-hoc Tukey tests indicated that there was a significant difference between assessments initially and one month as well as initially and six months ($p < 0.01$ in both cases) but not between assessments at one month and six months. There was no significant effect for group $F(1,36) = 1.70$, $p = 0.200$, or for the interaction between group and time $F(2,72) = 1.08$, $p = 0.346$.

Overall the LT group appeared to show more negative symptoms than the NM group at all time points, and the NM group seemed to show a greater reduction in negative symptoms than the LT group over the six month period as shown in Figure 8.2. However a two way ANOVA demonstrated a significant effect for group $F(1,36) = 5.98$, $p < 0.05$ but not for time $F(2,72) = 2.29$, $p = 0.109$ or for the interaction between group and time $F(2,72) = 0.36$, $p = 0.699$.

Neuroleptic dosage and side effects

The mean chlorpromazine equivalent doses (CPEQs) appeared to be higher for the LT group than in the NM group at all time points, and the mean doses appeared to decrease over the sixth month period in both groups as

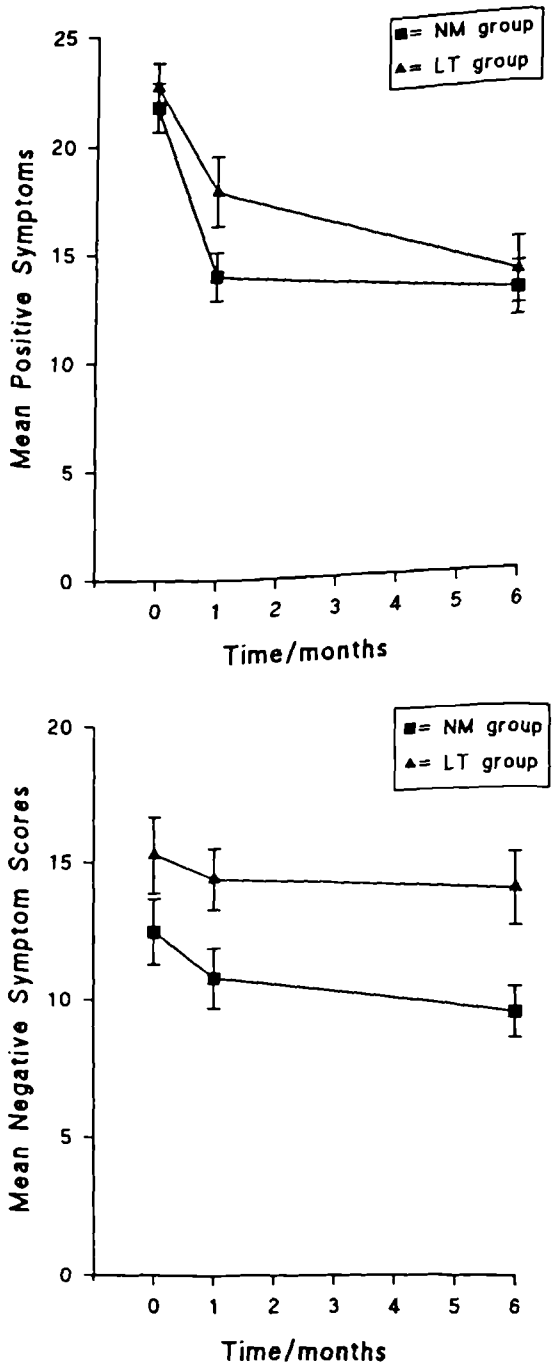


Figure 8.2 To show changes in mean positive symptom scores and mean negative symptom scores as measured using the Positive and Negative Syndrome Scale over the six month study period. Mean values are shown for the Newly Medicated (NM) group and the Long Term (LT) group ± standard error of the mean.

shown in Figure 8.3. A two-way ANOVA demonstrated a significant group effect $F(1,37) = 5.48$, $p < 0.05$, and a significant effect for time $F(2,74) = 4.92$, $p < 0.05$. Post-hoc Tukey tests indicated a significant difference between CPEQs calculated initially and at six months and between CPEQs calculated between one month and six months ($p < 0.05$ in both cases), but not between initially calculated CPEQs and CPEQs at one month. However there was no significant effect for the interaction between time and group $F(2,74) = 0.07$, $p= 0.937$. This indicated that the LT group were prescribed significantly higher doses than the NM group and that doses significantly decreased in both groups over the six month period.

Figure 8.3 also shows that side effects, as measured using the LUNSERS, appeared to decrease in both groups over the six month period but there was no difference between the groups in the amount of side effects experienced. A two way ANOVA revealed a significant time effect $F(2,68) = 12.25$, $p < 0.001$, but no group or interaction effects. Post-hoc Tukey tests indicated that there was a significant difference between side effects measured initially and at six months ($p < 0.01$) and between side effects measured at one month and at six months ($p < 0.05$) but not between side effects measured initially and at one month. This was a similar temporal pattern to the changes in chlorpromazine equivalent doses, although there was no significant difference between the side effects experienced by each group.

Attitude towards neuroleptic medication

Mean attitudes to neuroleptics as measured by the Drug Attitude

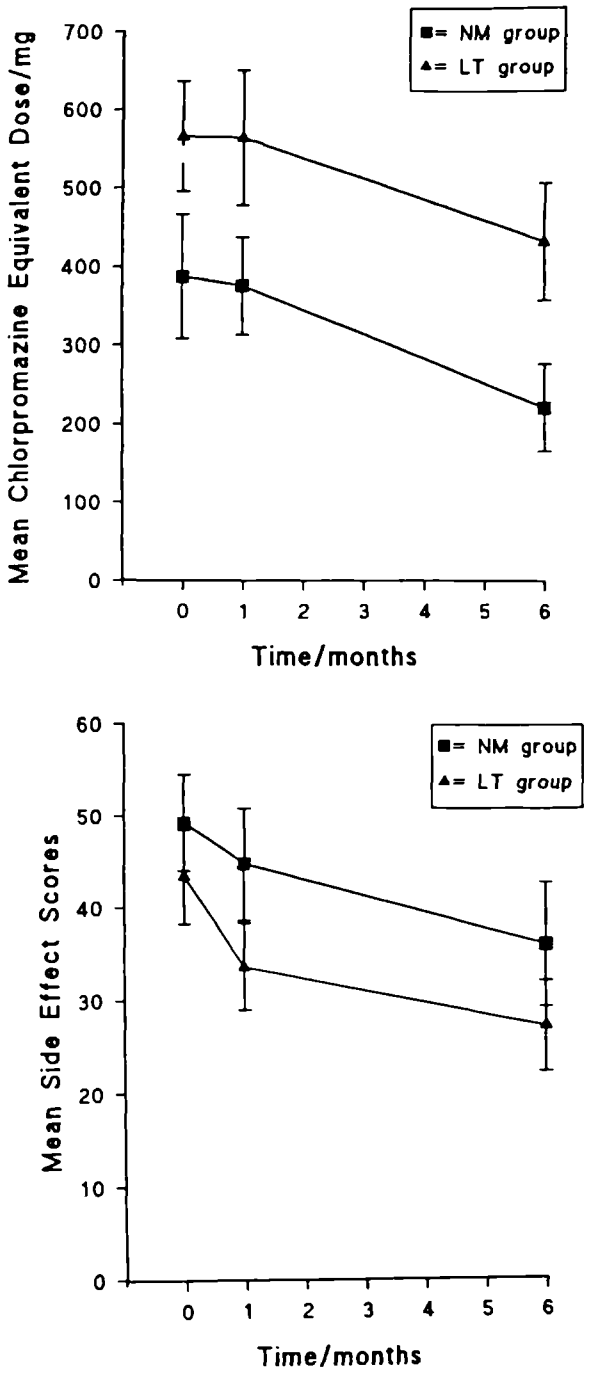


Figure 8.3 To show changes in mean chlorpromazine equivalent doses and mean side effect scores as measured using the LUNSERS over the six month study period. Mean values are shown for the Newly Medicated (NM) group and the Long Term (LT) group ± standard error of the mean.

