Treatment of First Episode Schizophrenia with Low-Dose Haloperidol: A Study in the Western Cape Province of South Africa

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Dissertation presented for the Degree of Doctor of Philosophy

at the University if Stellenbosch

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March 2003

Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

Abstract

Although schizophrenia is traditionally viewed as an illness with a very poor prognosis, research over the last few years indicates that early intervention may substantially improve the long-term outcome of this disorder. Several studies suggest that patients with first-episode psychosis (FEP) are more sensitive to, and require lower doses of antipsychotic medications than patients with more chronic forms of illness. However, the optimal dose of first-generation antipsychotics in patients with FEP has not been explored extensively and continues to be a controversial subject. This study evaluated the efficacy and safety of low-dose haloperidol in a South African cohort with FEP.

The study was conducted in two phases:

Phase 1 was an open-label, naturalistic study of 57 subjects with FEP who were commenced on 1mg of haloperidol for 4 weeks, after which gradual escalation of doses were allowed, if required. Subjects who failed to respond at haloperidol 10mg per day were switched to thioridazine. Failure to respond to thioridazine 600mg per day was interpreted to indicate treatment resistance. These subjects were then commenced on clozapine. The principal finding of this phase of the study was that the majority of subjects could be stabilized and maintained on very low doses of haloperidol (1.7 ± 1.0 mg/day at 12 months and 1.3 ±0.8 mg/day at 24 months). Ratings for extra-pyramidal side-effects did not increase significantly from baseline over the duration of the study, except in the case of tardive dyskinesia (TD), where a substantial number of subjects (12.3%) developed TD within 12 months of starting treatment.

Phase 2 of the study was a double-blind, randomized controlled trial of low-dose (2mg/day) versus "standard dose" (8mg /day) haloperidol. Forty subjects were included in this phase of the study; 20 in each treatment arm. The main finding was that there were no significant differences in treatment reponse between the two treatment groups. There were, however, significant differences between the two treatment groups in extrapyramidal side effects (EPSE), with the 8mg per day group exhibiting significantly higher levels of EPSE than the 2mg per day group. This was manifested by significant differences in scores on the Extrapyramidal Symptom Rating Scale (ESRS) and the Simpson-Angus Rating Scale. Furthermore, subjects in the 8mg haloperidol per day group required significantly higher doses of anticholinergic medication and had significantly higher mean levels of prolactin at the end of the study period.

This study indicates that a majority of subjects with first-episode psychosis can be treated and maintained successfully with very low doses of haloperidol. It also shows that low-dose treatment is as effective as, and better tolerated than, "standard" doses. Despite the success with the low-dose treatment, however, there was still a much higher than expected incidence of tardive dyskinesia, a serious and potentially irreversible side-effect of neuroleptic treatment.

Abstrak

Hoewel skisofrenie tradisioneel gesien is as 'n siekte met 'n uiters swak prognose, dui navorsing oor die afgelope jare daarop dat vroeë ingryping die langtermynuitkoms van hierdie toestand drasties mag verbeter. Resultate van verskeie studies dui daarop dat pasiënte met eerste-episode psigose (EEP) nie net meer sensitief is vir antipsigotiese middels nie, maar ook laer dosisse daarvan benodig tydens behandeling as pasiënte met meer kroniese vorms van psigotiese siekte. Desondanks is die kwessie van die korrekte dosis van eerste generasie antipsigotika in hierdie groep nog onvolledig nagevors en bly dit 'n omstrede onderwerp. Hierdie studie het ten doel gehad om die effektiwiteit en veiligheid van lae dosis haloperidol in 'n Suid-Afrikaanse populasie van pasiënte met EEP te evalueer.

Die studie is uitgevoer in twee fases:

Fase 1 was 'n oop, naturalistiese studie van 57 pasiënte met EEP wat aanvanklik behandel is met 1mg haloperidol per dag vir 4 weke, waarna geleidelike verhoging van dosisse toegelaat is, soos nodig. Diegene wat nie bevredigende respons getoon het op haloperidol 10mg per dag nie, is oorgeskakel na tioridasien. Ontoereikende respons teen 600mg/dag tioridasien is

geïnterpreteer as 'n aanduiding van behandelingsweerstandigheid en behandeling met klosapien is begin.

Die belangrikste bevinding van hierdie fase van die studie was dat die meerderheid pasiënte gestabiliseer en in stand gehou kom word op baie lae dosisse haloperidol (1.7 ± 1.0 mg/dag op 12 maande en 1.3 ±0.8 mg/dag op 24 maande).

Metings van ekstra-piramidale newe-effekte (EPNE) het nie beduidend toegeneem oor die duur van die studie nie, behalwe in die geval van tardiewe diskinese (TD), waar 'n beduidende aantal pasiënte (12.3%) TD ontwikkel het binne 12 maande na aanvang van behandeling.

Fase 2 van die studie was 'n dubbelblinde, ewekansig gerandomiseerde studie waarin behandeling met lae dosis haloperidol (2mg/dag) vergelyk is met "standaard" dosis haloperidol (8mg/dag).

Veertig pasiënte is ingesluit in hierdie fase van die studie, 20 in elke behandelingsarm. Die hoofbevinding was dat daar geen beduidende verskille in respons op behandeling was tussen die twee groepe nie.

Daar was egter beduidende verskille in EPNE, waar die 8mg/dag groep beduidend hoër vlakke van EPNE gehad het as die 2mg/dag groep.

Hierdie verskil in EPNE is aangedui deur 'n statisties beduidende verskil in tellings op die Extrapyramidal Symptom Rating Scale (ESRS) en die Simpson-Angus Rating Scale. Verder het pasiënte in die 8mg/dag groep beduidend hoër dosisse antikolinerge medikasie benodig en ook hoër gemiddelde prolaktienvlakke gehad teen die einde van studie.

Hierdie studie dui dus daarop dat die meerderheid van pasiënte met EEP suksesvol behandel en in stand gehou kan word met baie lae dosisse haloperidol. Die studie wys ook daarop dat behandeling met lae dosisse net so effektief is en beter verdra word as behandeling met "standaard" dosisse. Ten spyte van die suksesvolle gebruik van lae dosisse medikasie het die studie egter ook getoon dat daar 'n baie hoër as verwagte insidensie was van TD, 'n ernstige en potensieel onomkeerbare newe-effek van neuroleptiese behandeling.

Contents

Introduction

The history of psychiatry has often been one of misunderstanding, prejudice and neglect. Despite revolutionary discoveries in the field, particularly in psychopharmacology[1], many laymen, but also medical colleagues, view psychiatry and psychiatrists with a mixture of fear and contempt.

In the medical fraternity, psychiatric illness is often seen as "not real", "self-inflicted" or as having such a poor prognosis that treatment resources are better applied elsewhere. This negative mindset reflects the prejudice of society as a whole, where the primeval "fear of madness" seems to be as strong today as ever.

Discrimination on the grounds of mental illness is reflected in the fact that psychiatry remains the most poorly funded of medical specialties, with many medical aid funds in South Africa either excluding or severely restricting benefits for mental illness[2]. This is also the case in the state sector, where funds available for the treatment of mental illness are considerably less than those spent on other specialties. In fact, most of the secondary hospitals in South Africa do not even offer any psychiatric inpatient services, thereby increasing the load on the already overburdened psychiatric hospitals where funds and services had been severely cut in the drive for deinstitutionalization.

The last decade of the twentieth century saw the publication of a number of important papers that exposed the danger of disregarding mental health. One of the most important of these papers was the Global Burden of Disease Study[3]. This study was the first to employ the concept of "Disease adjusted life years" (DALY's) and showed neuropsychiatric illness to be one of the principal causes of disability and loss of productivity in the world. At the time of the study in the mid-1990's, neuropsychiatric illness already accounted for more than 10% of DALY's worldwide. Even in the developing world, this figure was more than 9%.

Of all the illnesses that psychiatrists treat, Schizophrenia is the most costly[4]. It is also an illness viewed by most as having a very poor prognosis, with inevitable deterioration and permanent disability as the only likely outcome. Studies of first episode psychosis (FEP) changed this perception for some, who came to realize that, with appropriate and timeous intervention, patients could remain or once more become active members of society.

However, the problem seems to be that many patients, who do well with initial treatment, discontinue their medication due to side effects and then relapse into psychosis again and again, with catastrophic consequences in terms of long-term outcome. Poor compliance, mostly as a result of side effects, therefore is a major contributing factor to the long-term impairment that patients with Schizophrenia suffer. It is imperative that we as researchers and clinicians do our utmost to ensure minimal side effects from the medication we prescribe, so that patients will be encouraged to continue using their medication in order to ensure the optimal outcome.

Chapter 1

Schizophrenia – Etiology, Epidemiology, Symptoms and Signs

Although Schizophrenia has probably been around as long as humanity itself, it has, until fairly recently, been a disorder veiled in myth and prejudice.

Emil Kraepelin (1856 – 1926) and Eugene Bleuler(1857 – 1939) were the two most important historical figures in the medicalization of this disorder. Benedict Morel who first used the term *demense precoce*, but it came to be associated with our current concept of Schizophrenia as a result of Kreapelin's description of what he termed *dementia praecox*.

Bleuler introduced the term ***Schizophrenia*** to describe what he saw as a schism between emotion, behaviour and thinking[5].

Although the interpretation of the concept of Schizophrenia and the diagnostic boundaries thereof varied widely over the years, the introduction of the DSM-III in the early 1980's helped to standardize the diagnostic criteria for this disorder. Today, clinicians across the world have access to a standard set of reliable, tested and proven criteria in the form of the DSM-IV[6]. This has helped not only to improve diagnostic accuracy, but has also advanced research into and, consequently, treatment of Schizophrenia.

The DSM-IV criteria for Schizophrenia are as follows:

A. ***Characteristic Symptoms***: Two or more of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

   1. Delusions
   2. Hallucinations
   3. Disorganized speech
   4. Grossly disorganized or catatonic behaviour
   5. Negative symptoms, i.e. affective flattening, alogia, or avolition.

   Note: Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. ***Social/Occupational Dysfunction***: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations or self-care, are markedly below the level achieved prior to the onset.

C. ***Duration***: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms that meet criterion A (i.e. active phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A in an attentuated form. (E.g. odd beliefs, unusual perceptual experiences.)

D. ***Schizoaffective and Mood Disorder Exclusion***: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either: 1) no major depressive, manic or mixed episodes have occurred concurrently with the active phase symptoms or 2) if mood episodes have occurred during active phase symptoms their total duration has been brief relative to the duration of the active and residual periods.

E. ***Substance/ General medical condition exclusion***: This disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

F. ***Relationship to a pervasive developmental disorder***: If there is a history of autistic disorder or another pervasive developmental disorder the additional diagnosis of Schizophrenia is only made if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated.)

Epidemiology

Schizophrenia has a prevalence rate of approximately 1% in the general population[5]. Despite its fairly low prevalence however, its chronic, often debilitating course leads it to consume a considerably larger proportion of health expenditure than it's prevalence would suggest[4;7]. In fact, Schizophrenia is not only the most expensive disorder that psychiatrists treat in terms of direct cost, but has also – as discussed earlier - been shown to be one of the leading causes of disability in the world[3].

Although Schizophrenia is equally prevalent in the sexes, its mean age of onset in men, at between 15 – 25 years of age, is about a decade earlier than in women. Schizophrenia occurs all over the world and in all population groups, however it is not equally distributed throughout the world, with higher prevalence in some areas. In industrialized societies for example, Schizophrenia is more common in low socio-economic groups and also in immigrant populations[8].

Etiology

Despite many years of research, the cause(s) of Schizophrenia continues to elude us. From the end of the nineteenth century, up to the middle of the twentieth century, psychoanalytic theory was dominant in psychiatry. The concept of an ego defect and ego disintegration with a return to a time before the ego had been established was put forward as the cause of psychosis.

Regression in response to conflict and frustration was central to this theory, and was elaborated on by many authors in this field[9].

Towards the second half of the twentieth century however, there was a major change in thinking about the cause of psychiatric illness in general and Schizophrenia in particular. With technological advances in brain imaging and neuropathology, evidence slowly mounted for a biological cause for Schizophrenia. The strongest evidence for the biological underpinnings of the disorder however came with the discovery of chlorpromazine and subsequent studies that proved the efficacy of antipsychotic medications in the treatment of Schizophrenia[10].

Evidence from a variety of sources, including neuro-imaging and neuropathology, suggest abnormalities of brain structure in patients with Schizophrenia[11-13]:

a) *Neuro-imaging studies* show patients with Schizophrenia to have larger lateral ventricles[14] and, to a lesser extent, third and fourth ventricles as well as the loss of the normal asymmetry seen in the human brain[15]. These abnormalities seem to be present at the onset of symptoms and remain static[12;13], although some authors [16] suggest that they may be progressive.

b) *Neuropathological findings* have confirmed these neuro-imaging findings, and also report reduced cortical volume and neuronal density[17], loss of grey matter in selected areas such as the hippocampus and amygdala, reduction in number and abnormal arrangement of neurons[18] and lack of gliosis[19]. This lack of gliosis supports the idea that the insult occurs early in the development of the foetal

brain, as gliosis will only occur after the second trimester of pregnancy. Also, neuropathological findings in post-mortem examination of the brains of patients with Schizophrenia are suggestive of abnormal neural migration in the developing brain[18]. Taken together, these findings support the widely held theory that Schizophrenia is a neurodevelopmental disorder[20].

Further support for the neurodevelopmental theory of Schizophrenia comes from evidence of increased risk with obstetric complications[21;22], maternal malnutrition[23] and influenza during pregnancy[24]. All of these risk factors may be expressed in a "final common pathway" that leads to the development of Schizophrenia.

On the synaptic level, the dopamine theory has long been the prevaling theory of the etiology of Schizophrenia[25]. In it's most basic form, this theory states that excess dopamine causes psychosis. Most authors realize that this is a gross oversimplification of the psychobiology of the disorder, however, some dysregulation of dopaminergic neurotransmission is clearly involved (see full discussion of dopamine receptor later).

The Symptom Complex of Schizophrenia

Delusions and hallucinations have long been regarded as the hallmark of Schizophrenia and also the focus of its treatment. This came to be despite the fact that the so-called "first-rank" symptoms of Schizophrenia are neither necessary nor sufficient for the diagnosis of the disorder. To this day, many clinicians still see the presence of hallucinations and delusions as the principal diagnostic features. It is therefore important to reiterate the fact that there is not a single symptom or sign that is pathognomonic for Schizophrenia, as they may also occur in other psychiatric or neurological disorders[5].

It was Timothy Crow who proposed the concept of type I and Type II Schizophrenia[26], thereby emphasizing the presence (or absence) of the "positive" (hallucinations, delusions, positive thought disorder) and "negative" (affective flattening, alogia, avolition-apathy, social withdrawal, attention problems) symptoms of Schizophrenia.

More recently, factor analysis of the Positive and Negative Syndrome Scale (PANSS)[27] has revealed 5 symptom clusters in Schizophrenia, namely: positive symptoms, negative symptoms, cognitive symptoms, mood symptoms and aggression/hostility[28]. This is of great importance, as each of these symptom-clusters may impact on the eventual outcome and deserve treatment in it's own right. Each should therefore be evaluated, rated and followed closely. Clinicians should be aware of the fact that medication that treats the positive symptoms of the disorder may not be effective in treating other domains of the illness and may

make some of the other symptoms worse.[29] This fact makes an intimate knowledge and close follow-up of each target symptom cluster imperative.

Let us consider each of the symptom clusters:

Positive symptoms

Hallucinations, Delusions, Positive Thought Disorder.

These are the best-known symptoms of Schizophrenia. They are however not specific to Schizophrenia and may be present in a variety of other psychotic disorders, such as psychotic mood disorders, substance induced psychotic disorders and others. Although they are therefore classic symptoms, they are neither necessary nor sufficient for a diagnosis of Schizophrenia. This does not detract from the fact that they cause great distress to both patients and carers and should be a major focus of treatment. In fact, recent studies suggest that our aim should be to eradicate these symptoms altogether, as symptoms of psychosis, however mild, may reflect an ongoing "toxic" effect on the brain with negative implications for long-term outcome[30;31].

Negative Symptoms

These symptoms are also known as deficit symptoms and describe a loss of normal function. Andreasen[32] describes the following negative symptoms:

1. ***Affective flattening*** (such as paucity of expressive gestures, poor eye contact, affective non-responsivity, etc.)
2. ***Alogia*** (poverty of speech, thought blocking, increased response latency, etc.)
3. ***Avolition- Apathy*** (poor grooming and hygiene, physical anergia, impersistence in school/work)
4. ***Anhedonia- Asociality*** (reduction in recreational interests, reduced sexual interest, fewer interpersonal contacts, relationships.)
6. ***Attention*** (social inattentiveness, inattentiveness during testing)

These symptoms are of importance, and clinicians should distinguish between primary and secondary negative symptoms[33]. Primary negative symptoms are those symptoms that are seen as "core" features of the disorder, whereas secondary negative symptoms may be the result of side effects of medication, secondary to positive symptoms, secondary to depressive symptoms or due to lack of environmental stimulation. Secondary negative symptoms are therefore more likely to respond to appropriate treatment or adjustments in medication.