Inventory appeared to increase in both groups over the six month experimental period, as shown in Figure 8.4, but this effect was not statistically significant $F(2,74) = 1.07$, $p = 0.347$. There was also no statistically significant effect for group, $F(1,37) = 0.09$, $p = 0.768$, or interaction between group and time $F(2,74) = 0.33$, $p = 0.717$. As none of these main effects or interactions were statistically significant, post-hoc tests were not carried out on these data.

One factor which has been implicated in noncompliance is living alone (Altman, Brown & Sletten, 1972) In the present study, 13 of those in the LT group and 5 of those in the NM group lived alone. A three way ANOVA (group x living status x time) was therefore carried out on the DAI data. However, none of the main effects or interactions in this analysis reached statistical significance.

Knowledge of Neuroleptic Medication

Results from the Neuroleptic Knowledge Questionnaire (NKQ) on the first testing are presented here in detail, because they give some indication of the extent to which patients were informed, or had acquired knowledge in other ways, about the purpose and consequences of neuroleptic therapy. The changes in knowledge scores (specific and general) were then examined in both groups over the six month period.

No difference was observed between the two groups for many of the responses obtained on the first testing. However, a total of 21 respondents in the NM group attributed tiredness as a side effect of medication, as opposed to

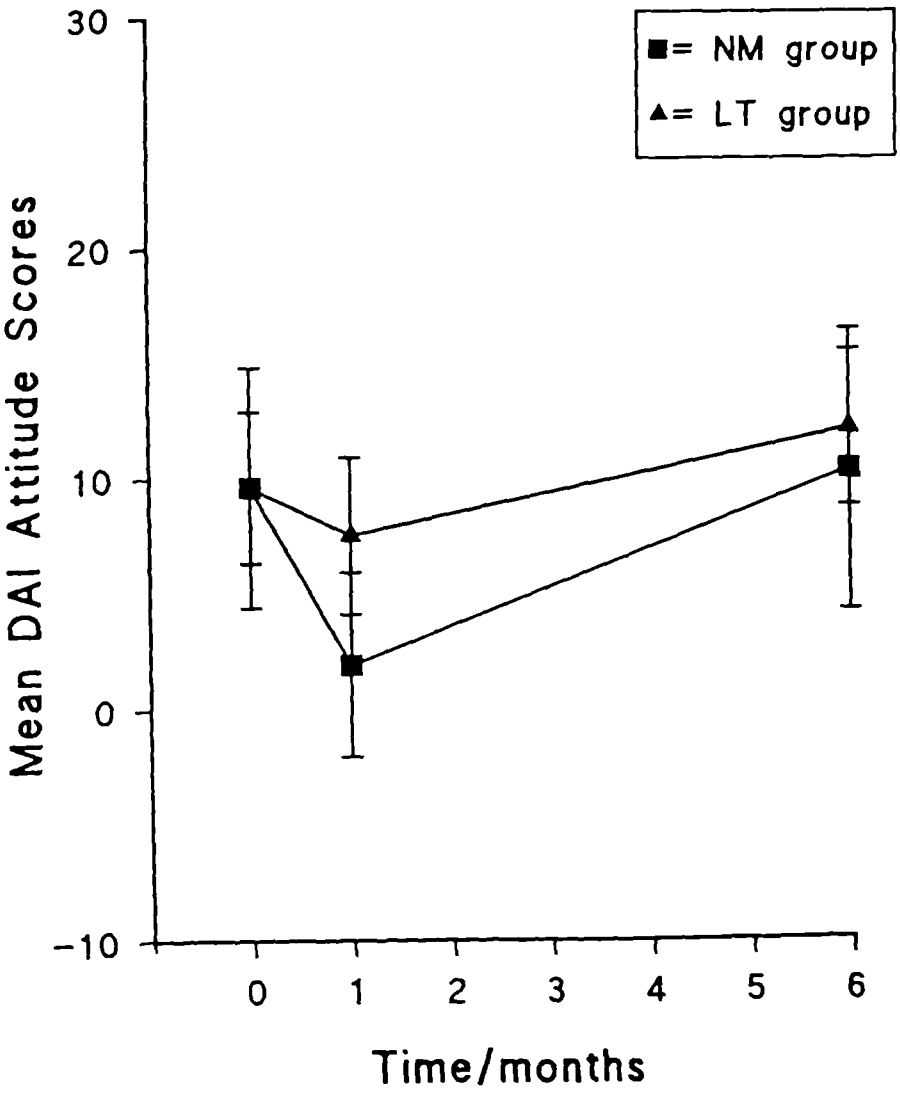


Figure 8.4 To show changes in mean attitude to neuroleptic medication scores as measured using the Drug Attitude Inventory over the six month study period. Mean values are shown for the Newly Medicated (NM) group and the Long Term (LT) group ± standard error of the mean.

only 9 in the LT group and this was statistically significant ($Chi^2 = 13.80$, $p < 0.001$). The LT group was more likely to respond "don't know" (6 LT versus 1 NM) when asked which symptoms were possible side effects of medication ($Chi^2 = 4.21$, $p < 0.05$). LT members were more likely to assert that they took medication for schizophrenia, with 13 LT respondents responding positively to this item, as opposed to just 2 NM respondents ($Chi^2 = 11.97$, $p < 0.001$). This may be due to uncertainty in diagnosis in the early stages of prescription of neuroleptic medication as for the NM group. All other responses showed no significant difference between the two groups. As there were few differences between the two groups the remainder of the results from the NKQ will now be described for both groups considered together.

In the responses recorded on the knowledge questionnaire results for both groups at the first testing indicated that more than half of the respondents (25/46, 54%) felt that they did not know enough about their medication. Only 24 respondents (52%) correctly classified their medication as a neuroleptic, 16 stated that it was an antidepressant, 5 a laxative, 1 an antihistamine, 2 a vitamin and 17 (37%) responded "don't know". (Respondents could tick more than one box if they wished, hence these numbers do not sum to 46.) Respondents were asked to indicate which symptoms listed were common side effects of neuroleptic medication (the list included 5 known side effects and 5 red herring items) and the greatest proportion of volunteers stated that tiredness (65%), restlessness (59%) and shakiness (49%) were common side effects but were least likely to tick ingrowing toenails (2%), weak fingernails (11%) and high blood pressure (15%). Interestingly, 12 members (26%) of the sample stated that

hearing voices was a side effect of medication.

Knowledge of tardive dyskinesia was poor, with only 6 out of 46 (13%) subjects indicating that tardive dyskinesia was a long term side effect of medication. A few respondents indicated that tardive dyskinesia was a type of medication (1/46), a type of behaviour therapy (3/46) or a medical term for vulnerability to sunburn (1/46). The majority of respondents (38/46, 83%) indicated that they did not know what tardive dyskinesia was. When asked why they were taking medication, 16 out of 46 (35%) indicated that it was to help with certain types of symptoms (e.g. delusions or hallucinations), 15 out of 46 (33%) indicated that it was for schizophrenia, 14 out of 46 indicated that it was for anxiety (30%), 1 out of 46 (2%) indicated that it was "to stop you feeling tired" and 10 (22%) responded "don't know".

Changes in Knowledge with time

General knowledge scores and specific knowledge scores measured over the six month experimental period are shown in Figure 8.5. For specific knowledge, a maximum score of +6 was achieved if respondents correctly reported the name, dosage and frequency of neuroleptic medication they were taking (as identified from the patients current prescription in the case notes). At the initial assessment 8 out of 20 (40%) of the LT group and 6 out of 19 (31%) of the NM group achieved a maximum score. After one month the proportion of respondents achieving a maximum score had increased to 55% in the LT group and 53% in the NM group. The proportion with a maximum score further increased at six months to 70% in the LT group and 84% in the NM group.