Mood Symptoms

Despite the fact that mood disorders and Schizophrenia are traditionally conceptualized as separate disorders, mood symptoms are common in Schizophrenia[34]. Whereas they were previously thought to be uncommon in the acute phase of the illness, it is now recognized that depressive symptoms are a key feature of the acute psychotic episode, and that the majority of these symptoms resolve with antipsychotic treatment[35]. From the available data, it would appear that mood symptoms in the acute phase of Schizophrenia might be associated with a favourable outcome[36], while persistent depressive symptoms appear to be negative prognostic indicators[37-39].

Cognitive Symptoms

Problems in cognitive functioning in Schizophrenia have been described since the time of Kraepelin. In recent years, more detailed research has shown that the cognitive dysfunction in Schizophrenia, although wide spread, seems to involve the areas of memory, attention and executive functions in particular[40]. More importantly, these deficits seem to be the principal indicators of poor outcome in terms of skills learning and work rehabilitation[41]. These deficits are not irreversible, but can be treated.

Aggression/Hostility

A patient experiencing a psychotic episode may become hostile, aggressive and violent. This behaviour is, however, not unique to psychosis or even to psychiatric disorders, although a diagnosis of Schizophrenia increases the risk thereof. Psychotic patients may act on the instructions of command-type hallucinations, may respond to delusions or may act out in disorganized or excited states. The role of the clinician is to be aware of the risk, to assess and treat it appropriately, always with the patient's best interest at heart.

Outcome

Early studies on the long-term outcome of persons suffering with Schizophrenia started with that of Bleuler in 1966[42]. We now know from this study and others[43;44] that approximately 20% of patients recover, with a further 25% who make signifcant improvements. This leaves at least fifty percent of patients with a chronic, unremitting course of illness, requiring care and follow-up.

Chapter 2

Why should we be paying special attention to the patient with a first episode of psychosis?

In the 1980's, a number of researchers began to investigate the early phases of psychotic illness. Their findings have lead to the realization that this subpopulation of patients may offer unique opportunities in the treatment of Schizophrenia[45-50].

There are now a number of well-established first-episode programmes around the world. In South Africa however, this area has been poorly studied and there are no known publications that refer specifically to a South African population of patients with first-episode psychosis. There are numerous reasons why a specific and special focus on first-episode psychosis is important:

a) Kraepelinian doctrine holds that dementia praecox is a deteriorating illness with poor long-term outcome. Bleuer, on the other hand, suggested that patients deteriorate early in the course of illness but then reach a plateau of relative stability in psychopathology[42].

More recent work has supported Bleuler's notion of early deterioration and stabilization[51], eventually leading to the introduction of the concept of the "critical period" by Birchwood et al[45;52]. Birchwood[52] suggests "the early phase of psychosis is a critical period for intervention, offering major opportunities for

secondary prevention of the impairments and disabilities that accompany psychosis" (S31).

In this theory deterioration in function occurs in the prodrome, as well as in the early phases of the illness, but stabilizes after 2-5 years (the so-called plateau[53]). There may even be some improvement in functioning in certain patients later in their illness. Intervention should therefore be aimed at getting the patient to effective treatment before they have progressed too far down the slope of deterioration, preferrably within a few weeks or months after the onset of illness, if not before.

b) It is a well-established fact that patients with a first episode of psychosis show better response to treatment than patients with chronic illness [54-57]. In published trials of short-term treatment of first-episode patients that lasted several weeks, response rates were around 60%[58-60]. Even though this was a high early response rate, it has been pointed out that this may be an underestimation of the responsiveness of first-episode patients to treatment, as the time to response may be considerably longer. In the study of first-episode psychosis from the New York Group, it was found that a cumulative response rate of more than 80% was achieved after one year of treatment[59]. First-episode patients also required lower doses of medication than patients with chronic illness[61;62] and were more vulnerable to side-effects[63].

c) Another, related factor suggesting intervention as early as possible in the "critical period", is the effect of the duration of untreated psychosis (DUP).

The period of untreated psychosis immediately before the first contact is a highly traumatic time for both patient and family and there are often many obstacles preventing the patient from reaching appropriate help. From a psychological point of view, patients who have an insidious onset of symptoms with a lenghty prodromal phase may be dysfunctional over a long period of time in many spheres of life. This is very likely to lead to vocational and educational underachievement, but may also cause social isolation and disruption of interpersonal relationships with reluctance on the behalf of others to help. Fear, bewilderment, denial and a combative coping style coupled with prejudice on behalf of patients, carers and helping professionals are all features of this phase that work against appropriate diagnostic and treatment interventions[64;65].

There have also been claims of a relationship between DUP and outcome on a biological basis. Wyatt was the first to suggest that untreated psychosis may have a "biologically toxic" effect on the brain, with obvious implications for outcome and treatment resistance[31;66;67]. This theory has been supported by a number of studies which found a relation between the DUP and outcome on a variety of measures[46;48;68-71]. Although others have questioned these findings[72;73], the available data seems to suggest that a longer DUP may either be the cause or the signal of a deteriorating course[74].

d) Mood symptoms, and in particular depression, are known to be more common in first episode patients than in patients with chronic illness, with resulting increased risk of suicide[34;35]. Patients with first-episode psychosis are exposed to many traumatizing events that doctors often overlook:

1) The effects of the psychosis itself, with potentially frightening delusions and hallucinations.

2) The first contact with mental health services, which is very often not a positive or helpful one and which may lead to severe distress[46]

3) The process of hospitalization (which is often involuntary),

4) The unpleasant experience of so-called "intensive care units" filled with many psychotic, often agitated and sometimes-violent fellow-patients,

5) Medication (often administered against the patient's wishes) and it's side effects.

These experiences are so unpleasant that patients may develop symptoms of post-traumatic stress disorder[65].

e) From the researcher's point of view, the first episode presents that rare opportunity to evaluate the natural course of the illness, from its earliest phases. Furthermore, patients can be evaluated without the confounding factors of medication and it's side effects. This may tell us more about the many features of Schizophrenia, including the cognitive dysfunctions, the brain abnormalities and the presence or absence of neurological deficits before medication is initiated. A number of findings on the unique biological features of first-episode psychosis have been published and it was found that at least some of the known biological changes seen in patients with Schizophrenia might already be present early in the course of the illness:

A variety of computerized tomography (CT) and magnetic resonance imaging (MRI) studies have shown that patients with first-episode psychosis have

enlarged lateral ventricles (ventricle-brain ratio)[75-77], third ventricles[12], reduced brain volume and a reduction in the normal hemispheric asymmetry of the brain when compared to normal controls. Although this was seen by some as supporting a neurodevelopmental disorder[13], it was also noted to be less prevalent and less severe than in patients with chronic Schizophrenia[11].

Lieberman et al[78] found that patients with a first-episode of psychosis and questionable or definite brain pathomorphologic features took significantly longer to recover and also achieved poorer levels of remission. In this same study, abnormal basal growth hormone levels were also found to be an indicator of longer time to remission.

In conclusion it can be said that there is now ample evidence that early intervention in Schizophrenia may prevent, and in some cases even reverse, deterioration in functioning. Early intervention significantly improves the likelihood of remission in symptoms and return to functionality. A very specialized programme of treatment is needed however, if we hope to make the kind of interventions that will allow maximum effect and compliance with treatment with minimum side effects.

Chapter 3

Current treatment strategies for Schizophrenia and First-Episode Psychosis

The treatment of Schizophrenia is a complex endeavour, requiring skilled clinicians with a thorough knowledge of biological, psychosocial and environmental intervention strategies. Whereas custodial care was the model for the treatment of severe psychiatric disorders during most of the twentieth century, the last two decades of the previous millenium saw a new emphasis on cost-effectiveness and deinstitutionalization.

Although there have been marked improvements in many areas of care, psychopharmacological intervention remains the cornerstone of the treatment of Schizophrenia[10]. Whereas patients were treated with high doses of antipsychotics in the past, recent years have seen a greater realization of the heterogeneity in response to medication, both in terms of effect and side effects. Also, many researchers have published data to show that large doses of medication afford no additional benefits and will not induce more rapid response[61;79-83]. However, the 1970's and 1980's saw a continuous increase in the use of high doses of high potency antisychotics, despite the lack of research data to support this practice[84].

Despite the fact that more clinicians are becoming aware of first-episode patients as a unique group (see Chapter 2), there are still no clear guidelines on how they should be treated. This is reflected both in the literature and the psychopharmacological treatment trials:

Guidelines and books

The more recent past has seen the publication of a number of guidelines to advise clinicians on the correct treatment of Schizophrenia in general[85;86], but also for the treatment of first-episodes of psychosis[87-89].

As an example, the PORT treatment recommendations[86] suggest doses of antipsychotic medication for Schizophrenia of between 300 – 1000 chlorpromazine (CPZ) equivalents. For first-episode psychosis, their recommendation is the following:

"Persons experiencing their first acute symptom episode should be treated with an antipsychotic medication other than clozapine, but dosages should remain in the lower end of the range mentioned…" (Page 2). In their table of treatment options, the dose range suggested for haloperidol is 6 – 20mg during the acute phase and 6 – 12 mg during the maintenance phase. Baldessarini also suggested doses of between 10- 12 mg for acute treatment, while 6 – 12 mg is suggested for maintenance therapy[79].

At the lower extreme, Aitchison et al[87] suggests that "..an appropriate treatment protocol for first-episode psychosis would be to initiate antipsychotic treatment at a very low dose (eg 2mg haloperidol or 100mg chlorpromazine equivalents)" (page 51).

Acute treatment studies

In the first-episode study of risperidone and haloperidol by Emsley et al.[90], 183 patients with a first episode of psychosis were treated with either risperidone or haloperidol in a double blind, flexible-dose design over a six week period. In this study, it was found that low doses of both medications were effective and better tolerated than high doses. In this study, the mean daily dose of haloperidol was 5.6mg per day. It also found that doses of 6mg or less were effective and better tolerated than doses greater than 6mg per day.

Recommendations of even lower doses came from the Toronto Group, who, on the basis of their positron emission tomography (PET) findings, suggested doses as low as 2 – 6mg per day for the treatment of first-episode psychosis[89]. There are, however very few clinical studies to back up this recommendation[61;62], while there are also studies to suggest that these doses may in fact, be too low[82;91;92]

In the study by the Scottish Schizophrenia group, patients were randomized to treatment with either pimozide or flupenthixol for 5 weeks of double-blind treatment. The doses in this study started at 10mg and went up to 40mg per day in the case of pimozide and 50mg per day in the case of flupenthixol. Patients

were evaluated with the Research Diagnostic Criteria (RDC)[93] and Feighner criteria[94]. Sixty-three percent of patients were classified as responders to medication. Non-responders were more likely to be male, have neurological signs, cognitive deficits and negative symptoms. The mean daily dose of medication was 18.8 mg of pimozide and 20mg flupenthixol per day. What was of significance here was that most patients in this study required anti-parkinsonian medication for EPS and that plasma neuroleptic levels showed compliance to be extremely poor.

In an open treatment protocol of first-episode psychosis patients with DSM-IV defined Schizophrenia, Kopala et al[58] used risperidone as treatment, starting on 1mg twice daily and increasing doses slowly. The mean daily dose for risperidone in this study was 4.7(±1.5) mg per day and they reported a 59% response.

What was to become probably the best known and most widely-quoted first-episode study in the world was conducted by Lieberman et al[47;55;59;78;95-102] in New York. In this large, open trial at Hillside Hospital, patients were included if they had definite or probable Schizophrenia according to RDC, were aged between 16- 40 and had no serious medical illness.
Patients were treated with sequential trials of fluphenazine (20mg for 6 weeks, then 40 mg for 4 weeks), haloperidol (20mg for 6 weeks, then 40mg for 4 weeks), molindone (up to 300mg per day) and clozapine (up to 900mg per day). It seems, therefore, not surprising that 62% of patients developed extra-pyramidal side effects[103]!

A most interesting study of treatment of first-episode psychosis is that by Zhang-Wong et al[62]. In this study, 36 patients were treated with haloperidol according to the following protocol: In the first week, all patients received haloperidol 2mg per day. The dose of haloperidol was then increased weekly until either a) PANSS had improved by 15% or b) side-effects developed. Drug doses were standardized to 5mg at day 8, 10mg at day 15, and 20mg at day 22. Doses were frozen for the remainder of the study period once the optimal dose was reached. The median optimal daily dose of haloperidol in this group was 5mg per day. However, 42% of subjects in this group achieved optimal response at haloperidol 2mg per day, whereas only 8% of patients responded at 20mg per day. The authors found that EPS were rare at the low doses and they remarked that, had the trial period at each level been extended beyond one week, more patients might have responded.

Studies of maintenance treatment

In the Northwick Park Study[104], first-episode patients were not treated uniformly during admission to hospital. However, after discharge from hospital, 120 patients formed part of a placebo-controlled, randomized trial of maintenance neuroleptic medication. Minimum doses of medication were set, but no upper limits. In the case of haloperidol, this minimum dose was set at 3mg per day, but, by the end of the study, the mean daily dose of haloperidol was 11.75mg per day. The study had a high relapse rate of 46% of patients on active treatment and 62% of patients on placebo within two years of discharge form hospital.

Better outcome was reported by Kane et al[54], who found no relapses after 1 year in the group of first-episode psychosis patients treated with fluphenazine (either oral 5-20mg per day or depot 12.5 – 50mg bi-weekly). This was considerably better than the 7/17 that relapsed on placebo.

A small group of 15 patients from the Scottish First Episode Schizophrenia Study, who were stable on treatment for one year after their initial episode, were randomized into treatment with either flupenthixol or pimozide as active treatment, or placebo[105]. This treatment regime was followed for a further 12 months. The mean daily dose at the end was 18.8mg pimozide and 20mg flupenthixol. Of the 8 patients on active treatment, none relapsed, whereas 4 of the 7 patients on placebo relapsed and were readmitted.

Chapter 4

The role of dopamine and serotonin in psychosis and its treatment

Before the age of modern psychopharmacology, institutionalization was often the only treatment option available for patients with chronic mental illness and, by the middle of this century, reached it's zenith when almost 560 000 patients were residents of psychiatric institutions in the United States alone[106]. The serendipitous discovery of chlorpromazine, however signaled the start of a revolution in mental health care[1]. More and more attention was focused on medical and specifically pharmacological intervention in the treatment of psychiatric disorders.

Although clinicians had no idea as to the molecular mechanisms underlying the antipsychotic effects of chlorpromazine at its introduction in the mid 1950's, it became clear during the next twenty years that the major effect was mediated through the ability of the medication to block dopamine receptors in the brain. At least 5 subtypes of dopamine receptor have since been identified[107]. They are

divided into two broad families: the D_1-like (including D_1 and D_5 subtypes) and the D_2-like (including D_2, D_3 and D_4) receptor subtypes.

Although there is good evidence for the D_2 receptor subtype's involvement in Schizophrenia, the clinical role of the other subtypes remains uncertain.
The classic observation by Seeman and others[108] that the potency of antipsychotic medications correlated with their affinity for dopamine D_2 receptors in the basal ganglia remains one of the principal components of the dopamine theory of psychosis. Whatever else they may do, all antipsychotic medications have this in common: they block D_2 receptors[109]. In fact, no medication that did not block these receptors has ever been proven as a successful antipsychotic treatment.

Four major pathways have been identified for dopaminergic neurotransmission in the human brain[110]:

1. ***Mesolimbic pathway***. Cell bodies arise in the ventral tegmental area of the brainstem and project to limbic areas of the brain, such as the nucleus accumbens. It is thought that it is dopaminergic dysregulation in this pathway that is responsible for the so-called positive symptoms of Schizophrenia.
2. ***Mesocortical pathway***. Cell bodies arise in the ventral tegmental area of the brainstem and project to the cerebral cortex. Dysregulation in this pathway is thought to be implicated in the negative and cognitive features of Schizophrenia.

3. ***Nigrostriatal pathway***. Cell bodies project from the substantia nigra in the brainstem to the striatum. Dysregulation in this pathway is implicated in movement disorders such as Parkinson's disease, chorea and tics.
4. ***Tuberoinfundibular pathway***. Cell bodies project from the hypothalamus to the anterior pituitary. These neurons normally inhibit prolactin secretion.