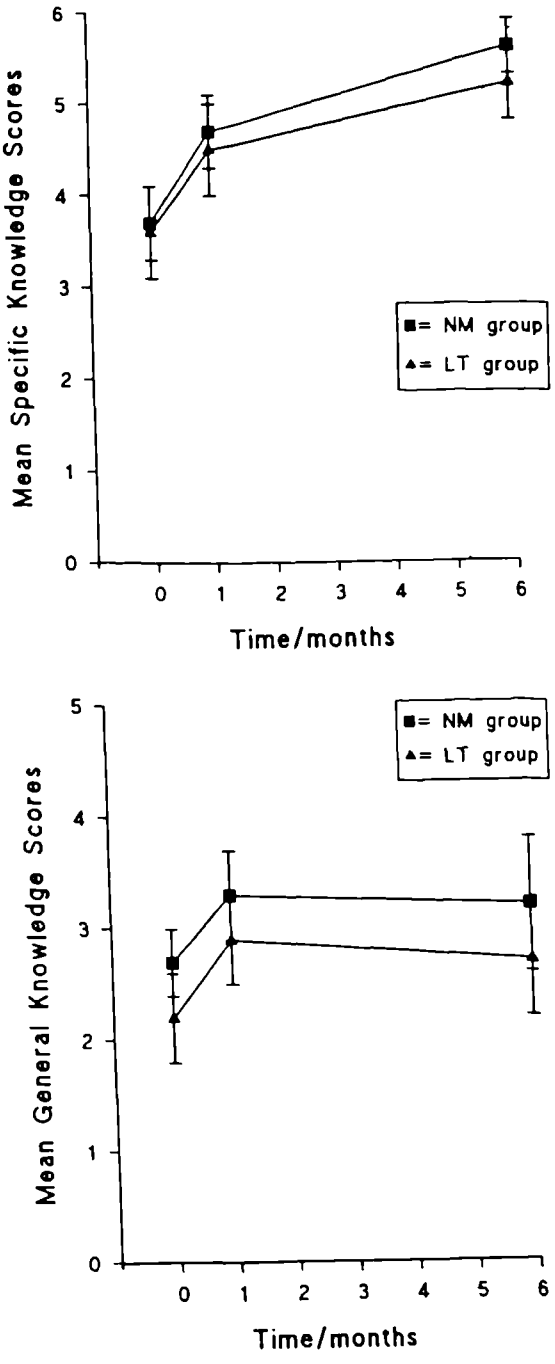


Figure 8.5 To show changes in mean specific knowledge scores and mean general knowledge scores as measured using the Neuroleptic Knowledge Questionnaire over the six month study period. Mean values are shown for the Newly Medicated (NM) group and the Long Term (LT) group ± standard error of the mean.

To determine whether knowledge scores changed over time, two way ANOVAs were carried out on both the specific and the general knowledge data. The ANOVA carried out on the specific knowledge scores confirmed a significant effect for time, $F(2,72) = 13.99$, $p < 0.001$. Tukey HSD tests indicated that differences in subjects' specific knowledge about their medication were significant for comparisons between each of the time points, p at least < 0.05. The group main effect was not significant, $F(1,36) = 0.01$, $p = 0.916$, and the interaction also failed to reach significance, $F(2,72) = 0.39$, $p = 0.682$. For general knowledge scores, there was no significant effect for group $F(1,36) = 1.45$, $p = 0.236$, time $F(2,72) = 2.21$, $p = 0.117$ or for the interaction between group and time $F(2,72) = 0.17$, $p = 0.846$.

8.3.4 Regression Analyses

In order to determine which variables best predicted attitudes to neuroleptic medication at the six month follow up, stepwise multiple regression was carried out on the data collected at the initial assessment. This statistical technique estimates the best equation using one variable as a dependent variable, in this case DAI scores at six months, and other variables as independent or predictor variables, in this case symptom scores, knowledge scores, neuroleptic side effects, dysphoria and chlorpromazine equivalent doses measured at the initial assessment. The equation in this case is linear and can be simplified as follows:

$$y = a + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_n x_n + e$$

In this equation y is the dependent variable, in this case DAI scores, a is the intercept or the value of y when the sum of the independent variables equals zero, $ß_1$ to $ß_n$ are the partial slope coefficients and x_1 to x_n are the independent variables, in this case symptoms, side effects etc. as described above, and e is the error term. The error term is the deviation of y from the mean value of the distribution obtained by repeated observation of y values for cases each with fixed values for each of the independent variables. The error term may represent any effects on y accounted for by variables not explicitly included in the equation as well as a residual random element in the dependent variable. Thus, regression analyses were carried out in this study to investigate the contribution of variables, measured on admission to a psychiatric ward , to attitudes towards neuroleptic medication measured at six months. This may give an insight into the factors involved in the patient's decision to continue taking medication once discharged into the community.

In stepwise regression the variable which is the best predictor is first included in the equation and then the variable with the next best predictive property is selected and so on. Due to missing cases and the limited numbers in each of the groups at the six month follow up, the subjects in the study were considered as a whole, rather than as separate LT and NM groups. (When a regression analysis was carried out using group as an independent variable, group did not have any predictive power for attitudes at six months.).

Stepwise multiple regression analysis demonstrated that initial dysphoria measured using the Van Putten scale and initial side effects measured using the LUNSERS, had some predictive ability for DAI scores measured at the six

month assessment. When dysphoria alone was used to predict attitudes the adjusted R^2 value was 0.285 ($F(1,34) = 13.57$), indicating that the equation or model accounted for 28.5% of the variance in DAI scores at six months. In the next step, side effects scores measured with LUNSERS were added to the equation and this increased R^2 to 0.403 ($F(2,33) = 11.15$), and using this model 40.3% of the variance was accounted for. None of the other variables had a statistically significant predictive ability, although specific knowledge of medication approached significance ($p = 0.068$). In order to assess the contribution of specific knowledge to attitudes in combination with dysphoria and side effects, the entry criteria for variables to be included in the equation were relaxed from a p of 0.05 to a p of 0.1, for theoretical interest. The equation which resulted from this analysis accounted for 31.8% of the variance in DAI scores at six months, with an R^2 value of 0.318, ($F(3,33)= 6.61$). Thus, adding specific knowledge to the model decreased its predictive value.

As shown in the correlational analyses, Van Putten and DAI scores are strongly related. This may mean that they are measuring the same attribute. If this is the case it would not be surprising that dysphoria scores predict DAI scores at six months. In order to identify the predictive ability of variables when excluding this effect the regression was carried out without Van Putten dysphoria scores. In this case, specific knowledge was the only variable which had any statistically significant predictive ability for DAI scores at six months. However, the equation resulting from this analysis predicted only 14.9% of the variance in DAI scores, with an R^2 of 0.149 ($F(1,34) = 5.90$).

The model which accounted for the maximum amount of variance in DAI scores at six months was that which included side effects and Van Putten dysphoria scores measured at the initial assessment as predictors.

8.4 Discussion

This study attempted to investigate the hypothesis that schizophrenic patients' attitudes to neuroleptic medication may change over time and that Newly Medicated patients' attitudes to and response to neuroleptic medication may differ from that of patients who have been prescribed neuroleptic medication for a longer time period. The results of this study showed that there is wide variation in the attitudes held by schizophrenic patients towards neuroleptic medication but that there was no statistical difference in attitudes when measured over a six month follow up period. There was also no overall difference in attitudes held by the recent onset patients when compared to the long-term patients. Indeed there were very few statistically significant differences between the groups. Long-term patients were more likely to have more negative symptoms than recent onset patients but the response of negative symptoms to neuroleptic medication did not differ between the two groups. Both groups showed a decrease in positive symptoms over the follow-up period but not in negative symptoms which replicates the work of other researchers that indicates a differential effect of neuroleptics on positive symptoms (Lydiard & Laird, 1988).