While antipsychotic medications reduce positive symptoms of Schizophrenia through its effects on the mesolimbic dopaminergic pathway, the first-generation antipsychotic medications seem unable to discriminate between different areas of the brain in terms of dopamine blockade. By blocking D_2 receptors in the other three dopaminergic pathways in the brain, they cause the well-known side effects of this class of medication:

1. ***Nigrostriatal pathway*** – pseudo-parkinsonism, akathisia, dystonia, tardive dyskinesia.
2. ***Mesocortical pathway*** – cognitive dulling, secondary negative symptoms, secondary mood symptoms.
3. ***Tuberoinfundibular pathway*** – hyper-prolactinaemia

Recently, much attention has been focused on the role of the serotonergic system in the effects of antipsychotic medications. It has been suggested that manipulation of the serotonergic system and it's interaction with the dopaminergic system can reduce EPS and even enhance antipsychotic efficacy[111;112].

Serotonergic projections from the dorsal raphe project to the substantia nigra, where they have an inhibitory effect on dopaminergic neurons[113]. This inhibition is mediated via the $5HT_{2A}$ receptor, which is located on the somatodendritic surface of the dopaminergic neuron. Similar projections via the median forebrain bundle connect the raphe nuclei to the frontal cortex. Here, too, serotonergic stimulation inhibits the release of endogenous dopamine.

Because of this mechanism, particular emphasis has been placed on the serotonergic $5HT_{2A}$ receptor. It has been proposed that blockade of this receptor, in addition to the blockade of the D_2 receptor, may explain the "atypicality" of the second- generation antipsychotics, at least to some extent[114]. Firstly, it seems that blockade of the $5HT_{2A}$ receptor widens the therapeutic "window" between antipsychotic effect (usually around 70% D_2 occupancy) and the threshold for the development of EPS (around 80% D_2 occupancy)[115]. Secondly, it has been suggested that serotonergic receptor blockade may be the mechanism by which the second-generation antipsychotics treat the negative symptoms of Schizophrenia[112]. This is based on animal studies that found antagonism of the $5HT_{2A}$ receptor to increase dopamine in the limbic system[116]. The idea is therefore that, depending on which dopamine pathway we care to look at, different results of $5HT_{2A}$ blockade will be observed:

1. In the nigrostriatal pathway, blockade of $5HT_{2A}$ reverses the inhibitory effect of serotonin on dopamine, thereby promoting dopamine release into the synaptic cleft and overcoming EPS. As there are relatively higher numbers of D_2 receptors in this area when compared to $5HT_{2A}$ receptors, this effect is

only partially successful and dose dependent, i.e. for some of the second-generation antipsychotics, high doses of medication will overcome the protective effect of $5HT_{2A}$ blockade and EPS will appear.

2. In the mesocortical pathway, the balance of receptors favours $5HT_{2A}$ over D_2. Therefore, blockade of the $5HT_{2A}$ receptors may have a more profound pro-dopamine effect in the frontal areas than in the striatum. This may be involved in the suggested better effect on cognition and negative symptoms with second-generation antipsychotic medications. Studies with ritanserin[117;118] support this theory: in a study with ritanserin, which is a blocker of both $5HT_{2A}$ and $5HT_{2C}$, it was found to be effective in the treatment of negative symptoms. A second, non-dopaminergic mechanism may also be involved here: serotonergic projections have a direct inhibitory effect on prefrontal neurons that is not dependent on dopamine. Blockade of $5HT_{2A}$ receptors may therefore lift this inhibitory effect as well.

3. In the tubero-infundibular pathway, dopamine inhibits prolactin secretion, whereas serotonergic stimulation of the $5HT_{2A}$ receptor promotes prolactin secretion. With the first-generation antipsychotic medications, the blockade of D2 receptors leads to hyperprolactineamia. With the second- generation antipsychotics, though, there are not only reduced D_2 blocking properties, but also the mitigating effect of $5HT_{2A}$ blockade and therefore less promotion of prolactin secretion.

4. In the mesolimbic pathway, the atypical antipsychotic achieves enough D_2 receptor antagonism that is not reversed by $5HT_{2A}$ antagonism to have a profound and effective antipsychotic effect.

Probably the best clinical example of this dopamine-serotonin interaction is seen in the clinical effects of risperidone, one of the second-generation antipsychotic medications. Risperidone has been shown to be equipotent to haloperidol at the D_2 receptor. However, at doses below 6mg per day, risperidone seems much less likely to cause EPS than haloperidol. In doses beyond 6-8mg per day, the risk of EPS between risperidone and haloperidol becomes indistinguishable[119].

The reason for this seems to be that, up to a dose of 6mg per day, risperidone demonstrates higher $5HT_{2A}$ occupancy than D_2 occupancy, and the serotonergic disinhibition is therefore able to prevent/overcome the risk of EPS. As we move beyond this threshold dose however, the D_2 occupancy becomes higher than $5HT_{2A}$ occupancy, resulting in the appearance of EPS.

It has to be kept in mind though, that many different subtypes of the serotonin receptors have been and continue to be cloned and may therefore have a role in "atypicality". For example, some authors suggest that clozapine's high affinity for the $5HT_6$ receptor may be the key to its unique properties as an antipsychotic medication[120]. Also, with this theory in mind, one would expect medications that increase serotonin levels in the brain to worsen the side effects of antipsychotic medications. This is partly true: some studies have found selective serotonin reuptake inhibitors (SSRI's) to cause EPS, akathisia, tremor and dystonia[112].

However, others have found significant improvements in negative symptoms with SSRI's. Some authors suggest that this may in fact be a result of the effect of SSRI's on mood symptoms that are masking as negative symptoms, however the specific mechanism remains unclear.

Although the dopamine-serotonin interaction therefore seems to be important, the classic interplay as seen with risperidone is not seen with all the second-generation antipsychotic medications. Other second-generation antipsychotic medications are as effective as risperidone, but show lower affinity for the D_2 receptor, with clozapine and quetiapine the two medications at the extreme of the spectrum. Both of these medications cause virtually no EPS at any dose, primarily because of the fact that the "threshhold" for EPS is not reached. In fact, clozapine's occupancy of D_2 receptors has been reported in a number of studies to vary from 20% - 67%[121]. Indeed, the existence of a "glass ceiling" has been suggested to describe the relationship between clozapine dose and D_2 occupancy[115].

The traditional concept of potency in terms of affinity for D_2 receptors seemed to be lost therefore, with the introduction of the second-generation antipsychotics. Although clozapine has been proven to be a highly effective antipsychotic medication, it's occupation of D_2 receptors in the striatum was found to be considerably less that the 70% or more thought to be needed for antipsychotic effect[115;121]. This has lead to the idea that other mechanisms may be involved in the antipsychotic effect of what has become known as the multi-receptor antagonists.

One such putative mechanism is via the blocking of the dopamine D_4 receptor subtype[122]. This receptor subtype was suggested as a candidate on the basis of clozapine's very high affinity for it and a report of higher levels of this receptor in the brains of patients with Schizophrenia[123]. However, a study with the selective D_4 antagonist L745,870 proved to be unsuccessful as a treatment for acutely psychotic patients[124].

More recent findings regarding the pharmacokinetics of antipsychotic medications have introduced a completely new concept to the issue of atypicality, this being the notion of "loose" and "tight" binding at the level of the receptor. To understand this, we need to consider carefully the pharmacokinetics at the receptor level. Strange et al[125] points out that the level of dopamine at the synapse is not fixed, and may change over time. These changes in levels of dopamine may affect the effects of antipsychotic medications by competing for dopamine receptors. Medications with a high dissociation constant (Kd) will bind to the dopaminergic receptor more loosely than medication with a low Kd. Examples of medications with high Kd are clozapine and quetiapine. Examples of medications with low Kd are haloperidol and chlorpromazine. The latter two will therefore not dissociate rapidly from the receptor. The rapid dissociation of the medications with a high Kd may explain at least some of the "atypicality" of these compounds and provide additional protection against the development of EPS. What this may also imply is that, contrary to what we believed up to now, the second-generation antipsychotic medications (in particular clozapine and quetiapine), do in fact bind with the D_2 receptors to the same extent as do the

first-generation antipsychotics, but this binding is only transient. This was shown to be the case with quetiapine in a PET-study by Kapur et al[126], which showed that the D_2 occupancy by this medication declined rapidly from 58% three hours post dose to only 20% at 12 hours post dose. This may call into question many of the D_2 occupancy studies where patients received medication and the occupancy was measured approximately 12 hours later.

Kapur and Seeman[127] recently suggested that the multireceptor hypotheses may, in fact, be wrong and that the basis for atypicality may lie in the fast dissociation of certain compounds from the D_2 receptor. According to these authors, "the blockade of other receptors (other than D_2) is neither necessary nor sufficient."

Chapter 5

Extrapyramidal side-effects

Although extrapyramidal symptoms are often mentioned in research protocols and textbooks of psychiatry, they seldom receive the attention it deserves in clinical settings. The side-effects of dystonia, parkinsonism, akathisia and tardive dyskinesia seem to interest clinicians only when overwhelmingly obvious, and sometimes not even then.

There are many reasons why the recognition and treatment of EPS are important in psychiatry, such as their disfiguring, stigmatizing nature and the fact that they may, at times, be life-threatening[128;129]. But it also has an important role in the ongoing problem of non-compliance.

Poor compliance remains one of the largest problems in psychiatry, with some studies showing levels of non-compliance of up to 74% within two years after

discharge from hospital[130]. At least two important studies have shown that the side effects of medication are either a major reason or the principal reason for medication non-compliance amongst patients taking antipsychotic medications[131;132]. What is of even greater concern though, is the fact that clinicians are so poorly skilled at detecting EPS. Hoge et al[131] showed that, whereas 35% of patients rated side effects as the principal reason for their non-compliance with treatment, only 7% of the clinicians treating them did so. Also, in the study by Weiden et al[130], it was shown that clinicians fail to recognize side effects in the majority of patients, recognizing akathisia in only 26% of cases and tardive dyskinesia in only 10% of cases[130]. This has not only become a major clinical dilemma, but has, in many parts of the world, also become a medico-legal issue, as patients and families become more aware of the rights of the patient and the responsibilties of the physician.

For those clinicians who work in the developing world and who have to rely on medications such as haloperidol for the treatment of psychotic illnesses[133], it is important to know that medication-induced parkinsonism is more likely to occur with the high potency medications (such as haloperidol), than with low potency medications. Also, it should be remembered that, whereas tremor is a common sign of Parkinson's disease, the medication-induced parkinsonism of antipsychotic medication seldom has tremor as a prominent feature. Rigidity and bradykinesia are more common signs, often missed by psychiatrists who believe them to be features of negative symptoms.

Akathisia is probably the most distressing of the EPS, with an incidence of approximately 25% in most major studies[134]. It is first experienced as a subjective restlessness, before objective signs become evident. It is often confused with psychotic agitation or anxiety and may result in even larger doses of antipsychotic medication being administered, thereby worsening an already distressing situation.

Acute dystonic reactions are not only painful and distressing to the patient, but may also be dangerous – dystonia may cause severe respiratory impairment as a result of laryngeal adductor spasm as well as dysphagia as a consequence of pharyngeal dystonia[135]. Acute dystonia seems to occur more commonly with the use of high potency antipsychotics, and young, first-episode patients who are medication-naïve seem to be at particular risk of developing this problem[136].

Although EPS are known to occur in never-medicated populations[137;138], they are certainly less prevalent and more subtle than in patients treated with antipsychotic medication[103]. First-episode patients are more sensitive to the side effects of medication and more likely to develop acute EPS[63].

Dyskinetic movement disorders are also known to occur in patients who have never been exposed to antipsychotic medication[139;140], but are considerably more prevalent in patients treated with antipsychotic medication[141]. In a large study, Woerner et al[142] reported prevalence rates in patients treated with antipsychotic medications to be around 23%, whereas prevalence rates of tardive dyskinesia (TD) in patients never treated with antipsychotics were below 3%.

In clinical settings, tardive dyskinesia remains very much an underdiagnosed and, therefore undertreated disorder[143]. Incidence studies report figures of approximately 5% per year of treatment with antipsychotics[144]. A similar figure of 4.8% has been reported for the first year in a first-episode psychosis group, with figures increasing to about 16% after four years[145]. In this study from Hillside Hospital, both dose of medication and poor treatment response were significant predictors of time to onset of TD. In terms of the dose of medication, each 100mg-chlorpromazine equivalents increased the hazard of developing TD by 5%. Other authors have also suggested dose as a risk factor for the development of TD[144].

Other risk factors for TD that have been reported are medication-free intervals[146], race[147], affective symptoms[148], increasing age and female sex[141]. The expression of EPS also significantly increases the risk of developing TD at a later stage[138].

Clozapine was the first antipsychotic medication with a proven, reduced risk for inducing TD[149] and it has even been suggested that this medication may, in fact, treat TD[150;151]. It therefore seems logical that, as other second-generation antipsychotic medications are also less likely to cause EPS than first generation medications, their risk for causing TD will be lower[152]. In support of this notion, a review of long-term studies show the risk of tardive dyskinesia to be substantially lower with olanzapine than with haloperidol[153]. However, other authors have argued that the evidence for this remains preliminary and inconclusive[154].

Another possible way to minimize the risk of TD would be to use first generation

antipsychotics in low doses, thereby reducing their risk of causing EPS and, perhaps, TD[155].

Although the low-dose strategy is not necessarily clear-cut as a solution to the problem, Owens[152] suggests it as prudent that "doses of antipsychotics in all phases of treatment must be kept to the minimum necessary to achieve the primary aims of the management plan." (p215)

Chapter 6

Prolactin

Prolactin is a polypetide hormone synthesized by and excreted from the anterior pituitary gland. Its principal role in human physiology is to induce and promote milk production.

Prolactin secretion is controlled by complex mechanisms, of which dopamine is the principal inhibitory component. This inhibitory effect is mediated via the tubero-infundibular dopaminergic pathway[156]. Prolactin secretion is promoted by various factors, including oestrogens (and, of course, the removal of the inhibitory tone of dopamine). Serotonin also stimulates prolactin secretion. It achieves this by at least two mechanisms: by inhibiting the effect of dopamine and by increasing the activity of prolactin-secreting factors.

According to a number of studies, normal serum concentrations of prolactin in men and non-pregnant, non-lactating females are between 5 – 25 ng/ml[157;158]. Measuring prolactin is, however, not a simple endeavour: the levels of the hormone vary considerably among individuals, but also have pronounced circadian variation and even some seasonal variation. Furthermore, the circadian variation of prolactin secretion depends primarily on sleep, rather than on an intrinsic rhythm.

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Studies on patients with schizophrenia, who are not taking antipsychotic medication, show that prolactin levels are normal in these subjects[159].

Treatment with first-generation antipsychotics has a profound effect on prolactin levels, producing increases of around two to three times above the norm in the majority of patients[160]. There are however, individual cases that experience increases far greater than this. These increases appear to be dose related, particularly for haloperidol[161] and are mediated via the effects on D_2 receptors. In a recent study by Kapur et al[162], small doses of haloperidol were added to an existing treatment regime of clozapine. Prolactin levels were measured at baseline and again 4-8 weeks after addition of the haloperidol. Receptor occupancy was also measured with [(11)C]raclopride and positron emission tomography imaging. It was found that the addition of haloperidol increased D_2 receptor occupancy from 55% to 79% and also significantly increased the prolactin level.

Increased prolactin levels caused by antipsychotics do not return to baseline immediately on discontinuation of medication, but remain high for a period of approximately two to three weeks[163]. However, there are some indications that a subset of patients may develop tolerance to the prolactin-elevating effects of antipsychotic medications[164].

The second-generation antipsychotic medications have much less of an effect on prolactin, although there are great differences between different compounds. Clozapine has little, if any, effect on prolactin[165], while olanzapine produces a

transient increase in prolactin levels[166]. With risperidone, the effect is largely dose-dependent, with higher doses causing a marked increase in prolactin levels[167]. Quetiapine does not seem to have any effect on prolactin, either early or later in treatment[166].

The effects of hyperprolactinaemia

Patients with schizophrenia show lower levels of sexual interest and activity than normal controls, even in the premorbid, unmedicated state[168]. Although treatment of psychosis may improve social behaviour and, by implication, also sexual behaviour, elevated prolactin levels are well-known to disturb sexual activity in terms of desire, erection and orgasm in the male and may even cause hypogonadism[169].

A study by Ghadirian et al[170] showed that, although also high, complaints of sexual dysfunction were considerably lower in women (30%) with elevated prolactin levels than in men (81%). However, there are indications from this and other studies that elevated levels of prolactin in females cause menstrual disturbances and galactorrhoea.

Bone loss and osteoporosis is another area of concern in patients with hyperprolactinaemia. There is considerable evidence that high levels of prolactin are associated with reduced bone density[171]. This does not seem to be a direct consequence of the elevated prolactin levels though, but rather secondary to amenorrhoea and reduction in gonadal function. Reduction in bone density as a

result of treatment with antipsychotic medication has been shown in both men and women[172].