A number of interesting observations were made in this study. For example the study demonstrated that people prescribed neuroleptic medication

are limited in their knowledge of this treatment. More than half of the sample asserted that they did not know enough about their medication. The fact that only six out of the subjects (13%) correctly defined tardive dyskinesia suggests that people prescribed neuroleptic medication are not routinely informed about the possibility of developing this side effect. It was interesting to note the source of information which had informed some of the respondents about tardive dyskinesia. Some respondents had been informed of the possible risks of developing tardive dyskinesia either by their prescriber or by a nurse, but the majority had obtained their information from local libraries, user groups such as MIND and one patient had learnt about it on a documentary programme broadcast on Channel 4. The results obtained regarding knowledge of neuroleptic medication are similar to those obtained by other investigators. For example Linden & Chaskell (1981) found that 93% of 85 chronic schizophrenic outpatients could correctly identify the neuroleptic they were taking but that only a minority could identify specific therapeutic effects of medication such as improvement in thought organisation (21%) and hallucinations (30%). This study found that only 40% of the sample were able to correctly identify even one side effect of neuroleptic medication. Geller (1982) also found in a study of 281 psychiatric in-patients in a U.S. state hospital, that patients knowledge of medication was poor and indicated that 54% of patients evidenced no understanding of the medication they were taking. Macpherson, Double, Rowlands, & Harrison (1993) carried out a similar study of 100 long stay psychiatric in-patients receiving neuroleptic medication in Sheffield, England. This study found that 72% of the sample had no understanding of their medication and that only 7 of 100 had heard of tardive dyskinesia. These results can be interpreted in two ways. In the American

literature, which is more concerned with the ever increasing risk of litigation which prescribers face, emphasis is placed on the interpretation that patients have a poor knowledge of medication because they are thought disordered and cognitively impaired, and therefore unable to give informed consent. However another interpretation could be given to this finding and that is that schizophrenic patients are not routinely informed about their medication by health professionals.

One implication of the observation that schizophrenic patients had poor knowledge of their medication, is that it is doubtful whether this sample could be said to have given proper informed consent to taking neuroleptic medication. This may reflect a fear on behalf of the prescribing psychiatrists that informing schizophrenic patients about this side effect will increase patient anxiety and reduce compliance. In fact there is little evidence for this common belief. Myers & Calvert (1978) carried out a number of studies which indicate that informing patients about all possible side effects of anti-depressant medication does not decrease compliance or increase the report of side effects. Kleinman, et al. (1989), in a study of 48 schizophrenic outpatients, informed one group (n=21) of the risks of tardive dyskinesia and another group (n=27) were left uninformed. The informed group showed significantly increased knowledge after six months. However there was no significant difference between the two groups in frequency of psychiatric admission, noncompliance with medication or the need for increased anti-psychotic medication over the six months follow-up period. In a small study of 30 chronic schizophrenic and schizoaffective outpatients (Brown, et al., 1987) found that instruction about medication did not affect compliance as measured by patients' reports and pill counts. In a

non-psychiatric study Kerrigan, Thevasagayam, Woods, McWelch, Thomas, & Shorthouse (1993) found that detailed information about the risks of a hernia operation (including possible loss or permanent shrinkage of a testicle or possible death from pulmonary embolism following the operation) did not significantly increase anxiety as assessed by the Hospital Anxiety and Depression Scale (HADS). These studies suggest that the widespread beliefs which professionals have about the hazards informing patients of the possible adverse effects of their medication may be unfounded. It would be interesting to carry out a more detailed and carefully controlled study to investigate this question further.

The study indicated that six months from an in-patient admission, symptoms, neuroleptic dosage and side effects of neuroleptic medication decrease. These observations replicate the work of many other researchers. However attitudes to medication and general knowledge of medication did not show any changes with time. This was a surprising finding as it was hypothesised that attitudes may be affected by the variables which did show changes with time. The most significant factor which affected attitudes to medication was dysphoria as measured on Van Putten's dysphoria scale. This association was shown significantly both in the correlations and in the regression analysis. This strong association, which was stable over a six month time period, replicates the work of Hogan & Awad (1992) who observed a correlation of $r = 0.76$ ($p < 0.001$, $n=52$) 24 hours after and $r = 0.74$ ($p < 0.0001$, $n=49$) 48 hours after a test dose of chlorpromazine. It is difficult to know whether the two scales are measuring aspects of the same attribute, or if they were measuring closely (perhaps causally) related variables. The item

content is different between the scales for many of the items. Some items are similar however, for example one Van Putten item asks "Did it (the medication) make you feel calmer?" and one of the items on the DAI is "Medications make me feel more relaxed" to which the respondent replies true or false. Whilst this item is clearly similar the DAI also includes a number of items covering issues such as control (for example "If I take medication it is only because of pressure from other people") which are not included in Van Putten scale. Further work would have to be carried out in order to clarify the relationship between the two variables.

Side effects did not have a consistent statistically significant relationship with neuroleptic attitudes at particular time points but side effects at the initial assessment did predict future attitudes. This may mean that monitoring and treating side effects on in-patients wards could be crucial in maximising compliance with neuroleptics six months later when most patients are back in the community and at their most vulnerable time for noncompliance. Objective monitoring of side effects is not routinely carried out on acute psychiatric in-patient wards in the Merseyside area.

The findings of the present study have considerable relevance to the care of people with schizophrenia. This is particularly significant when the correlation between the length of hospital admission, attendance at out patients appointments and DAI scores are considered. In the NM group positive attitudes to neuroleptic treatment were associated with increased attendance at out-patient appointments. This raises an obvious important problem, in that those patients who are least likely to take medication and thus more likely to

relapse are also those who are less likely to attend out patient appointments. It would seem pertinent to assess DAI scores during hospital admissions and carefully follow up patients with low DAI scores, perhaps with home visits. In the LT group lower DAI scores were correlated with an increased hospital stay and this exemplifies the clinical and financial importance of patients who have a negative attitude towards their treatment. Further research into attitudes towards medication and the trial of client-centred interventions to enhance compliance are justified.

Positive symptoms in the early assessments were associated with negative attitudes towards neuroleptic medication. However positive symptoms did not have any predictive ability for attitudes at six months. This suggests that it would be beneficial in any study which investigates an intervention designed to increase compliance with neuroleptic medication to also measure psychotic symptoms. Also lack of insight as assessed on the PANSS psychopathology item was correlated with negative attitudes towards neuroleptic medication. This suggests that when people have the most severe psychotic symptoms they are more likely to think negatively about their medication and that this may be related to lack of insight. This corroborates the observations of other researchers which also correlated negative attitudes to medication with positive symptoms such as persecutory delusions, grandiosity and lack of insight (Bartko, et al., 1988; Lin, et al., 1979; Van Putten, et al., 1976; Wilson & Enoch, 1967). However there is one major limitation in both the present study and those previously carried out. The limitation is that when rating patients on the "lack of judgement and insight" PANSS item, an expression of not wanting to take medication or a denial of the need for

medication automatically achieves a score of 6 on this item (7 is maximum). Thus it is true by definition that lack of insight correlates with negative attitudes towards medication. Insight scales assume that denying the need for medication means that individuals have no insight into their problem or symptoms. However individuals may deny the need for medication for a number of reasons other than not being aware of their symptoms. For example some 20-30% of people remain unresponsive to neuroleptic medication and there are people who are well aware of their symptoms (for example auditory hallucinations) but are happier to live with those symptoms rather than be "controlled by neuroleptic medication". McEvoy, et al. (1989b) and Buchanan (1992) observed that the relationship between insight and compliance is more complex than has previously been thought as discussed in Chapter 3 (section 3.6.1.). Insight is a poorly defined concept (Birchwood, Smith, Drury, Healy, Macmillan, & Slade, 1994) and caution must be used in interpreting the results of studies which have correlated lack of insight with negative attitudes to treatment without separately considering the cognitive aspects of lack of insight such as general attributions about illness and specific attributions about symptoms from the components which measure perceived need for treatment. The assertion that lack of insight is a lack of perceived need for treatment is paternalistic in that it assumes that if a prescriber perceives a need for treatment she or he is always right.

Several of the items included in the LUNSERS are identical to those included in the PANSS general psychopathology scale, for example depression, tension and motor retardation, which may explain the correlation observed between the these variables. This highlights the problems of the similarity

between some of the symptoms commonly experienced by people with psychotic symptoms and side effects of neuroleptic medication. It is difficult to differentiate between the side effects of neuroleptic medication and psychological symptoms. The use of a scale which is intended to measure either symptoms or side effects is not enough on its own to differentiate between the different aetiologies as they are not mutually exclusive. Thus a symptom may be identified from a side effect measure and a side effect may be identified on a symptom measure. This is an important point for researchers carrying out future work in this area.

There was an association between specific knowledge of medication and attitudes towards medication both in the correlations and in the regression analysis. This association was not as strong as that of side effects or dysphoria but was significant. It was a surprising finding that specific knowledge, that is, the name dose and frequency of medication, and not general knowledge, which included information about the indication for and side effects of medication, was associated with attitudes towards treatment. The implication of this could be that if patients are specifically informed about the name of their medication in the initial stages of a psychotic episode, they are more likely to have positive attitudes towards medication at a later stage. This finding may also be influenced by the relationship between ward staff and the patient. Thus some staff may inform patients of the name of medication and this may lead to patients having a more positive attitude towards medication. Conversely if patients are not informed of the name of their medication they are more likely to have a negative attitude towards their medication. However it would be expected that this would be the case for general knowledge of medication also. Another explanation for this observation could be that patients who have a more positive attitude towards

their medication are more likely to be interested and ask questions about their medication and therefore they will have significantly more knowledge.

This study was complex and difficult to carry out for a number of reasons, including stringent entry criteria and the relatively infrequent admission of patients experiencing a first episode psychosis to an in-patients psychiatric ward (approximately one per month at each hospital site used in the study). The patients who took part completed a large number of questionnaires and assessments and at times this involved more than one meeting. These difficulties explain the relatively small number taking part, which is one of the limitations of the study. There was also a disproportionably high number of males who took part in the study, which may be a consequence of the fact that males are more likely to be admitted to psychiatric in-patient wards than females. It has been suggested that there is a gender specific decline in the incidence of schizophrenia (Waddington & Youseff, 1994). There were also a large number of refusals to take part in the study which is probably a consequence of the distress which patients experience as a result of psychotic symptoms and hospital admission, as well as the fact that the author was not previously known to volunteers. For these reasons the results of the study must be interpreted with some caution and broad generalisations to other populations are not advisable. However some of the findings of previous researchers have been replicated, such as the lack of response of negative symptoms to neuroleptics, which offers some validity for the findings of the study and thus the response bias may not have compromised the study to a great extent.

CHAPTER 9

Final Conclusions and Implications for Practice

The main findings from the studies described in this thesis can be summarised as follows. First, in the Q-methodological study it was shown that patients' attitudes towards neuroleptic medication are highly heterogenous, and cannot be simplified along a unidimensional continuum. Second, in the study designed to develop a scale for measuring neuroleptic side effects, it was shown that schizophrenic patients can accurately self-rate their own side effects on a simple check-list. Third, a survey of psychiatrists revealed that their self-reported intention to inform patients about side effects was a function of their perceived distress and prevalence of side effects. However, although the psychiatrists could accurately estimate prevalence of neuroleptic side effects, they were poor judges of the distress experienced by patients as a result of side effects. In a final longitudinal study, little difference was found between newly medicated patients and those who had a longer experience of neuroleptic medication. Attitudes to medication measured at six month follow-up were predicted by side effects and dysphoria measured at the initial assessment. These findings will now be put into the perspective of recent government publications, and implications for practice in the treatment of people with a diagnosis of schizophrenia will be discussed.

Recent changes in policy have had significant impact on the care of people with serious enduring mental health problems such as schizophrenia. The emphasis of care has been switched from hospital based services to

community based services and maintained compliance with neuroleptic medication is seen as an important part of community care. The Care Programme approach was introduced in April 1991 in which each patient has a key worker and the emphasis is on ensuring that key services for the mentally ill are available when they move into the community. The Government's strategy for health "The Health of the Nation" identifies mental illness as one of five key areas in which improvements could be made. As discussed in Chapter 1, there are three main areas which are outlined in the Health of the Nation's targets for mental health, and two of these targets are relevant to people with a diagnosis of schizophrenia. These are; (1) to improve significantly the health and social functioning of mentally ill people and (2) To reduce suicide rate of the severely mentally ill by at least 33% by the year 2000. In January 1993 the Department of Health launched the Key Area Handbook on Mental Illness, which supported the further move of services away from the large hospitals, and offered practical advice for those involved in developing local strategies to improve mental health.

Since the present study has been carried out a number of official documents have been published which are relevant to the findings. The Royal College of Nursing along with the Department of Health published a document in 1994 entitled "Good Practice in the Administration of depot neuroleptics. A guidance document for mental health and practice nurses". This document makes a number of recommendations which are intended to improve the quality of care for people prescribed depot neuroleptic medication. This document states that most patients prescribed depot medication receive their injection in a depot clinic, and that there is often insufficient time for nurses to offer any

therapeutic input apart from the administration of the depot injection. This document recommends that mental health nurses have a crucial role to play in the assessment of mental state, and assessment of the side effects of medication. Systematic assessment of side effects is recommended in order to determine the minimum therapeutic dose with minimum side effects. This recommendation is directly relevant to the present research as the LUNSERS would be a useful clinical tool in order to assess side effects. A number of mental health professionals around the United Kingdom (and Europe) are now considering using the LUNSERS in clinical practice. It is also incorporated into a depot review protocol written in St Helens and Knowsley (Henderson & Day, 1993) which recommends objective assessment of neuroleptic side effects at least every year. The Good Practice document also highlights the insufficient information provided by health professionals and user's dissatisfaction with the poor quantity and quality of information provided. Guidelines pertinent to this issue include the recommendation that users should be provided with improved information by members of the multidisciplinary team, including the reason for the injection being given and possible side effects, and that users should be given the opportunity to give fully informed consent when treatment commences. The present work supports the recommendation in this document in two particular respects: the objective assessment of neuroleptic side effects and the provision of full information concerning neuroleptic medication including side effects. The obvious next stage of this work would be a controlled trial to assess the effects of providing information about neuroleptic medication and routinely assessing neuroleptic side effects and dysphoria on the long-term outcome of schizophrenic patients.

Another document recently produced is the "Guidelines for the management of schizophrenia" which was developed from a meeting of an independent multi-disciplinary working party in 1994 and chaired by Professor Malcolm Lader of the Institute of Psychiatry (Independent working party, 1994). This document also recommends in it's guideline that "patients and carers should be given comprehensive high quality information and counselling to improve the likelihood of compliance with drug and other forms of treatment". There is an assumption within this statement that improving information will improve compliance, but informing patients about neuroleptic medication has not always been found to improve compliance. Improving compliance should not be the only incentive for professionals to provide comprehensive information regarding patient's treatments. Improved information would increase the involvement of the user and should be an ethical right.

The guidelines in these documents suggest useful changes in current practice regarding the care of people prescribed neuroleptic medication. However they also open up a number of needs, not only for the users of services, but also for mental health professionals involved in the implementation of these guidelines. The present study has outlined that even psychiatrists may not be expert in estimating distress caused by neuroleptic side effects and this may also be the case for other health professionals including pharmacists, mental health nurses and general practitioners. Training is required in the prevalence and treatment of side effects and in the objective assessment and monitoring of side effects before this recommendation can be carried out. Training would also be required in communications skills and effects of

informing clients about their medication, before implementation. Health professionals must overcome their fears of the hazards of informing patients before they can carry out this task. These recommendations must also be objectively assessed in terms of patients' outcomes in order to determine any benefits or disadvantages associated with changes in practice. If found to improve patient care, the recommendations alone are not enough, they must be implemented and regular audits of practice should be carried out in order to maintain adequate standards of care.