In conclusion, first-generation antipsychotics are known to elevate serum prolactin levels, thereby causing sexual dysfunction (particularly in men) and loss of bone density. There have also been reports that this increase in prolactin may increase the risk for breast cancer[166]. Treatment options for hyperprolactinaemia as a result of antipsychotic medication have been to either reduce the dose or to treat the patient with a prolactin-lowering agent such as bromocriptine, cabergoline or amantadine[166].

The data with second-generation antipsychotics is less clear, but clozapine, olanzapine and quetiapine seem to have very little risk in this regard.

Chapter 7

Haloperidol

Paul Jansen from Belgium introduced haloperidol to the world in the middle of the previous century. It proved to be a very powerful antipsychotic medication, with less sedative effect than chlorpromazine. The original antipsychotics were considered "dirty" medications, which did not only affect the D_2 receptor (the desired effect), but also a number of other receptors, such as muscarinic cholinergic receptors, alpha adrenoreceptors and others (undesired effects).

It was therefore considered a major step forward when high potency D_2 receptor antagonists such as haloperidol were introduced to the market. The more specific the action of a medication on the D_2 receptor, the safer and more tolerable it was considered to be. In time, haloperidol became the most widely used antipsychotic medication in the world.

Haloperidol is a butyrophone derivative, a purely synthetic product and the first of the butyrophenone series of major tranquilizers.

Chemical structure

Haloperidol's chemical structure is: $C_{21}H_{23}C_1FNO_2$ and it has a molecular weight of 375.9[173]. It's chemical name is: 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone. It has a pKa of 8.3.

Haloperidol is insoluble in water, but is soluble in alcohol, chloroform, methanol-acetone and benzene.

Pharmacokinetics[174;175]:

Haloperidol is readily absorbed from the gastro-intestinal tract and is extensively metabolized by the liver in the first-pass effect. There is wide intersubject variation in plasma concentration. Haloperidol is highly bound to plasma proteins (>90%). It is widely distributed in the body and crosses both the placenta and the blood-brain barrier. Its volume of distribution is 18 l/kg.
Haloperidol has a half-life of 13-40 hours (mean 20 hours) and is metabolised primarily by the liver. Systemic clearance is 11,8 ml/min/kg. This rate is increased in children and reduced in the elderly. Haloperidol is excreted via urine (26%) as well as via bile and faeces. Enterohepatic recycling of about 40% occurs.

Indications

Although haloperidol is best known as an antipsychotic medication that is used in the treatment of schizophrenia or psychotic mood disorders, it is also indicated for the treatment of Tourette's disorder, hiccups and agitated and aggressive behavioural disturbances[176].

Contra-indications

Haloperidol is contra-indicated in comatose states, Parkinson's disease and in late pregnancy. It should also be used with caution in patients with hyperthyroidism and in patients on lithium[177].

Haloperidol in the treatment of schizophrenia

Although haloperidol is clearly an effective antipsychotic, there are at least 2 major problems with this medication:

a) It is not universally effective and a substantial portion of patients show partial, poor or no response to this medication.
b) It has the potential to produce serious side effects, some of which may be irreversible (tardive dyskinesia) while others may be fatal (neuroleptic malignant syndrome).

Even so, because of its relative safety, it is often used as a comparator in clinical trials and has become the gold standard of antispychotics[178].

In a recent Cochrane review of haloperidol in the treatment of schizophrenia, comment was made however, on the lack of data available on this compound[178]. This review showed that, although haloperidol is a markedly effective antipsychotic medication with a Number Needed To Treat (NNT) of only 3, it has

a high risk of causing untoward effects, such as dystonia (1 in 5), akathisia (1 in 6) and parkinsonism (1 in 3).

The authors conclude that, although effective, other antipsychotics should be chosen before haloperidol. They furthermore suggest that its initial cost-saving effect (due to low direct acquisition cost) may be offset by the consequences of adverse events, including poor compliance.

Chapter 8

The Case for lower doses

The first antipsychotic medication synthesized was chlorpromazine, first used in anaesthesiology in France in the early 1950's. When its antipsychotic effect was reported by Delay and Deniker, it presented psychiatry with the first real tools for treating severe mental illness, offering hope to many[1].

However, as experience with the earliest antipsychotics increased, the limitations of these medications became clear. Whereas they were effective in relieving the positive symptoms in 70% of patients[179] they brought with them a series of side effects that would become the hallmark of antipsychotic treatment over the next 40 years. Extrapyramidal side-effects (EPS) of parkinsonism, akathisia, dystonia and tardive dyskinesia were soon recognised by patients and clinicians alike as the single, largest drawback of the antipsychotics. Additional problems included sedation, weight gain, orthostatic hypotension and other cardiovascular side effects. Furthermore, these medications were found to be less effective in the treatment of the negative symptoms of the illness[180].

Although antipsychotics therefore have undisputed, beneficial effects on many aspects of psychosis, patients often experience treatment as unwanted, uncomfortable and preferably to be avoided. They are often sceptical about

treatment, with high levels of non-compliance (up to 60% on oral medication[181] and 40% on depot medication[182]). Among the reasons for negative attitude to treatment are:

1. Poor insight into the disease
2. Poor doctor-patient interaction and
3. Societal prejudice against drug treatment for mental problems[183].
4. However, the single, most important contributing factor to non-compliance remains the side-effects of antipsychotic medication[131;132].

We therefore have treatments that help our patients, but only to a limited degree. Patients are still left impaired in many areas of functioning. Also, the side effects of these medications leave many patients unwilling and unlikely to take them over the extended periods required.

As many patients fail to show response in their psychotic state in the early part of treatment with antipsychotic medication, clinicians have tended to increase doses of neuroleptics rapidly, hoping to accelerate the rate of improvement. In 1994, the Royal College of Psychiatrists published a consensus statement[184], warning against the use of high doses of antipsychotics and pointing to the dangers inherent in this practice. These dangers include sudden cardiac deaths, neuroleptic malignant syndrome, respiratory depression and others. Other authors[185] have also suggested the use of effective, but minimum doses of antipsychotics. Even so, high doses of antipsychotics are still employed in the treatment of psychotic illness in many hospitals. Recent evidence has once again shown that a reappraisal of traditional prescribing habits is imperative and that

careful reconsideration of the dose-effect characteristics of traditional antipsychotics may enhance their clinical use, reduce iatrogenic morbidity and, ultimately, improve the quality of life of patients.

In a comprehensive survey of dose-effect relationships in treatment of psychosis, Baldessarini et al[79] did not find any support for the use of antipsychotics in high doses above 500 -600 mg chlorpromazine equivalents. They suggested that rapid neuroleptization and other forms of high dose treatment, which gained prominence in the 1970's, may lead to continued and detrimental overtreatment in patients who would have responded to moderate doses of medication, given enough time for the full effect of the lower dose to take effect.

Other authors have gone even further: Van Putten et al[82] found that patients who received 20mg of haloperidol per day, did significantly worse than those receiving 10mg per day on a variety of measures, with significant deterioration on some BPRS items as well as akinesia and akathisia ratings. Furthermore, 35% of their patients receiving 20 mg of haloperidol per day insisted on leaving the hospital against medical advice, as opposed to only 4% of those receiving 5 or 10 mg per day. They suggested that high doses of haloperidol might have significant psychotoxic effects and proposed doses as low as 5 mg per day after the first 2 weeks of treatment. Other studies have also borne out this finding, showing clearly that doses of haloperidol above 10mg per day have no added clinical benefit and in fact may be less effective than lower doses[80;81].

McEvoy et al[61] revisited the concept of "neuroleptic threshold" in 1991. Neuroleptic threshold (NT) was defined as the lowest neuroleptic dose at which individual patients develop slight increases in rigidity on neurological examination. Using this construct, it was found that the mean haloperidol dose at which their 106 patients crossed the NT was 3,7 mg per day. Of 58 patients exposed only to NT doses of haloperidol, 72% clinically recovered within the 5-week trial. Further increases in dose given to other patients did not lead to greater improvent in psychosis, only to significant increases in EPS. They also pointed to a significant difference in the dose required to reach neuroleptic threshold in neuroleptic-naive patients (median 2 mg) versus previously exposed patients (median 4 mg).

Some studies of maintenance treatment show similar results to the acute-phase studies. Eklund and Forsman[186] conducted a study of 56 patients of whom 41 were randomized into treatment with haloperidol decanoate (HD) injection or placebo for 48 weeks of double-blind treatment. Patients receiving HD were given doses of 60mg every 4 weeks, corresponding to a daily dose of approximately 3,6mg of oral haloperidol per day. Their results showed that these low doses of HD prevented relapse in a majority of patients, with minimal subjectively experiended side effects that differed only slightly from placebo patients.

Modern research tools like PET have also helped to add more impetus to the argument in favour of low-dose treatment. It is known that EPS is the result of D_2 receptor occupancy in the basal ganglia and that typical antipsychotics block D_2

receptors in direct correlation to their clinical potency[187]. Some authors of PET studies have suggested a threshold of around 70-80% D_2 receptor occupancy for the introduction of EPS, which seems to be higher than the threshold for antipsychotic effect[121].

Recently, Kapur et al[109;188-190] found in a series of PET studies that high levels of D_2 occupancy could be achieved at very low doses of haloperidol. In one study, seven patients with schizophrenia were treated with 2 mg per day of haloperidol. PET showed D_2 receptor occupancy of ranging from 53% to 74%, with 5 patients showing substantial clinincal improvement. None of these patients showed important side effects. In another study by the same group[190], it was demonstrated that 2 - 5mg of haloperidol would be expected to induce 60 - 80% D_2 receptor occupancy, suggesting that the conventional use of more than 10mg per day of haloperidol may be too high.

Looking at the evidence from another angle, the issue of plasma levels should be considered. Although no clear evidence for a relationship between plasma levels of haloperidol and clinical response have been found, a number of studies[83;191] have identified plasma levels above which no further improvement is likely to occur and where further increases may actually be detrimental. A recently published study[192] showed that patients treated with haloperidol at plasma levels above 25ng/ml did significantly worse than those treated with doses lower than 18ng/ml, providing more compelling evidence that higher doses offer no additional benefit.

Not all of the evidence supports the use of low-dose conventional antipsychotics however, with some suggesting poorer efficacy for low-dose oral [92] or depot [51] medication. In the study by Zimbroff et al[92], haloperidol 4mg, 8mg and 16 mg per day was compared to sertindole 12mg, 20mg and 24 mg in the treatment of schizophrenia in a 8 -week, placebo-controlled, double-blind study. Although this study found that both medications were effective in the treatment of psychosis, haloperidol 4mg per day was not more effective than placebo on the final Clinical Global Impression (CGI). Also, the 8mg dose of haloperidol seemed to be the most effective dose in terms of all parameters. The study also found a fairly high rate of parkinsonism and akathisia with haloperidol, even at the 4mg per day level. The authors concluded that 4mg could be the minimally effective dose of haloperidol. What makes this study so significant, is the fact that this was the first multicentre, placebo-controlled assessment of the dose-response effects of haloperidol, despite it's use over many years as a standard reference in clinical trials.

The evidence from First-Episode Studies

As evidence accumulated that high doses of antipsychotic medication did not lead to more effective or rapid treatment, and EPS was found to be the principal cause of non-compliance[131], the practice of "rapid neuroleptization" lost favour in most centres of influence. Many clinicians came to realize that lower doses of antipsychotic medications might be even more important in neuroleptic-naïve patients than in patients with chronic psychotic illness. Doses far below those traditionally prescribed were reported in a few studies over the last

decade[61;62;90;92], with a number of other authors adding their voices in editorials and books[88;89;133;193].

In his classic study of the neuroleptic threshold, McEvoy[61] showed that patients with a first-episode of psychosis needed only half the daily dose of haloperidol required by patients with a more chronic illness. This is truly important, as the standard practices still do not reflect this finding. Furthermore, internationally accepted recommendations such as the PORT recommendations[86], although considerably more conservative than previous guidelines, still suggest a daily dose of 6 – 20mg of haloperidol.

More recently, Emsley et al[90] conducted a 6-week, double blind study in patients with first-episode psychosis in which risperidone was compared to haloperidol. In this study, patients started medication at 2mg twice daily. The medication could be titrated up or down in increments of 2mg. Maximum daily dose allowed was 8mg twice daily. At the end of the study, it was found that the mean daily dose of risperidone was 6.1mg and that of haloperidol 5.6mg. This paper also points to the particular importance of the dosing issue, in the light of previous work that showed that patients in the early phases of psychotic illness are more prone to EPS than patients with more chronic illness.

Another study that proposed to find the "optimal" dose of haloperidol for first-episode psychosis was conducted by Zhang-Wong et al[62], which has already been discussed (see chapter 3). Although this was a fairly brief study over only four weeks with a smallish sampe size of only 36 patients, they showed again

that the median optimal dose for the group as a whole was 5mg per day, which is considerably lower than the doses normally used.

What remains problematic though, is that most of these are brief studies of the treatment of first-episode psychosis, in the acute phase, over a period of only a few weeks. Consider then the New York group's finding that the median time to response in first-episode psychosis is 9 weeks[59]. This time lapse to response becomes even more meaningful when we realize that, in that study, they used doses far in excess of what would be considered acceptable today. It should be self-evident that blinded, randomized, but relatively brief studies, although very important, tell us perhaps too little of the "real" world, and should be interpreted with caution. Clearly, acute phase studies where medication is titrated up after just a few days will not take into consideration the adaptation that has to take place in gene expression[194] and the proven, slow response rate to treatment.

Chapter 9

The case for and against second generation antipsychotics

The re-approval of clozapine in the USA in 1989 marked the start of the "atypical era". This medication was shown to be more effective than the first generation medications in the treatment of both positive and negative symptoms of schizophrenia, particularly in those patients refractory to standard treatments. Importantly, it did so without the risk of EPS[195]. Unfortunately, clozapine's potential for causing agranulocytosis limits it's utility to those patients with proven treatment resistance. Despite this, it remains the gold standard against which all new antipsychotics should be compared.

Since the "rediscovery" of clozapine, the field of psychiatry has witnessed an unprecedented flood of new products to the antipsychotic market. All of these medications have one thing in common: in clinical trials comparing them to first-generation antipsychotics, they proved to cause fewer EPS. Thus this new class

of medications have become known as the second generation of antipsychotic medications.

The second-generation antipsychotics (also called "atypical" or "novel" antipsychotics) do not however, represent a homogeneous class of medications. In fact, even the definition of so-called "atypicality" is somewhat obscure. By the most conservative definition, a medication can be considered atypical based on the following three pharmacological and clinical criteria[196]:

1. Antagonism of both D_2 and $5HT_{2A}$ receptors
2. Lower risk of causing EPS than first-generation antipsychotics
3. As effective in the treatment of positive symptoms as first-generation antipsychotics.

But there is much more to the issue of second-generation antipsychotics than just these three factors. They have also brought with them the hope of enhanced clinical efficacy[197]. First-generation antipsychotics, although effective in treating the positive symptoms of schizophrenia in a majority of patients, show limited efficacy in treating the negative symptoms of the disorder[198] and are only minimally effective or ineffective in treating the cognitive symptoms thereof[199]. Furthermore, the side effect profiles of the first-generation medications limit patient compliance[131], leading to recurrence of illness and impacting negatively on prognosis.

The next second-generation antipsychotic medication (after clozapine) was introduced in 1994, with the marketing of risperidone (Risperdal®). The great advantage of this medication over clozapine was the absence of the risk of agranulocytosis. Since then olanzapine, quetiapine, sertindole, ziprasidone, amisulpiride and others have been introduced to the market.

Although these medications are grouped together as "second-generation antipsychotics", and even if there are some similarities in pharmacological profiles, these are very different compounds with vastly different receptor binding abilties. As already mentioned, they share the D_2-blocking mechanism with the first-generation antipsychotics, but also have the additional property of potent $5HT_{2A}$ antagonism. For the rest, they exhibit significant differences in activity at other receptor sites, such as the histaminergic, cholinergic and other serotonergic sites.

Clinical effects of second-generation antipsychotics

Positive symptoms

In short-term studies over 4-6 weeks, each of the second-generation antipsychotics has been proven to be as effective as the first-generation antipsychotics in treating the positive symptoms of schizophrenia[92;200-202]. Some studies even suggest superiority for the second-generation antipsychotics in treating positive symptoms of schizophrenia over first generation antipsychotics[203-205].

Negative symptoms

All antipsychotics treat negative symptoms, but do so to a lesser degree than positive symptoms. The effect of antipsychotic medications on negative symptoms is, however a highly complex and contentious issue. This complexity arises form the difficulty in defining negative sympoms and its different components, as well as the risk that side effects of medication may indeed make the negative symptoms worse[33]. Therefore, some medications may at the same time treat and exacerbate the negative symptoms of schizophrenia.