The guidelines in these documents concentrate on the assessment of medication in the community. However there are two reasons why it is also important (possibly more so) to assess neuroleptic side effects whilst people are experiencing acute psychotic relapse in hospital. Firstly the experience of side effects in an in-patients episode was a significant predictor of attitudes to treatment six months later in the community. Secondly health professionals may underestimate the prevalence of neuroleptic side effects and the distress associated with side effects. A recent pilot study of fifteen schizophrenic patients at Clatterbridge Hospital, Merseyside found that nurses and doctors working closely with schizophrenic patients significantly underestimate the extent of side effects experienced by patients. Further work is planned to investigate this hypothesis.

The research reported in this thesis has highlighted the complexity of attitudes towards neuroleptic medication. Although previous findings that side effects and knowledge of neuroleptic medication contribute to attitudes, there

are obviously other factors involved which may include more general health beliefs and may account for the unexplained 60% of the variance in attitudes. It would be unwise to make broad generalisation about attitudes to medication from the results of these and previous researchers' studies. The common belief that lack of insight and side effects are the two main reasons for noncompliance is simplistic. In order to assess attitudes to medication, the individual's assessment of medication and their beliefs must be sought, respected and discussed fully in each case. This work indicates that schizophrenic patients' viewpoints are important, and that their self reports of their experiences are valid. This must be the most important and interesting finding of the present research for mental health professionals, but especially for the empowerment of people who are diagnosed as schizophrenic.

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Appendix 1

LUNSERS

Assessment No ☐

Assessment Date ☐☐☐☐☐☐

Please indicate how much you have experienced each of the following symptoms in **the last month** by ticking the appropriate boxes.

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
1. Rash	☐	☐	☐	☐	☐
2. Difficulty staying awake during the day	☐	☐	☐	☐	☐
* 3. Runny nose	☐	☐	☐	☐	☐
4. Increased dreaming	☐	☐	☐	☐	☐
5. Headaches	☐	☐	☐	☐	☐
6. Dry mouth	☐	☐	☐	☐	☐
7. Swollen or tender chest	☐	☐	☐	☐	☐
* 8. Chilblains	☐	☐	☐	☐	☐
9. Difficulty in concentrating	☐	☐	☐	☐	☐
10. Constipation	☐	☐	☐	☐	☐
* 11. Hair loss	☐	☐	☐	☐	☐

The red herring items are shown by an asterisk. **N.B. These asterisks should be deleted before administration and are shown here for information only.**

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
* 12. Urine darker than usual	☐	☐	☐	☐	☐
13. Period problems	☐	☐	☐	☐	☐
14. Tension	☐	☐	☐	☐	☐
15. Dizziness	☐	☐	☐	☐	☐
16. Feeling sick	☐	☐	☐	☐	☐
17. Increased sex drive	☐	☐	☐	☐	☐
18. Tiredness	☐	☐	☐	☐	☐
19. Muscle stiffness	☐	☐	☐	☐	☐
20. Palpitations	☐	☐	☐	☐	☐
21. Difficulty in remembering things	☐	☐	☐	☐	☐
22. Losing weight	☐	☐	☐	☐	☐
23. Lack of emotions	☐	☐	☐	☐	☐
24. Difficulty in achieving climax	☐	☐	☐	☐	☐
* 25. Weak fingernails	☐	☐	☐	☐	☐
26. Depression	☐	☐	☐	☐	☐

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
27. Increased sweating	☐	☐	☐	☐	☐
* 28. Mouth ulcers	☐	☐	☐	☐	☐
29. Slowing of movements	☐	☐	☐	☐	☐
* 30. Greasy skin	☐	☐	☐	☐	☐
31. Sleeping too much	☐	☐	☐	☐	☐
32. Difficulty passing water	☐	☐	☐	☐	☐
* 33. Flushing of face	☐	☐	☐	☐	☐
34. Muscle spasms	☐	☐	☐	☐	☐
35. Sensitivity to sun	☐	☐	☐	☐	☐
36. Diarrhoea	☐	☐	☐	☐	☐
37. Over-wet or drooling mouth	☐	☐	☐	☐	☐
38. Blurred vision	☐	☐	☐	☐	☐
39. Putting on weight	☐	☐	☐	☐	☐
40. Restlessness	☐	☐	☐	☐	☐
41. Difficulty getting to sleep	☐	☐	☐	☐	☐

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
* 42. Neck muscles aching	☐	☐	☐	☐	☐
43. Shakiness	☐	☐	☐	☐	☐
44. Pins and needles	☐	☐	☐	☐	☐
* 45. Painful joints	☐	☐	☐	☐	☐
46. Reduced sex drive	☐	☐	☐	☐	☐
47. New or unusual skin marks	☐	☐	☐	☐	☐
48. Parts of body moving of their own accord eg foot moving up and down	☐	☐	☐	☐	☐
49. Itchy skin	☐	☐	☐	☐	☐
50. Periods less frequent	☐	☐	☐	☐	☐
51. Passing a lot of water	☐	☐	☐	☐	☐

Appendix 2

ATTRIBUTION SCALE

Please tick off how much you think the following symptoms have been due to your neuroleptic medication (see checklist) during the last month.

	NOT DUE TO MEDICATION	DON'T KNOW	DUE TO MEDICATION
1. Rash	☐	☐	☐
2. Difficulty in staying awake during the day	☐	☐	☐
3. Runny nose	☐	☐	☐
4. Increased dreaming	☐	☐	☐
5. Headaches	☐	☐	☐
6. Dry mouth	☐	☐	☐
7. Swollen or tender chest	☐	☐	☐
8. Chilblains	☐	☐	☐
9. Difficulty in concentrating	☐	☐	☐
10. Constipation	☐	☐	☐
11. Hair loss	☐	☐	☐
12. Urine darker than usual	☐	☐	☐
13. Period problems	☐	☐	☐
14. Tension	☐	☐	☐
15. Dizziness	☐	☐	☐
16. Feeling sick	☐	☐	☐

Please tick off how much you think the following symptoms have been due to your neuroleptic medication (see checklist) during the last month,

	NOT DUE TO MEDICATION	DON'T KNOW	DUE TO MEDICATION
17. Increased sex drive	☐	☐	☐
18. Tiredness	☐	☐	☐
19. Muscle stiffness	☐	☐	☐
20. Palpitations	☐	☐	☐
21. Difficulty in remembering things	☐	☐	☐
22. Losing weight	☐	☐	☐
23. Lack of emotions	☐	☐	☐
24. Difficulty achieving climax	☐	☐	☐
25. Weak fingernails	☐	☐	☐
26. Depression	☐	☐	☐
27. Increased sweating	☐	☐	☐
28. Mouth ulcers	☐	☐	☐
29. Slowing of movements	☐	☐	☐
30. Greasy skin	☐	☐	☐
31. Sleeping too much	☐	☐	☐
32. Difficulty in passing water	☐	☐	☐
33. Flushing of face	☐	☐	☐
34. Muscle spasms	☐	☐	☐

Please tick off how much you the following symptoms have been due to your neuroleptic medication (see checklist) during the last month;

	NOT DUE TO MEDICATION	DON'T KNOW	DUE TO MEDICATION
35. Sensitivity to sun	☐	☐	☐
36. Diarrhoea	☐	☐	☐
37. Over-wet/drooling mouth	☐	☐	☐
38. Blurred vision	☐	☐	☐
39. Putting on weight	☐	☐	☐
40. Restlessness	☐	☐	☐
41. Difficulty in getting to sleep	☐	☐	☐
42. Neck muscles aching	☐	☐	☐
43. Shakiness	☐	☐	☐
44. Pins and needles	☐	☐	☐
45. Painful joints	☐	☐	☐
46. Reduced sex drive	☐	☐	☐
47. New/unusual skin marks	☐	☐	☐
48. Parts of body moving of their own accord eg foot moving up and down	☐	☐	☐
49. Itchy skin	☐	☐	☐
50. Periods less frequent	☐	☐	☐
51. Passing a lot of water	☐	☐	☐

Appendix 3

LUNSERS - DISTRESS SCALE

Assessment No ☐

Assessment Date ☐☐ ☐☐ ☐☐

Please indicate how much you have been distressed or bothered by each of the following symptoms in **the last month** by ticking the appropriate boxes.

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
1. Rash	☐	☐	☐	☐	☐
2. Difficulty staying awake during the day	☐	☐	☐	☐	☐
3. Runny nose	☐	☐	☐	☐	☐
4. Increased dreaming	☐	☐	☐	☐	☐
5. Headaches	☐	☐	☐	☐	☐
6. Dry mouth	☐	☐	☐	☐	☐
7. Swollen or tender chest	☐	☐	☐	☐	☐
8. Chilblains	☐	☐	☐	☐	☐
9. Difficulty in concentrating	☐	☐	☐	☐	☐
10. Constipation	☐	☐	☐	☐	☐
11. Hair loss	☐	☐	☐	☐	☐

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
12. Urine darker than usual	☐	☐	☐	☐	☐
13. Period problems	☐	☐	☐	☐	☐
14. Tension	☐	☐	☐	☐	☐
15. Dizziness	☐	☐	☐	☐	☐
16. Feeling sick	☐	☐	☐	☐	☐
17. Increased sex drive	☐	☐	☐	☐	☐
18. Tiredness	☐	☐	☐	☐	☐
19. Muscle stiffness	☐	☐	☐	☐	☐
20. Palpitations	☐	☐	☐	☐	☐
21. Difficulty in remembering things	☐	☐	☐	☐	☐
22. Losing weight	☐	☐	☐	☐	☐
23. Lack of emotions	☐	☐	☐	☐	☐
24. Difficulty in achieving climax	☐	☐	☐	☐	☐
25. Weak fingernails	☐	☐	☐	☐	☐
26. Depression	☐	☐	☐	☐	☐

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
27. Increased sweating	☐	☐	☐	☐	☐
28. Mouth ulcers	☐	☐	☐	☐	☐
29. Slowing of movements	☐	☐	☐	☐	☐
30. Greasy skin	☐	☐	☐	☐	☐
31. Sleeping too much	☐	☐	☐	☐	☐
32. Difficulty passing water	☐	☐	☐	☐	☐
33. Flushing of face	☐	☐	☐	☐	☐
34. Muscle spasms	☐	☐	☐	☐	☐
35. Sensitivity to sun	☐	☐	☐	☐	☐
36. Diarrhoea	☐	☐	☐	☐	☐
37. Over-wet or drooling mouth	☐	☐	☐	☐	☐
38. Blurred vision	☐	☐	☐	☐	☐
39. Putting on weight	☐	☐	☐	☐	☐
40. Restlessness	☐	☐	☐	☐	☐
41. Difficulty getting to sleep	☐	☐	☐	☐	☐

	NOT AT ALL	VERY LITTLE	A LITTLE	QUITE A LOT	VERY MUCH
42. Neck muscles aching	☐	☐	☐	☐	☐
43. Shakiness	☐	☐	☐	☐	☐
44. Pins and needles	☐	☐	☐	☐	☐
45. Painful joints	☐	☐	☐	☐	☐
46. Reduced sex drive	☐	☐	☐	☐	☐
47. New or unusual skin marks	☐	☐	☐	☐	☐
48. Parts of body moving of their own accord eg foot moving up and down	☐	☐	☐	☐	☐
49. Itchy skin	☐	☐	☐	☐	☐
50. Periods less frequent	☐	☐	☐	☐	☐
51. Passing a lot of water	☐	☐	☐	☐	☐

41. Polyuria

Overall prevalence _ %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibilty of developing side effect

Definitely Probably Not sure Probably not Definitely not

Many thanks for your help in completing this questionnaire

Neuroleptic Side Effect Questionnaire

Please complete the following details:

Current Post/Grade _____

Gender M / F

Age/years _ _

Number of years of experience in Psychiatry _ _ _

Name (optional) _____

Specialty _____

Place of work _____

_____

_____

Please tick if you would be interested in seeing the results of this study and if you would like to be placed on a mailing list for related publications ☐

1. What in your clinical opinion is the overall percentage prevalence of **dry mouth** amongst patients who are prescribed neuroleptic medication ?
%

What in your clinical opinion is the percentage of patients prescribed neuroleptic medication who experience this symptom directly as a consequence of their medication (ie in whom this symptom is a side effect) ?
%

What level of distress, in your opinion, do patients typically experience when they are affected by this neuroleptic side effect?

Not at all Very little A little Quite a lot Very much

How likely would you be to inform a patient prescribed neuroleptic medication about the possibility of experiencing this side effect?

Definitely Probably Not sure Probably not Definitely not

2. Increased dreaming

Overall prevalence **%**

Prevalence as a side effect **%**

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please circle your answer

38. Increased skin pigmentation

Overall prevalence **%**

Prevalence as a side effect **%**

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

39. Dyskinesias

Overall prevalence **%**

Prevalence as a side effect **%**

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

40. Amenorrhoea

Overall prevalence **%**

Prevalence as a side effect **%**

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please circle your answer

Please refer to question 1 for the full question

35. Blurred vision

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

36. Reduced duration of sleep

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

37. Tremor

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

3. Failing memory

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

4. Akathisia

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please refer to question 1 for the full question

5. Fatigue

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

6. Depression

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

7. Constipation

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

32. Photosensitivity

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

33. Diarrhoea

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

34. Blurred vision

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please refer to question 1 for the full question

11. Weight gain

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

12. Lack of emotions

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

13. Diminished libido

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

26. Increased libido

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

27. Palpitations

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

28. Weight loss

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please circle your answer

Please refer to question 1 for the full question

23. Tension

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

24. Postural hypotension

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

25. Nausea

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

14. Skin rash

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

15. Dystonia

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

16. Pruritis

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please refer to question 1 for the full question

Please refer to question 1 for the full question

17. Anorgasmia

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

18. Hypersalivation

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

19. Headaches

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

20. Gynaecomastia

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

21. Difficulty concentrating

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

22. Menorrhagia (as % of all females)

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please refer to question 1 for the full question

Please circle your answer

29. Increased sweating

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

30. Increased duration of sleep

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

31. Micturition difficulty

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

8. Hypokinesia

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

9. Muscular rigidity

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

10. Daytime sedation

Overall prevalence %

Prevalence as a side effect %

Level of distress reported by patients experiencing side effect

Not at all Very little A little Quite a lot Very much

Likelihood of informing patient of possibility of developing side effect

Definitely Probably Not sure Probably not Definitely not

Please circle your answer

Appendix 5

List of items included in the "Positive and Negative Syndrome Scale (PANSS)."

- Positive Scale
  - Delusions
  - Conceptual disorganization
  - Hallucinatory behavior
  - Excitement
  - Grandiosity
  - Suspiciousness/persecution
  - Hostility
- Negative Scale
  - Blunted affect
  - Emotional withdrawal
  - Poor rapport
  - Passive/apathetic social withdrawal
  - Difficulty in abstract thinking
  - Lack of spontaneity and flow of conversation
  - Stereotyped thinking
- General Psychopathology Scale
  - Somatic concern
  - Anxiety
  - Guilt feelings
  - Tension
  - Mannerisms and posturing
  - Depression
  - Motor retardation
  - Uncooperativeness
  - Unusual thought content
  - Disorientation
  - Poor attention
  - Lack of judgement and insight
  - Disturbance of volition
  - Poor impulse control
  - Preoccupation
  - Active social avoidance

Appendix 6

Neuroleptic Knowledge Questionnaire.

Please answer the following questions;

1. What have you been told about your medication?

2. Have you asked anyone any questions about your medication?

YES ☐

NO ☐

If you have answered yes to this question please say who you have asked and what you have asked them.

3. What would you like to know about your medication?

4. Please tick which of the following you have been told about, concerning your medication?

☐ a) The name of the drug(s) you are taking
☐ b) How much medication you should take and when
☐ c) Why you have been prescribed this medication
☐ d) The things you should expect the medication to help with
☐ e) The side effects of the medication
☐ f) What side effects to tell your doctor or nurse about
☐ g) How long you will have to take the medication

Who told you this information?