There has been substantial evidence over the last few years to show that the second-generation antipsychotics are more effective in treating the negative symptoms of schizophrenia than the first generation antipsychotics. The most robust evidence here, once again, is for clozapine[206]. However, there have also been publications showing superior efficacy for other second-generation antipsychotics over first-generation antipsychotics in the treatment of negative symptoms[92;207]. Despite the results presented and the arguments put forward in sophisticated path analysis studies[207], it remains possible that these medications do not have any impact on the "core" or primary negative features of the disorder[197]. It is possible that their seemingly greater efficacy in treating negative symptoms result from the lower risk of EPS. In the case of clozapine, Carpenter

has argued that a superior effect on positive symptoms may explain the apparent change in negative symptoms[208]. The effect of second-generation versus first-generation antipsychotics in the treatment of negative symptoms remains, therefore, a controversial issue that will continue to be debated for some time[205].

Cognitive symptoms

As pointed out before, cognitive deficits are not only key features of schizophrenia, but have also been found to be the most important indicators of social and vocational re-integration[41]. First generation antipsychotics seem particularly poorly designed to treat these symptoms[209].

Evidence with the second generation antipsychotics show that there are improvements in attention and verbal working memory with risperidone[210], and of verbal production, visuomotor tracking and immediate verbal recall with clozapine[211] and olanzapine[212].

Side –effects

There is robust evidence that the second generation antipsychotic medications produce fewer EPS at recommended doses than the first generation antipsychotics[90;200;201]. This is again particularly true in the case of clozapine, where no EPS have been reported, even at high doses. However, similar findings have been made with the other second-generation antipsychotics, the mechanism of which is discussed elsewhere.

More recently however, more and more attention has been focused on side effects other than the neurological, for which the first generation antipsychotics have become so notorious. For example, a whole literature has developed around the single issue of weight gain secondary to the use of certain second-generation antipsychotic medications. This effect, together with the related effect on glycaemic control, have become major issues in the literature on the pharmacological treatment of psychosis[213-215]. It seems that second-generation antipsychotic medications vary in their weight gain liabilities and that clozapine and olanzapine are the two compounds that cause the most weight gain.

Despite the large literature suggesting superiority of the second-generation antipsychotic medications over the first generation antipsychotics, there have been some notable, dissenting voices. The arguments of those opposing the unequivocal acceptance of the second-generation antipsychotics' superiority are based in two broad principles:

a) Virtually all papers produced on the effects of second-generation antipsychotics are industry-sponsored (see chapter 9).
b) Trials of second generation versus first generation antipsychotic medications use the latter (particularly haloperidol) in doses that would ensure occurrence of EPS and other side effects.

In a recent paper, Geddes et al[154] conducted a systematic review of effectiveness and tolerability studies of second- versus first-generation

antipsychotics in the treatment of schizophrenia. However, in this study they also evaluated the effect of the dose of the comparator medication (in this case haloperidol), which they deemed important in evaluating the two parameters of outcome. The results of this meta-analysis showed that, when they controlled for the use of higher than the recommended dose of conventional (first-generation) antipsychotics in many studies, there was only a modest difference in favour of the second-generation antipsychotics in terms of EPS. Surprisingly however, there were no differences in overall efficacy and tolerabililty between the two groups. The authors go on to suggest that the "perceived benefits of atypical antipsychotics are really due to excessive doses of the comparator drug used in the trials."

Chapter 10

Purpose of this study

Studies with new, second-generation antipsychotics seem to suggest superior efficacy over haloperidol in the treatment of negative symptoms and mood and related symptoms. However, these studies used haloperidol in doses well in excess of 10mg per day[200;204], thereby creating a study environment biased to poor outcome in the haloperidol arm. This is true particularly in terms of side effects, but probably also in negative symptoms and even mood symptoms.

One of the most interesting - and controversial - developments in medicine in the last few years has been the very active participation of pharmaceutical companies in the field of research publications. A large number of papers published in the most prestigious journals are of studies sponsored by large multi-national pharmaceutical companies. This has lead to growing scepticism and a feeling among some scientists that this may be a form of covert advertising, rather than objective science[216;217]. It has indeed been confusing to some extent, as so many claims and counter-claims are published that the clinician has to be extremely well read to remain able to form an unbiased opinion.

Psychopharmacology has been no exception to this phenomenon. In the highly competitive marketplace for antipsychotic medication, it is often very clear that

the outcome of a study is determined even before the first patient is screened by a protocol that is "set up to win." It is marketplace common sense, and not scientific ethos or lack thereof, that lead pharmaceutical companies only to sponsor studies where a positive outcome for their product is likely.

Although it is therefore important to compare antipsychotics to determine differences in efficacy and side-effect profiles, we (as the scientific community) must be certain that we are comparing like to like: the issue of equivalent doses has, in our mind, not received enough attention in "head-to-head" studies, particularly those using haloperidol. To illustrate this point, let us consider a recent study[218] with two of the second-generation antipsychotic medications. Here olanzapine was found to be superior to risperidone on a variety of measures, among them treatment of negative symptoms. It must be noted that the doses of risperidone used in this study were titrated up to 6 mg per day within 3 days and that the mean modal dose of risperidone used in this study was 7,2mg per day. Now consider the fact that the chlorpromazine equivalence for risperidone is reported to be 1: 100 (i.e. 1mg of risperidone = 100mg chlorpromazine). Thus the chlorpromazine equivalents of risperidone used in this study was 720mg per day, far exceeding Baldessarini's[79] recommended maximum of 500 –600 mg chlorpromazine equivalents! For haloperidol, this factor must also be taken into account. Chlorpromazine equivalency for haloperidol is often not very clear, but seems to be in the region of 1:100 (1 mg haloperidol = 100 mg chlorpromazine), therefore doses in excess of 10mg per day would be far more than 500mg chlorpromazine equivalents.

With new technologies like single photon emission tomography (SPECT) and PET, as well as better-designed clinical trials, researchers should be able to generate more useful and accurate information on dosing of medication than ever before. However, with patents having expired long ago, pharmaceutical companies have very little incentive to spend money on research into the first-generation antipsychotics, unless it is to use them as comparator drugs against which to test their new molecules. Although these studies may at times serindipitously yield important information about the older medications[92], it is more likely than not that they are used as flogging horses against which to show off a new product.

In spite of a number of dissenting voices who claim that the second generation antipsychotics offer very little, if any benefits over first-generation medications[154], the first world seems to have largely abandoned the use of the first-generation antipsychotics in favour of the more user-friendly second-generation medications. In the developing world (including South Africa) however, this choice is not yet available[133].

It seems nothing less than ironic that most of the arguments regarding the relative merits of the first- versus the second-generation antipsychotics are based on comparisons to haloperidol when there is so little information available on the correct dosing of this medication. To this day, the "correct dose" of haloperidol remains largely the prerogative of the clinician or researcher. With the focus of research on the second-generation medications, it also seems unlikely that researchers in the first world will undertake large-scale studies to determine to

the correct dosing schedule for haloperidol. However, as it remains the antipsychotic of choice for most patients in the developing world, finding the correct dose of this medication continues to be of great importance.

In psychopharmacology research, the double blind, placebo-controlled, fixed dose study has become the gold standard. This has helped tremendously in providing unbiased information in clinical research. However, some of the problems with this kind of research are that protocols have very restrictive inclusion and exclusion criteria and often treat only a selected few patients for a very limited time. These studies invariably also have substantial dropout rates and provide more information on efficacy (a measure of the ability of the drug to treat whatever condition it is indicated for), rather than effectiveness (encompassing efficacy as well as tolerability and ease of use). Although therefore providing statistically pure data, they are often of limited value to the clinician who has to deal with patients with multiple pathologies, unclear diagnoses, co-morbid substance abuse and poor compliance over extended periods.

.It is therefore also of importance to do naturalistic studies where researchers attempt to approach the clinical setting, while adhering to sound research principals. These studies may be of greater clinical relevance that the double blind, fixed dose studies over a few weeks.

In the case of haloperidol in particular, the fixed dose studies are problematical. With wide inter-individual dose:plasma level variance, fixed-dose studies with this

medication may often result in unsatisfactory, biased data. As stated before, this medication has high affinity for the dopamine D_2-receptor, with an extremely narrow therapeutic index. Finding the "therapeutic window" in a particular patient should be an individual process, as there are so many factors that may eventually influence the concentration of the medication at the receptor site.

Considering the abovementioned, the purpose of this study was twofold:

1. Firstly, it was decided to use a naturalistic design to do a dose-ranging study in patients with first-episode psychosis. This arm of the study would therefore aim to determine the mean effective dose of haloperidol in patients experiencing a first psychotic breakdown. The mean effective dose would be the dose at which patients have response in psychotic symptoms, without unacceptable EPS or other side effects.

2. The second arm of the study would then compare this dose determined in the first part of the study with the standard dose of haloperidol. This was somewhat of a problem, as there were no "standard" doses to compare it with. The only "dose-finding" study that we could find with haloperidol was the sertindole study by Zimbroff et al[92], which showed haloperidol 8mg per day to be the most effective dose. It was therefore decided that 8mg would be used as the comparator dose.

Chapter 11

Subjects and method

Subjects were recruited from the Tygerberg-Stikland academic complex of hospitals. Both of these hospitals are affiliated with the University of Stellenbosch in Cape Town, South Africa. Subjects were recruited from the wards (i.e. insubjects), from the outsubjects department of the hospitals, as well as the clinic system and day hospitals within the hospitals' catchment area. Ethics approval was obtained through the ethics committee of the University of Stellenbosch. All subjects signed written, informed consent before any study-related procedures were undertaken.

All subjects were evaluated by Dr. P. Oosthuizen, who acted as the principal investigator. Dr. J.H. Turner acted as co-investigator and evaluated subjects when Dr. Oosthuizen was not available. These two investigators participated in regular interrater-reliability training sessions and a high level of interrater-reliability was maintained.

The following inclusion and exclusion criteria were applied:

Inclusion criteria

1. Male or female in- or outpatients.
2. Aged between 14 and 55 years. (inclusive)
3. DSM-IV diagnosis of schizophreniform disorder, or diagnosis of schizophrenia or schizo-affective disorder.
4. Current psychotic symptoms requiring antipsychotic treatment, in the opinion of the investigator.
5. Subjects who had, during their lifetime, been exposed to a maximum of 4 weeks of neuroleptic medication (This is, according to international protocol, the most practical cut-off point. More exposure to neuroleptics than this could significantly change some of the variables that we are measuring.)
6. Subject and/or legal guardian or representative has signed the informed consent form, according to the regulations of the ethics committee/s.

Exclusion criteria

Subjects meeting one or more of the following criteria could not be entered:

1. Evidence of alcohol or drug abuse in the last month before screening.
2. Subjects who had been treated with a long-acting depot neuroleptic.
3. Serious physical illness.
4. Mental retardation.

Withdrawal criteria

Subjects could be withdrawn from the study if:

1. The investigator considered it, for safety or efficacy reasons, in the best interest of the subject that he/she be withdrawn.
2. The subject withdrew his/her consent.

At baseline, after informed consent, the following information was obtained from the subject and/or guardian (All information was noted on a standardized form according to a semi-structured interview):

Demographic Data

Personal History

Psychiatric History

Medical History

Family History

History of previous treatment

History of concomitant medication

Each subject had a full physical examination at baseline, including a neurological evaluation.

Phase 1

Each subject had the following rating scales administered at baseline:

SCID (Structured Clinical Interview for DSM-IV)[219]

PANSS (Positive and Negative Symptom Scale)[27]

CGI (Clinical Global Impression)[220]

Y-BOCS (Yale-Brown Obsessive Compulsive Scale)[221]

Calgary Depression Rating Scale[222]

AIMS (Abnormal Involuntary Movement Scale)[220]

Barnes Akathisia Rating Scale[223]

Simpson-Angus Rating scale[224]

A blood sample for analysis of prolactin levels was also obtained at baseline.

After baseline evaluation, each subject had 19 scheduled visits over a 2-year period. Some subjects were seen more regularly due to unforseen events.

At each of these visits, subjects were evaluated with the following rating scales:

PANNS

CGI

CGI-CIS

Calgary Depression rating scale

AIMS

Barnes Akathisia Scale

Simpson-Angus Rating Scale

Diagnoses were re-evaluated at six-monthly intervals.

Prolactin levels were repeated at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months.

The treatment section of phase 1 of the study was a naturalistic, open-label study according to a treatment algorithm. In this treatment algorithm, all subjects were commenced on treatment with haloperidol 1mg per day. This dose was then maintained for at least the first four weeks, unless there was a significant deterioration in the subject's psychotic illness. If the subject's condition deteriorated significantly, the dose could be increased by 1 mg at day 7/ visit 1 (i.e. to 2 mg)

At week 4, subjects were evaluated with the full battery of rating scales as described above. If, at this point, the subject failed to show adequate response (here defined as 20% improvement in PANSS Total Score), the dose of haloperidol could be increased by 1 mg per week, until adequate response was achieved or a maximum of 10mg haloperidol per day was reached. Subjects who failed to improve on this dose could then:

a) Have a further increase in haloperidol up to a maximum of 20mg per day
b) Change over to thioridazine, starting on 100mg per day and increasing to 600mg per day
c) Change to clozapine

Although the protocol allowed 3 options, in practice all subjects who did not respond at 10mg haloperidol were changed to thioridazine 100mg, increased weekly by 100mg to 600mg and if there still was no response after 3 weeks on 600mg, changed to clozapine.

The dose of haloperidol could be titrated down at any time and by any dose-increment in the case of clinically significant treatment-emergent adverse events and/or if, in the treating doctor's judgement, a decrease was warranted.

Lorazepam could be used throughout the study if additional sedation was required. In case of acute disruptive behaviour that could not be contained within the limits of the protocol, or other extra-ordinary circumstances, subjects were allowed to "escape" the slow titration process, to allow for more rapid increase in the dose of haloperidol.

Orphenadrine and/or biperidine were allowed throughout the study for the treatment of EPS, if required. These medications were discontinued at the earliest possible opportunity.

If persistent comorbid Axis-I disorders such as major depressive disorder or obsessive-compulsive disorder were diagnosed, these were noted and treated.

Phase II

The second phase of the study was a double blind, randomised study of ultra-low dose versus standard dose haloperidol. In this part of the study, we used the clinical data obtained from phase 1 to determine the dose of medication that we would use. As the mean daily dose in the acute phase of the open label treatment was approximately 1,78mg per day[225], we decided to use 2mg per day as the treatment dose. Haloperidol 8 mg per day was used as the reference

medication. This was decided in the light of previous studies that suggested that doses higher than 10mg may be detrimental to the subject's mental health[83], and as a result of the only proper "dose finding" study with haloperidol, that by Zimbroff et al[92]. As discussed earlier, this study suggested 8mg per day to be the optimal dose of haloperidol.

At baseline in this phase of the study, subjects were evaluated with the following instruments:

SCID

PANSS

YBOCS

CGI

Calgary Depression Rating Scale

AIMS

Barnes Akthisia Rating Scale

Simpson Angus Rating Scale

Extrapyramidal Symptom Rating Scale[226]. This additional scale for the rating of EPS was added for two reasons:

a) To improve the sensitivity of ratings

b) To improve across-study compatibility with other studies

After baseline, subjects were randomized using a randomization table into one of the two treatment groups. Treatment was with identical-looking capsules,

containing either haloperidol 2mg per capsule or haloperidol according to a titration schedule (see table 12.1)

Table 11.1

Timelines for administration of double-blind medication during Phase II

	Day 1 - 2	Day 3- 4	Day 5 - 6	Day 7 – 42
Low Dose	2mg	2mg	2mg	2mg
Std Dose	2mg	4mg	6mg	8mg

Lorazepam was allowed as additional treatment for restless or agitated behaviour throughout the study. Orphenadrine and/or biperidine were allowed for treatment-emergent EPS. All concomitant medications were recorded.

Subjects were reassessed on a weekly basis, with the following rating scales:

PANSS

CGI

CGI-CIS

Calgary Depression Rating Scale

AIMS

Barnes Akathisia Rating Scale

Simpson Angus Rating Scale

ESRS

Blood sampling for prolactin levels were done at baseline and at endpoint.

Statistical Analysis

Statistical analysis was performed with the help of a specialized computer software package Statistica version 6 (Statsoft, Inc.). Dr. P. Oosthuizen performed the analyses under the guidance of a qualified and experienced medical statistician, Dr. MC Roberts.

An intent-to-treat design was used in this study, with last observation carried forward (LOCF) for any subject who did not complete either phase of the study. The primary measure of efficacy was the percentage change in PANSS total score form baseline to endpoint. Secondary measures of efficacy were percentage changes in PANSS subscale scores, as well as percentage changes in side-effect ratings.

Categorical variables were compared using chi-square or Fisher's exact test (two-tailed in all cases), depending on expected frequencies.
All numerical variables were first tested for normality of distribution using the Kolmogorov-Smirnov method. In cases where unrelated groups were compared in terms of numerical variables, we used either Student's t test (parametric) or

the Mann-Whitney U test (non-parametric). For correlations between pairs of numeric variables, we used either Pearson product moment correlation coefficient (parametric), or the Spearman rank order correlation coefficient (non-parametric).

As we were concerned that some of the results of the initial analysis of tardive dyskinesia were confounded, we performed a second analysis. In this analysis, Cox regression (also known as the proportional hazards method) was used to determine the effects of predictor variables and risk factors on the occurrence of TD. A significance level of 0.05 was used throughout.

Chapter 12

Results: General

Demographics, family and personal history

A total of 97 subjects were included in the two phases of the study.
Fifty-seven subjects were included in the open-label phase of the study and 40 subjects in the double-blind phase of the study. Fifty-four subjects (55.7%) from the combined group were male.

Age

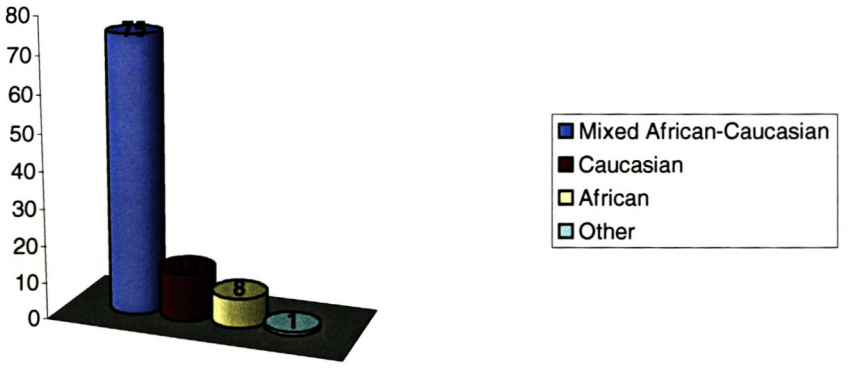
The mean age at inclusion into the study was 28.3 years (± 8.3). The mean age at inclusion for female subjects at 31.7 years (± 8.5) was older than that of male subjects at 25.5 years (±7.0). This difference in age at inclusion was highly statistically significant ($t = 3.8$; $df = 87$; $p = 0.0003$).

Ethnic distribution

The ethnic distribution of subjects is shown below in figure 13.1. All of the subjects, but one, were born in South Africa. The single exception was 1 female subject who was born in the Netherlands.

Figure 12.1

Ethnic Distribution of subjects



Marital Status

We had reliable information on the marital status of 91 subjects.
Of these, 16 subjects were married at the time of inclusion into the study (6 male, 10 female); 5 females subject had been divorced. Seventy subjects had never been married (45 male, 25 female). No subjects reported living in a de facto relationship at the time of inclusion into the study. There were more than twice as many females who had ever entered into marriage compared to males, a statistically significant difference between the genders (chi-square = 8.36; df = 1; p = 0.004). Marital status was not related to any of the psychopathology, side effect or depression factor ratings and did not affect changes in psychopathology or dose of medication used.

Fertility

We had reliable data on fertility rates for 87 subjects. Fifty-three subjects had never had children.

Table 12.1

Fertility Rates

Subject group	Phase I	Phase II	Total sample
Both sexes	0.8 (± 1.2)	1.0 (±1.4)	0.8(±1.3)
Females	1.2 (± 1.4)	1.5 (±1.6)	1.3(±1.5)
Males	0.4 (± 0.8)	0.7 (± 1.1)	0.5 (±0.9)

Female subjects had a significantly greater number of children than male subjects ($t = 3.11$; $df = 85$; $p = 0.003$).

Schooling

We had reliable information on the schooling of 83 subjects. Subjects left school at the median age of 18 years. Subjects achieved on average a standard 8 (grade 10) education. One subject held a Master's Degree and one subject held a Bachelor's degree at the time of inclusion into the study. There were no gender

differences in levels of schooling. Three subjects were full-time students and one a part-time student at the time of inclusion into the study.

Living arrangements/accommodation

Accommodation of subjects at inclusion into the study is presented below in table 12.2

Table 12.2

Accommodation of subjects at inclusion into study

Accommodation	Phase I	Phase II	Total Group
Homeless	2	1	3
Squatter Camp	1	2	3
Shelter	2	1	3
Rented Room	6	2	8
Rented House	9	6	15
Family Home	25	19	44
Own Home	6	2	8

Most subjects had been in their current accommodation for a considerable time, with a mean period of 98.2 months in the accommodation where they stayed just prior to admission (N = 83; Mean = 98.2; ±104.1 months)

There were a mean number of 5.0 (±3.0) occupants per home and the mean number of rooms per home (all rooms in the house, including kitchens and bathrooms) was 5.0 (±2.2).

Ninety percent of subjects had contact with their family on a regular basis. We obtained a reliable family history from 74 subjects. Of these, 29 subjects (39.2%) had a positive family history of psychiatric illness.

Table 12.3

Family History of Psychiatric Illness

Family History	Phase I	Phase II	Total Group
None	26	16	42
Schizophrenia	12	3	15
Depressive Illness	3	1	4
Bipolar Illness	0	0	0
Alcoholism	0	1	1
Panic Disorder	0	0	0
OCD	0	0	0
Social Phobia	0	0	0
Other	4	5	9
Unknown	12	14	26

Employment History

Table 12.4 presents data regarding the employment status of subjects at inclusion into the study:

Table 12.4

Employment status at inclusion into study

Status	Phase I	Phase II	Total Group	Percentage
Unemployed	38	22	60	62%
Full-time	9	6	15	15%
Part-time	1	2	3	3%
Casual	2	3	5	5%
Unknown	7	7	14	14%

Of the 38 subjects in phase I who were unemployed at inclusion into the study, 18 (47.3%) had never been fully employed in their lifetime. Of the 22 unemployed in phase 2, 11 (50%) had never been fully employed.

Personal and birth history

We had reliable information on maternal age at birth of the index subject in only 54 cases. The mean age of the mothers at the birth of the baby was 27.33 years (±6.1 years). Fathers were on average, about 4 years older (N = 55; mean = 31.6 years ± 9.4 years.)

Subjects came from fairly large families, with the mean number of siblings at 3.9 (±2.6).

Three male subjects and one female subject were known to be members of a set of twins. In all cases, the other twin was unaffected at the time of inclusion of the index subjects into the study.

Mother's health and lifestyle risks during pregnancy

The mothers of 3 subjects from phase I and 1 subject from phase II were admitted to hospital during the index pregnancy. The reasons for admission were:

Premature rupture of membranes in one case,

False labour in one case,

Severe oedema in one case

and threatening miscarriage in one case.

Four other mothers received medication during the index pregnancy – in three cases the mothers received treatment with iron supplements and in one case the mother received antihypertensives.

Of the 97 subjects included, only 39 (40.2%) could confirm that their mothers attended an antenatal clinic during the index pregnancy.

From the history alone, it seems that the subjects included in this study were all born at, or close to, full-term (Mean period of gestation = 39.9 weeks, stdv = 0.35 weeks)

Table 12.5

Mother's lifestyle risks during pregnancy with index subject

Type of risk	Phase I	Phase II	Total
Unknown	21	22	43
No risk behaviour	21	8	39
Cigarettes	11	9	19
Alcohol	7	2	9
Other substances of abuse	0	0	0
Medication	2	0	2
Physical abuse	1	0	1

Table 12.6

Mother's health during pregnancy with subject

Health related problem	Phase I	Phase II	Total
Unknown	24	23	47
Good health	28	14	42
Pre-eclampsia	3	0	3
Eclampsia	1	0	1
Hypertension	0	1	1
Diabetes	0	0	0
Placenta Praevia	0	0	0
Malnutrition	0	2	2
Psych illness	1	0	1
Infection	0	0	0

Table 12.7

Place of birth

Place of birth	Phase I	Phase II	Total
Home	9	4	13
Clinic	4	3	7
Rural hospital	5	1	6
Academic hospital	12	7	19
Private hospital	2	2	4
Unknown	25	23	48

Birth was induced in 9 cases (9%).

Thirty-six subjects were born as normal occipital presentations, whereas there was one case of a breach presentation and one case of limb presentation reported. Three subjects were born by caeserian section. Three subjects' births were assisted (forceps), there were 8 cases of prolonged labour and 1 case of vaginal tear during the birth process. Birth weight could not be assessed reliably, due to poor record keeping and uncertainty about the reliability of information obtained from caregivers.

Two subjects had to be resuscitated after birth, 7 were treated for jaundice and spent more than a couple of hours in the incubator. There was only one report in phase I of physical abnormality at birth. This was a subject who had a "growth"

(no further information available) removed from the side of her head shortly after birth. One subject in phase II reported a congenital abnormality of his left foot and one subject was born with an extra finger.

Duration of untreated psychosis (DUP)

The mean delay in diagnosis and treatment from first onset of psychotic features up to the day of first treatment is known as the duration of untreated psychosis (DUP). The DUP for the whole group of subjects is presented below in table 12.8.

Table 12.8

Duration of untreated psychosis (all subjects) in days

Group	N	Mean (days)	Std. Deviation
Total group	81	351.5	702.6
Male	44	390.1	842.9
Female	37	305.6	494.3

We found no gender difference in DUP ($t = -0.54$; $df = 79$; $p = 0.6$). DUP also did not show any significant correlation with any of the baseline psychopathology scores or outcome scores in phase II of the study.

However, in phase I, there was a significant, inverse correlation between DUP and improvement in negative symptoms over 2 years (see table 12.9)

Table 12.9

Spearman Rank Order Correlation between DUP and Percentage improvement in PANSS Negative Score over 24 months

DUP and:	Spearman R	t(N-2)	p
% Improvement 6 w	0.006	0.045	0.964
% Improvement 3 m	-0.048	-0.333	0.740
% Improvement 6 m	0.028	0.197	0.845
% Improvement 9m	-0.154	-1.079	0.286
% Improvement 12 m	-0.181	-1.276	0.208
% Improvement 15 m	-0.241	-1.718	0.092
% Improvement 18 m	-0.239	-1.708	0.094
% Improvement 21 m	-0.307	-2.237	0.030*
% Improvement 24 m	-0.318	-2.324	0.024*

* Significance at 0.05 level

Furthermore, the DUP also showed a significant inverse correlation with percentage improvement of PANSS Total Score at 24 months in phase I (see table 12.10)

Table 12.10

Spearman Rank Order Correlation between DUP and Percentage improvement in PANSS Total Score over 24 months

DUP and:	*Spearman R*	t(N-2)	p
% Improvement 6 w	-0.12	-0.82	0.41
% Improvement 3 m	-0.14	-1.00	0.32
% Improvement 6 m	-0.07	-0.49	0.63
% Improvement 9m	-0.19	-1.37	0.18
% Improvement 12 m	-0.25	-1.80	0.08
% Improvement 15 m	-0.27	-1.93	0.06
% Improvement 18 m	-0.21	-1.49	0.14
% Improvement 21 m	-0.26	-1.89	0.07
% Improvement 24 m	-0.29	-2.07	0.04*

* Significance at 0.05 level

Chapter 13

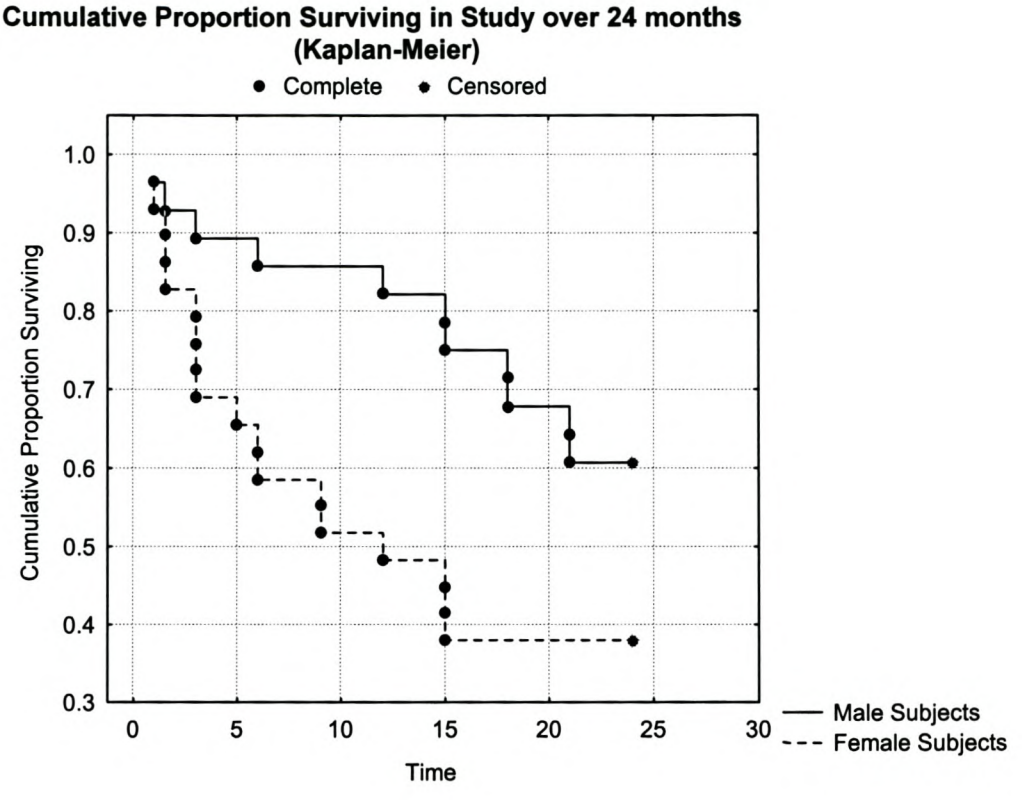
Results: Phase I

Fifty-seven subjects were included in this phase of the study. Thirty-nine subjects remained in the study for the first 12 months, and 28 subjects remained in the study for the full 24 months. Eighteen subjects (32%) dropped out of the study within the first 12 months. At the end of 24 months, a further 11 subjects had dropped out of the study, leaving 28 to complete the 24-month evaluation. This means that only 49.1% of subjects, who were included in the study, were seen at 24 months. Of the 29 subjects who had dropped out by 24 months, 23 were lost to follow-up, 5 were withdrawn and 1 had died.

Drop-outs

Female subjects were more likely than male subjects to drop out of the study within the first 12 months ($t = -2.489$; $df=55$; $p=0.02$) as well as over 24 months ($t= 2.75$; $df = 55$; $p = 0.008$). In the first 12 months, 14 female subjects dropped out of the study, compared to only 4 males. At 24 months, a total of 18 female subjects had dropped out, compared to 11 male subjects.

Figure 13.1



Gender differences

Despite the difference in drop-outs, there were no significant gender differences found in the following variables (all LOCF data):

Percentage change in PANSS Total Score and all subscale scores at 12 and 24 months.

Remission rates at 12 and 24 months.

Dose of medication at 12 and 24 months.

Risk of relapse at 12 and 24 months.

EPS (as measured by the Simpson-Angus Score) at 12 months and 24 months.

Medication

After baseline evaluation, all patients were commenced on haloperidol at 1mg per day. Doses were then adjusted according to protocol (see subjects and method section)

The mean dose of medication over 24 months (LOCF) are reported below in table 13.1.