5. Please tick which of the following you would like to have been told about?

☐ a) The name of the drug(s) you are taking
☐ b) How much medication you should take and when
☐ c) Why you have been prescribed this medication
☐ d) The things you should expect the medication to help with
☐ e) The side effects of the medication
☐ f) What side effects to tell your doctor or nurse about
☐ g) How long you will have to take the medication

6. Do you feel you know enough about your medication?

YES ☐

NO ☐

7. Is your medication :

☐ a) An anti-depressant
☐ b) A laxative
☐ c) A neuroleptic
☐ d) An antihistamine
☐ e) A vitamin
☐ f) Don't know

8. Common side effects of your medication include: (tick as many as you think apply)

☐ a) Muscle stiffness
☐ b) ingrowing toenail
☐ c) shakiness
☐ d) sensitivity to sunburn
☐ e) restlessness
☐ f) weight loss
☐ g) high blood pressure
☐ h) hearing voices
☐ i) tiredness
☐ j) weak fingernails
☐ k) Don't know

10. What is tardive dyskinesia?

☐ a) A type of medication
☐ b) A long term side effect of your medication
☐ c) A type of behaviour therapy
☐ d) A medical term for easily sunburned
☐ e) Don't know

11. You keep having/taking your medication because;

- [ ] a) You may relapse psychologically if you stop
- [ ] b) You are by now addicted to it
- [ ] c) It prevents brain damage
- [ ] d) Don't know

12. Why do you have your medication?

- [ ] a) To stop you feeling tired
- [ ] b) For schizophrenia
- [ ] c) For anxiety
- [ ] d) To help with certain types of symptoms, eg. delusions or hallucinations
- [ ] e) Don't know

13. What should you do if you feel that your medication doesn't agree with you?

- [ ] a) Learn to live with it
- [ ] b) Refuse further medication
- [ ] c) Discuss it with your doctor

Specifics

1. What is/are the name of your medication(s)?

2. What is the dosage?

Strength:

Number of times a day you take it:

3. All medication has two names. Do you know the other name for your medication?

6. Do you suffer from tardive dyskinesia?

- [ ] Yes
- [ ] No
- [ ] Don't know

Appendix 7

DAI-30

Name (print): _____

DRUG ATTITUDE INVENTORY (DAI-30)
Hogan and Awad (1983)*

The purpose of this questionnaire is to gain some understanding of how patients view the use of psychiatric medications and the nature of their experiences on these drugs. Your responses are used for research purposes only, are strictly confidential, and will in no way affect your treatment.

Read each statement below and decide whether it is true as applied to you or false as applied to you. If a statement is TRUE or MOSTLY TRUE, circle the T following the statement. If a statement is FALSE or NOT USUALLY TRUE, circle the F following the statement. If you want to change an answer, mark an X over the incorrect answer and circle the correct answer.

Please answer every question. If a statement is worded not quite the way you would express it yourself, decide whether it is mostly true or mostly false. Remember to give YOUR OWN OPINION --- there is no right or wrong answer. Do not spend too much time on any one item.

The medications referred to in the statements are psychiatric medications only.

D4130

1	I don't need to take medication once I feel better.	T F
2	For me, the good things about medication outweigh the bad. ---------->	T F
3	I feel weird, like a 'zombie', on medication. ------>	T F
4	Even when I'm not in hospital I need medication regularly. ---------->	T F
5	If I take medication it's only because of pressure from other people. ---------->	T F
6	I am more aware of what I am doing, of what is going on around me, when I am on medication. ------>	T F
7	Taking medications will do me no harm. ------>	T F
8	I take medications of my own free choice. ------>	T F
9	Medications make me feel more relaxed. ------>	T F
10	I am no different on or off medication. ------>	T F
11	The unpleasant effects of medication are always present. ---------->	T F
12	Medication makes me feel tired and slugggish. ------>	T F
13	I take medication only when I am sick. ------>	T F
14	Medication is a slow-acting poison. ------>	T F
15	I get along better with people when I am on medication. ---------->	T F
16	I can't concentrate on anything when I am taking medications. ---------->	T F
17	I know better than the doctor when to go off medication. ---------->	T F
18	I feel more normal on medication. ------>	T F
19	I would rather be sick than taking medications. --->	T F
20	It is unnatural for my mind and body to be controlled by medications. ---------->	T F
21	My thoughts are clearer on medication. ------>	T F

GO ON TO THE NEXT PAGE

DA130

22 I should stay on medication even if I feel alright. T F

23 Taking medication will prevent me from having a breakdown. ----------> T F

24 It is up to the doctor when I go off medication. ---> T F

25 Things that I could do easily are much more difficult when I am on medication. ----------> T F

26 I am happier, feel better, when taking medications. T F

27 I am given medication to control behaviour that <u>other</u> people (not myself) don't like. ------> T F

28 I can't relax on medication. ----------> T F

29 I am in better control of myself when taking medications. ----------> T F

30 By staying on medications I can prevent getting sick. T F

If you have any further comments about medication or this questionnaire, please write them below or overleaf.

DO NOT WRITE BELOW THIS LINE

CB _____ PC _____ _____

VPCAT _____ _____ _____

Appendix 8

Assessment of Subjective response (Van Putten & May 1978)

A. How does the medication agree with you?

B. Did it make you feel calmer?

C. Did it affect your thinking?

D. Do you think this would be the right medicine for you?

Instructions

Subjective: patient's direct statements only

Score: +11 (maximal positive) through 0 (no effect or equal good and bad) to -11 (maximal negative).

N.A.= patient couldn't answer, couldn't give information.

DEGREE

MAXIMAL	11
VERY GREAT	10
MARKED	9
SUBSTANTIAL	8
SIGNIFICANT	7
DISTINCT	6
MODERATE	5
FAIR	4
MINOR	3
SLIGHT	2
MINIMAL	1
ZERO	0

Appendix 9

List of items included in the Q-sort

1. I'm worried about my friends finding out I'm on neuroleptics
2. Neuroleptics aren't good for everyone
3. A lot of people would be unhappy if there were no neuroleptics
4. I don't really get any effect from my medication
5. I'm frightened of my medication controlling me
6. This medication drains my energy
7. My family don't like me being on this medication
8. My symptoms completely disappear when I'm on the medication
9. I believe people should have the minimum dose to keep their symptoms under control
10. I can't do without my medication
11. Neuroleptics make me happier
12. people wouldn't like me if they saw what I was like without the medication
13. I think all neuroleptics are the same so it doesn't matter which one I'm on
14. It is hell taking this medication
15. The medication doesn't cure the illness it just controls the symptoms
16. The neuroleptics make me feel timid and inadequate
17. Side effects put me off taking medication
18. Neuroleptics are just chemical strait jackets
19. My symptoms are still there but they just don't bother me as much when I've taken my medication
20. I see taking medication as an invasion of privacy
21. I don't have any side effects from my medication
22. I would never change my medication of my own accord
23. Neuroleptics make me see reality better
24. If I didn't take the medication I'd end up back in hospital
25. I don't think I should get involved in decisions about my treatment
26. This medication is harmless to me
27. The side effects of neuroleptics are worse than the symptoms I have
28. I know what level of neuroleptic I function best on
29. I've lost interest in things since I've been on neuroleptics
30. If I started getting any serious side effects I'd stop taking my medication
31. I don't think it was the medication that made me feel better
32. I come to get my medication to meet people
33. I don't know why I take my medication
34. I know when I'm due for my next dose of medication
35. If a doctor prescribes something I think I should stick to it
36. Neuroleptics give me control over my life
37. Neuroleptics aren't as good as they're made out to be
38. I don't think my medication is totally suited to me
39. I don't like taking any medication
40. Neuroleptics make me less tense
41. I'd feel happier taking my medication if I knew more about it
42. I feel more sociable on neuroleptics
43. I'm worried about what will happen if they stop my medication
44. Neuroleptics make the brain work better
45. Neuroleptic make me think clearer