Table 13.1

Mean dose of haloperidol (mg/day)

Time	Valid N	Mean dose	Std.Dev.
6 Weeks	54	1.5	0.7
3 Months	53	1.6	0.9
6 Months	50	1.7	1.2
9 Months	48	1.6	1.0
12 Months	48	1.7	1.0
15 Months	46	1.6	1.1
18 Months	46	1.3	0.7
21 Months	45	1.3	1.0
24 Months	44	1.3	0.8

Psychopathology

Baseline, 12 month and 24 month scores on the PANSS Total and subscale scores are tabulated below:

Table 13.2

Psychopathology scores at baseline, 12 month and 24 month follow-up (LOCF)

PANSS Scale	Positive	Negative	General	Total
Baseline	25.8 (±4.0)	23.6 (±7.4)	43.9 (±8.9)	93.3 (±16.6)
12 Months	11.8 (±5.9)	16.4 (±6.7)	26.8 (±8.0)	54.9 (±17.3)
24 Months	12.5 (±6.5)	17.6 (±7.6)	27.3 (±9.5)	56.9 (±21.1)

Changes in psychopathology

The percentage changes in PANSS Total and subscale scores were as follows (all LOCF data):

Table 13.3

Percentage Change in Psychopathology Scores over 12 months and 24 months as measured with PANSS

PANSS Scale	12 Months	24 Months
Positive	53.75 (±23.78)	50.61 (±25.93)
Negative	26.34 (±30.67)	22.00 (±31.75)
General	37.16 (±20.62)	36.14 (±22.79)
Total	39.80 (±19.7)	37.98 (±22.31)

Figure 13.2

Changes in positive and negative symptoms over 24 months

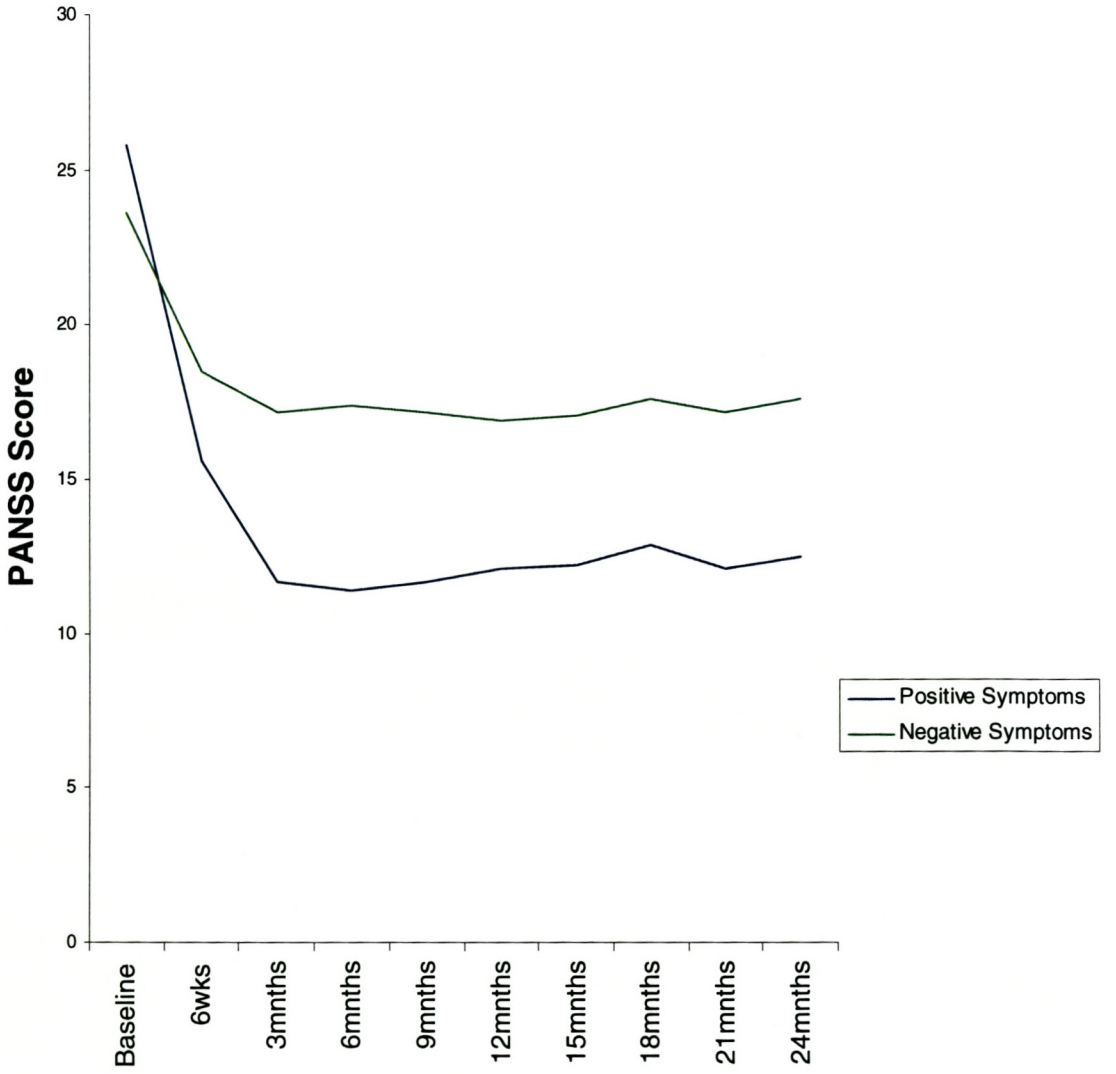


Figure 13.3

Change in PANSS Total Score over 24 months

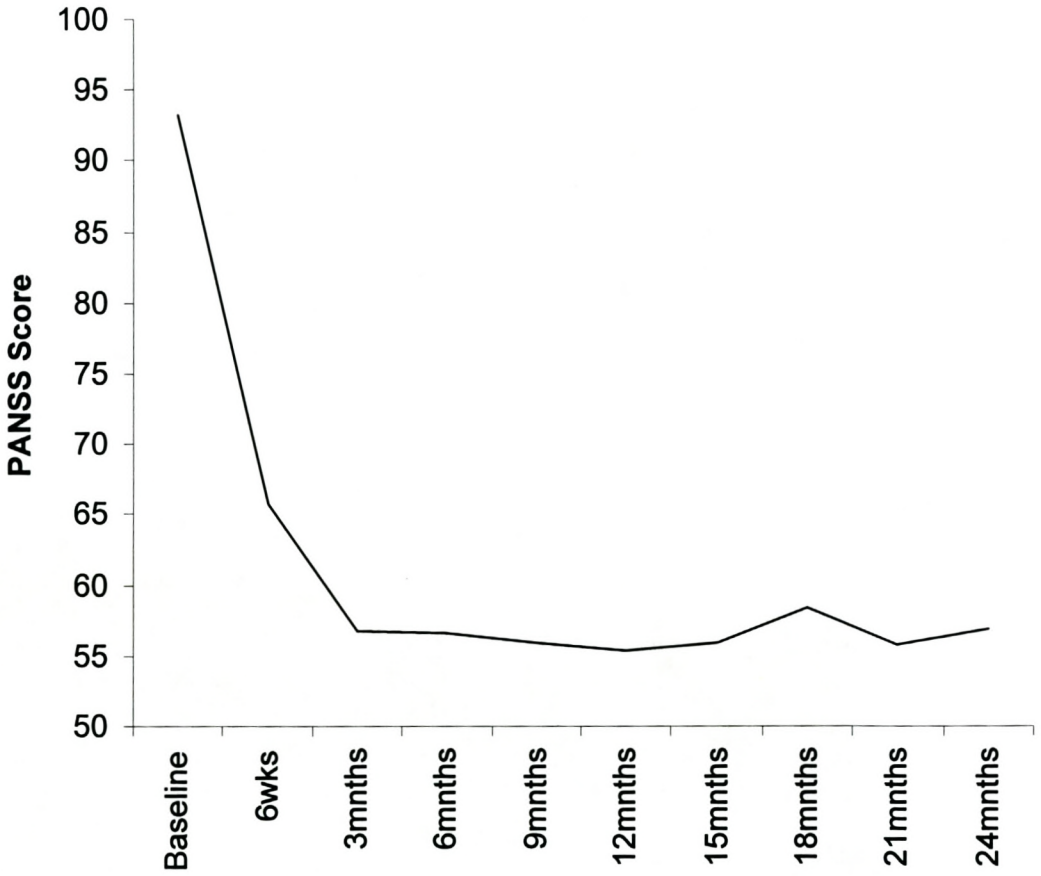
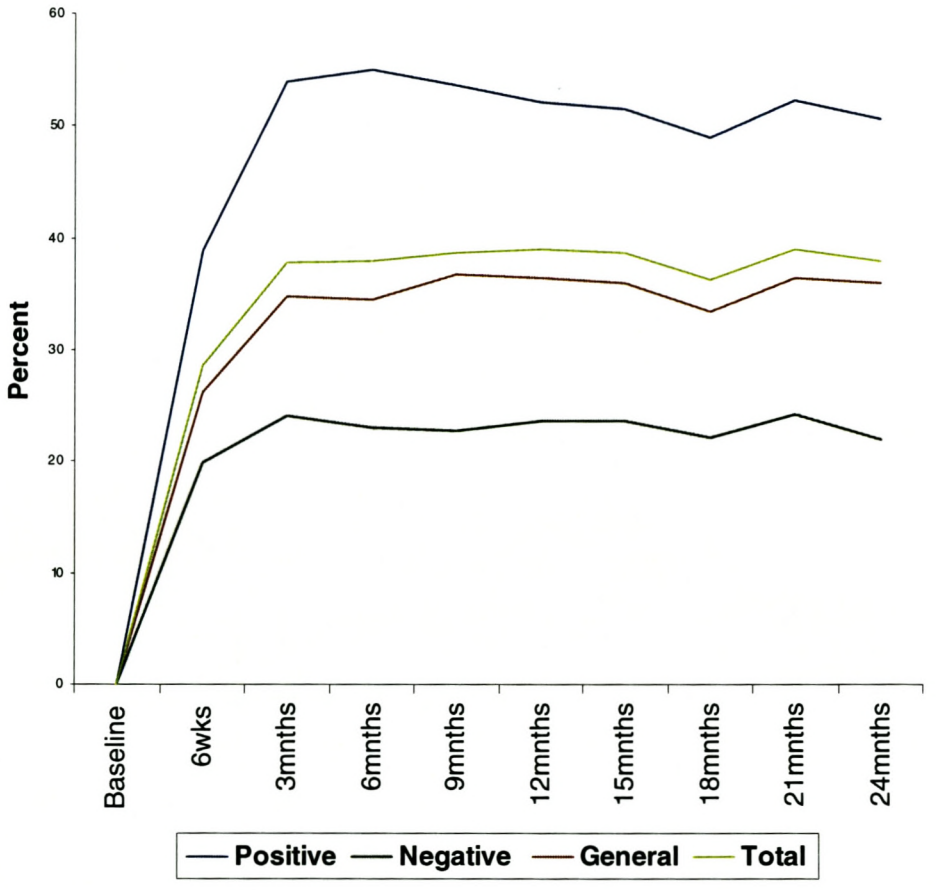


Figure 13.4

Percentage Improvement in PANSS Total and subscale scores over 24 months



Mood symptoms

Mood symptoms in phase I were evaluated in two ways

a) The depression factor of the PANSS

b) The Calgary Depression Rating Scale

The depression factor of the PANSS

Here, depressive symptoms were measured by means of the depression factor identified by Kay in his original factor analysis of the PANSS[28]. This factor comprises the composite score for the PANSS items of somatic concern (G1), anxiety (G2), guilt feelings (G3), and depression (G6)

Results are presented below in table 13.4.

Table 13.4

PANSS Depression Factor Score over 24 Months (LOCF)

Evaluation	N	Mean
Baseline	57	8.3 (±4.0)
6 Weeks	57	5.5 (±2.1)
3 Months	57	5.4 (±2.3)
6 Months	57	5.7 (±2.3)
9 Months	57	5.4 (±2.1)
12 Months	57	5.6 (±2.4)
15 Months	57	5.6 (±2.4)
18 Months	57	5.8 (±2.6)
21 Months	57	5.5 (±2.6)
24 Months	57	5.5 (±2.3)

We found no group differences in terms of mood score or changes in mood score over time in terms of the following variables:

Gender

Race

Marital Status

Remission

There were however, group differences in the following variables:

Risk of relapse and depression factor score at 9 months ($t = 2.03$; $df = 41$; $p = 0.049$) and risk of relapse and depression factor score at 12 months ($t = 2.4$; $df = 41$; $p = 0.02$).

Risk of tardive dyskinesia and depression factor score at 6 months (see results in section on tardive dyskinesia.)

We evaluated the correlation between the depression factor score and a number of psychopathology variables. The only correlation that we found was between the depression factor score at baseline and improvement in negative symptoms over the first six months. Although it was no longer significant from 9 months (with the exception of 18 months), the trend is still evident to the end of the study (compare to results for Calgary Depression Scale).

Results are presented below in table 13.5 and figure 13.5.

Table 13.5

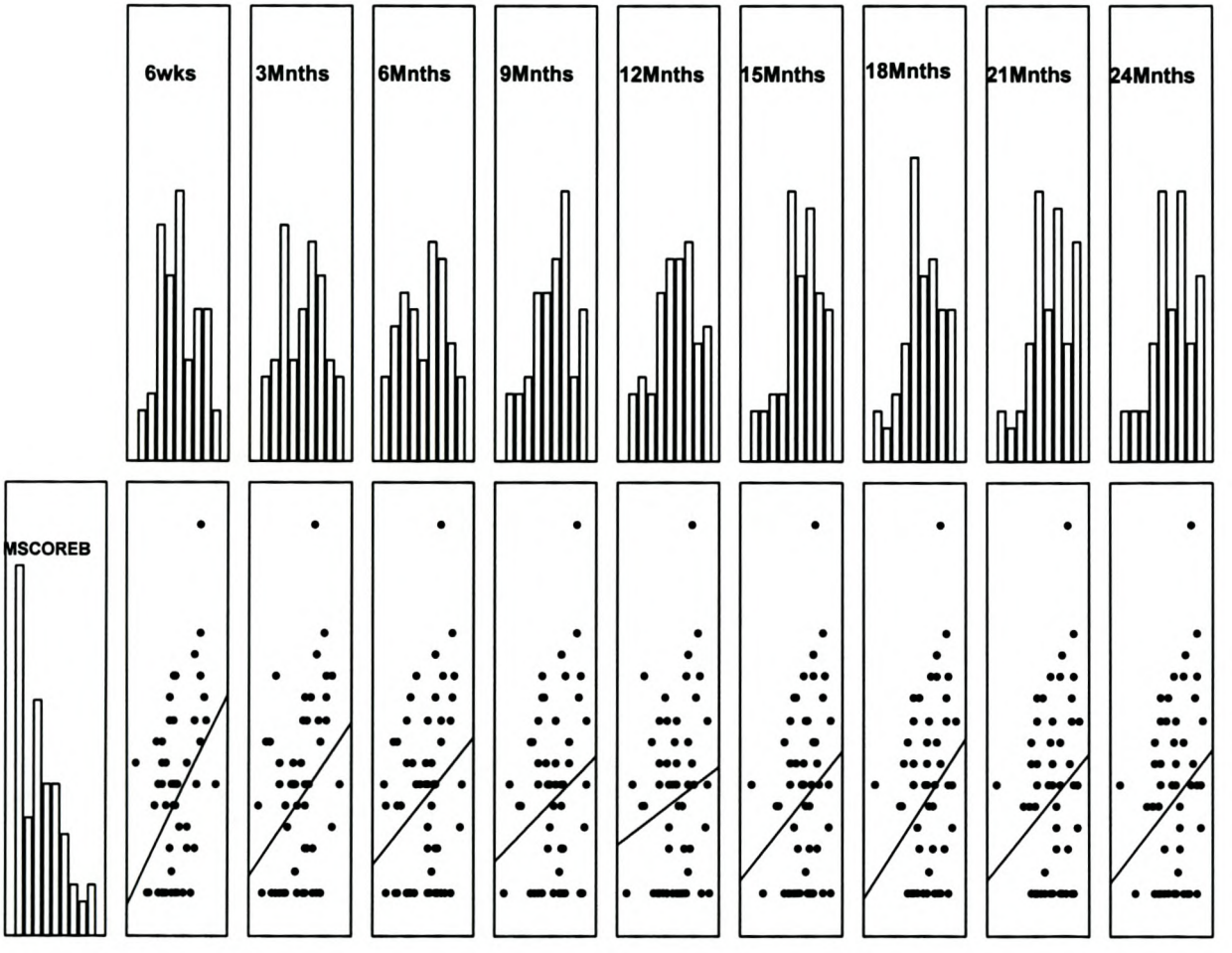
Correlation between PANSS depression factor score and Percentage Improvement in PANSS Negative Score

Time	N	Spearman R	t	p-value
6 weeks	57	0.4	2.98	0.004*
3 months	57	0.3	2.52	0.015*
6 months	57	0.3	2.30	0.025*
9 months	57	0.2	1.44	0.156
12 months	57	0.2	1.26	0.214
15 months	57	0.3	1.93	0.059
18 months	57	0.3	2.40	0.020*
21 months	57	0.2	1.81	0.076
24 months	57	0.2	1.82	0.075

*Significance at the 0.05 level

Figure 13.5

Correlations between PANSS depression factor score at baseline and percentage improvement in negative symptoms



The Calgary Depression Rating Scale

Similar analyses were performed with the Calgary Depression Rating Scale data as with the PANSS depression factor. In terms of categorical variables, we found only a difference in score on the Calgary scale at 12 months and the risk of relapse by 12 months ($t = 2.07$; $df = 41$; $p = 0.04$). Subjects who relapsed therefore were more likely to have a higher Calgary Score at 12 months, as could be expected. This finding was not replicated with the data at 24 months.

Notably, we did not, in this analysis, find the difference in Calgary Score at baseline between those who later developed TD and those who did not (see section on TD).

When we analysed the data (as we did for the PANSS Depression Factor Score) for correlations with parameters of psychopathology, findings were considerably more robust. Here, the correlation between the Calgary Depression Score at baseline and improvement in PANSS Negative Symptom Score was sustained for the full 24 months. Furthermore, we also found a significant correlation between the Calgary Depression Score at baseline and improvement in PANSS

Positive Symptom Score, PANSS General Psychopathology Score and PANSS Total Score. Results are presented below in table 13.6 and figure 13.6.

Table 13.6

Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS Negative Score over 24 months

Time	N	Spearman R	t	p-value
6 weeks	57	0.4	3.19	0.002*
3 months	57	0.3	2.23	0.030*
6 months	57	0.3	2.60	0.013*
9 months	57	0.3	2.32	0.024*
12 months	57	0.3	2.04	0.046*
15 months	57	0.4	3.10	0.003*
18 months	57	0.4	3.43	0.001*
21 months	57	0.3	2.54	0.014*
24 months	57	0.3	2.46	0.017*

* Significance at the 0.05 level

Figure 13.6

Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS Negative Score over 24 months

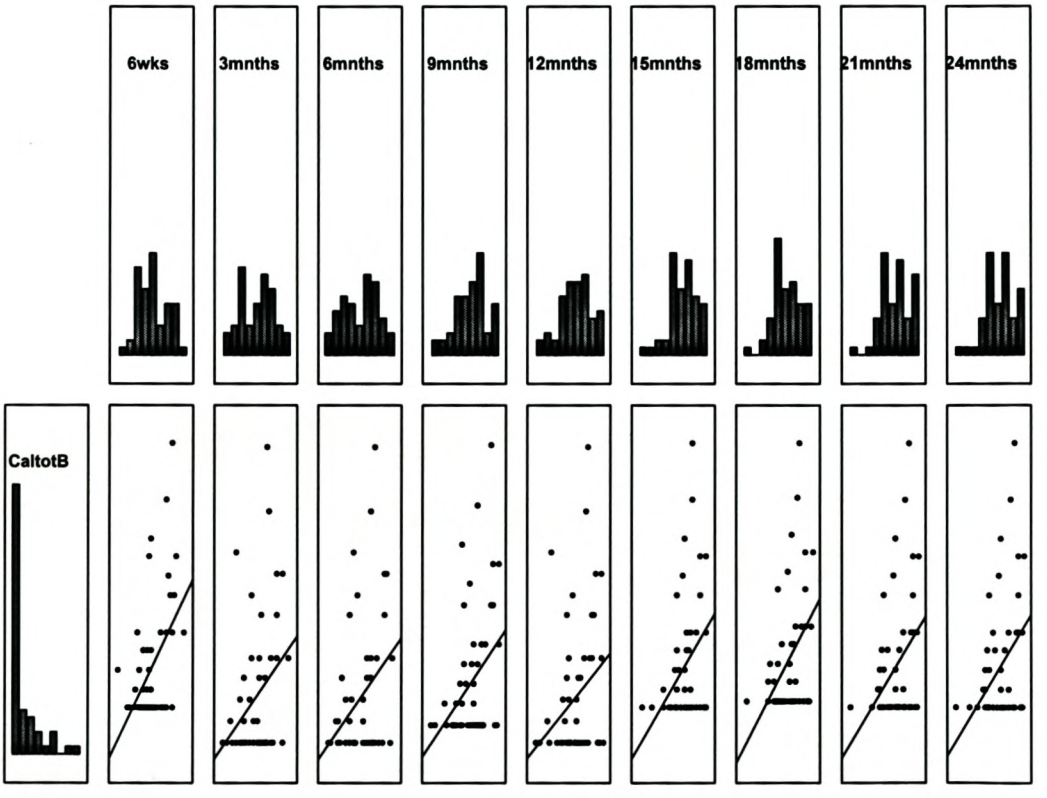


Table 13.7

Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS Positive Score over 24 months

Time	N	Spearman R	t	p-value
6 weeks	57	0.2	1.61	0.114
3 months	57	0.2	1.60	0.118
6 months	57	0.2	1.31	0.196
9 months	57	0.2	1.33	0.188
12 months	57	0.2	1.60	0.116
15 months	57	0.3	2.11	0.039*
18 months	57	0.3	2.63	0.011*
21 months	57	0.3	1.96	0.055
24 months	57	0.3	2.04	0.046*

* Significance at the 0.05 level

Figure 13. 7

Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS Positive Score over 24 months

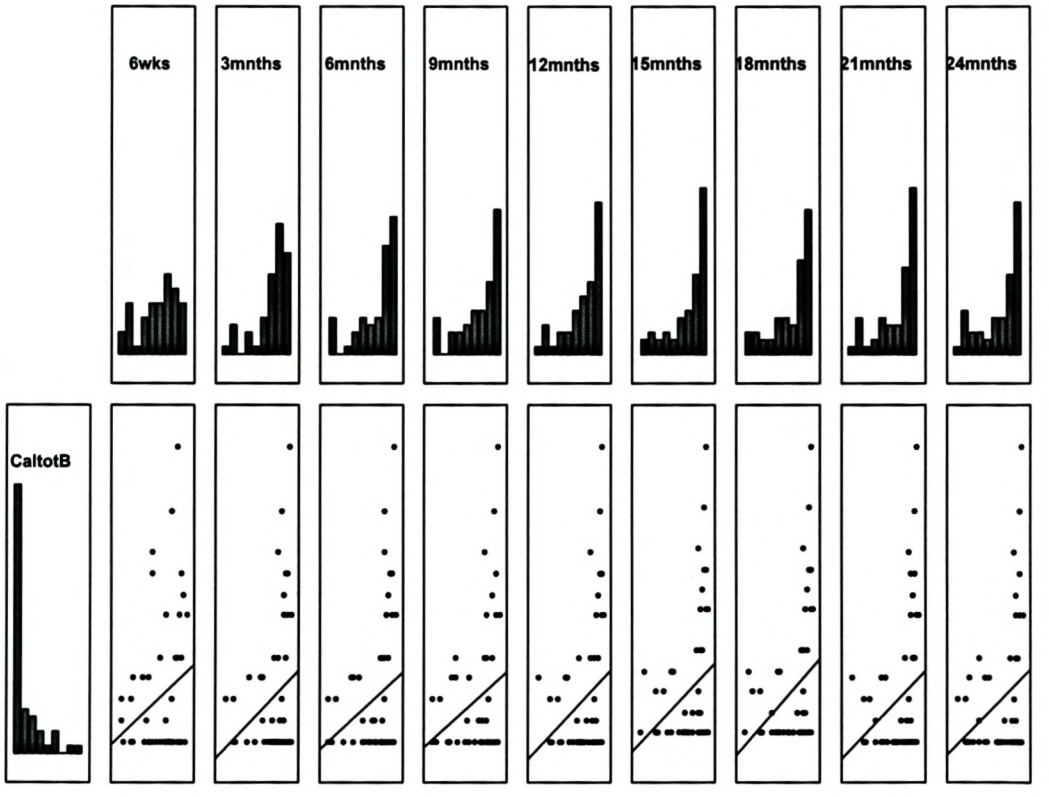


Table 13.8

Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS General Psychopathology Score over 24 months

Time	N	Spearman R	t	p-value
6 weeks	57	0.4	3.66	0.001*
3 months	57	0.4	2.89	0.006*
6 months	57	0.4	3.54	0.001*
9 months	57	0.4	2.88	0.006*
12 months	57	0.4	3.38	0.001*
15 months	57	0.5	4.02	0.000*
18 months	57	0.5	4.70	0.000*
21 months	57	0.5	3.97	0.000*
24 months	57	0.4	3.51	0.001*

* Significance at the 0.05 level

Figure 13.8

Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS General Psychopathology Score over 24 months

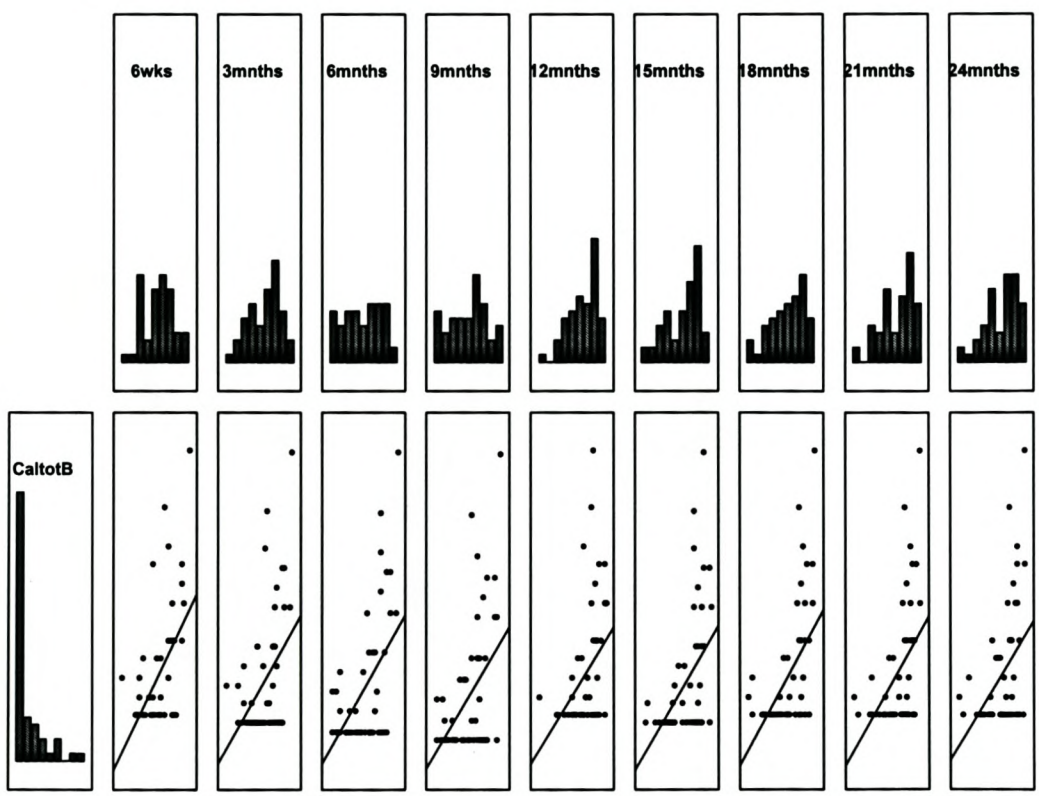


Table 13.9

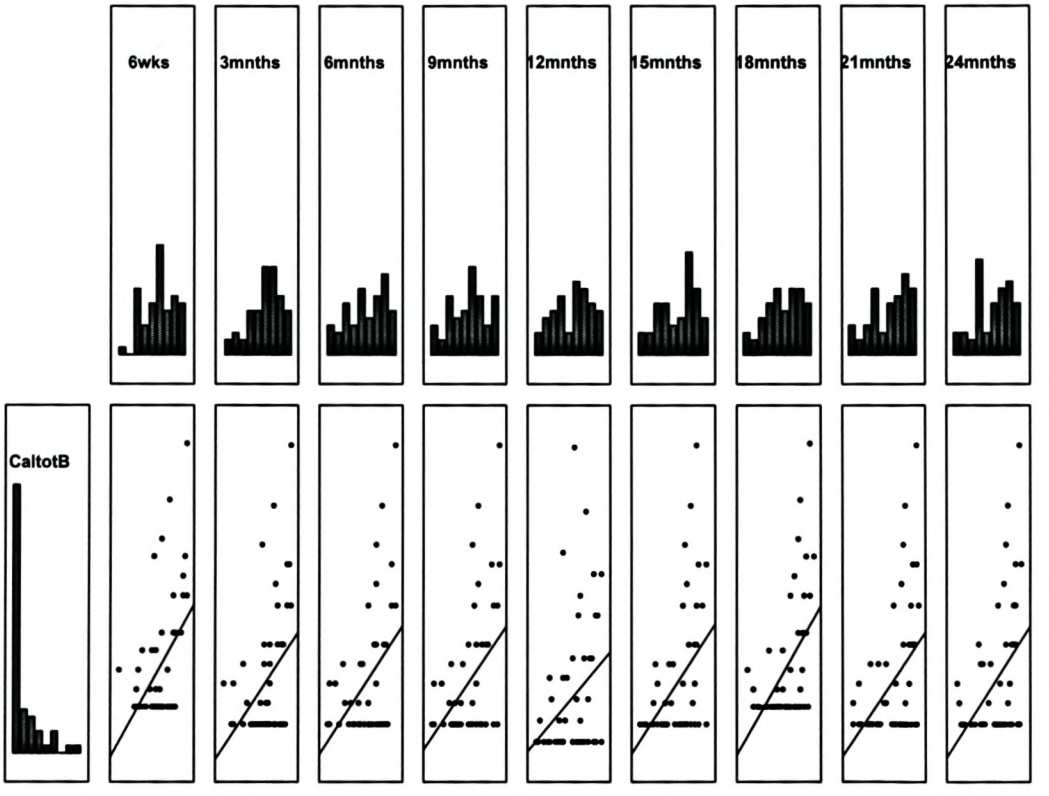
Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS Total Score over 24 months

Time	N	Spearman R	t	p-value
6 weeks	57	0.4	3.00	0.004*
3 months	57	0.4	2.75	0.007*
6 months	57	0.4	3.00	0.004*
9 months	57	0.3	2.51	0.015*
12 months	57	0.3	2.32	0.024*
15 months	57	0.4	3.47	0.001*
18 months	57	0.5	4.23	0.000*
21 months	57	0.4	3.51	0.001*
24 months	57	0.4	3.05	0.003*

* Significance at the 0.05 level

Figure 13.9

Correlation between Calgary Depression Rating Scale Score at Baseline and Percentage improvement in PANSS Total Score over 24 months



Remission

Subjects were considered to be in remission if they had no PANSS Positive Subscale score > 3 and a rating of "Much improved" or "Very much improved on the CGI Response Item. At the end of 12 months, 38 subjects (67%, LOCF data) were considered to be in remission and at the end of 24 months, 39 subjects were in remission (68%, LOCF data). We found no gender difference in rates of remission at the end of 12 months (LOCF data: chi-square = 0.57; df = 1; p = 0.45) or 24 months (chi-square = 0.22, df = 1; p = 0.64).

Relapse

The first 12 months

Although 39 subjects completed the first 12 months of the study, a further 4 subjects who had earlier been lost to follow-up were seen at or around the time of the 12 month visit. Therefore, we had relapse data on 43 subjects by 12 months.

11 Subjects relapsed within the first 12 months. This was equal to 19% of the total group or 26% of the group where we had 12-month data available.

Of the subjects who relapsed, 9/11 (82%) are male. This did not however, achieve statistical significance (p = .15; Fisher's exact test, two-tailed).

Risk of relapse was not associated with any of the following variables:

Age

Dose of medication

Diagnosis

Tardive Dyskinesia

Risk of relapse at 12 months was, however associated with the following variables:

PANSS Positive score at 12 months (p = 0.02)

PANSS General Psychopathology Score at 12 months (p = 0.02)

Percentage change in PANSS Positive Subscore at 12 months (p = 0.01)

Depression factor score at 12 months (p = 0.005)

The direction of all of these associations was as would be expected, with subjects who relapsed having higher scores on each of the variables compared to those subjects who did not relapse.

For subjects who relapsed within the first 12 months, the following were judged to be the principal causes of the relapse:

Table 13.10

Relapse in phase I (12 month data)

Reason for relapse	Number of subjects
Non-compliance with treatment	7
Non-compliance and substance abuse	2
Change in medication	1
Trauma/assault	1

Months 12 – 24

For this analysis, we used LOCF data from the first and second year. Seven subjects relapsed in the second year. Of these, two subjects had more than one relapse. Three of the 7 subjects, who relapsed in the second year, had also had a relapse in the first year and 4 subjects relapsed for the first time in the second year of treatment.

There were no statistically significant differences between subjects who relapsed by 24 months and those who did not in terms of the following variables:

Age

Gender

Marital status

Duration of untreated psychosis

Dose of medication at either 12 or 24 months

Risk of TD

Percentage change on any of the psychopathology scores at 24 months

Mood symptoms as evaluated by the Calgary Depression Rating Scale

For subjects who relapsed between 12 and 24 months, the following were judged to be the principal causes of the relapse

Table 13.11

Relapse in phase I (data for year 2)

Reason for relapse	Number of subjects
Non-compliance with treatment	6
Non-compliance and substance abuse	1

Side-effect ratings

Extra-pyramidal side-effects

Parkinsonism

The mean scores for the Simpson Angus Rating Scale between baseline and 24 months are presented below in table 13.12:

Table 13.12

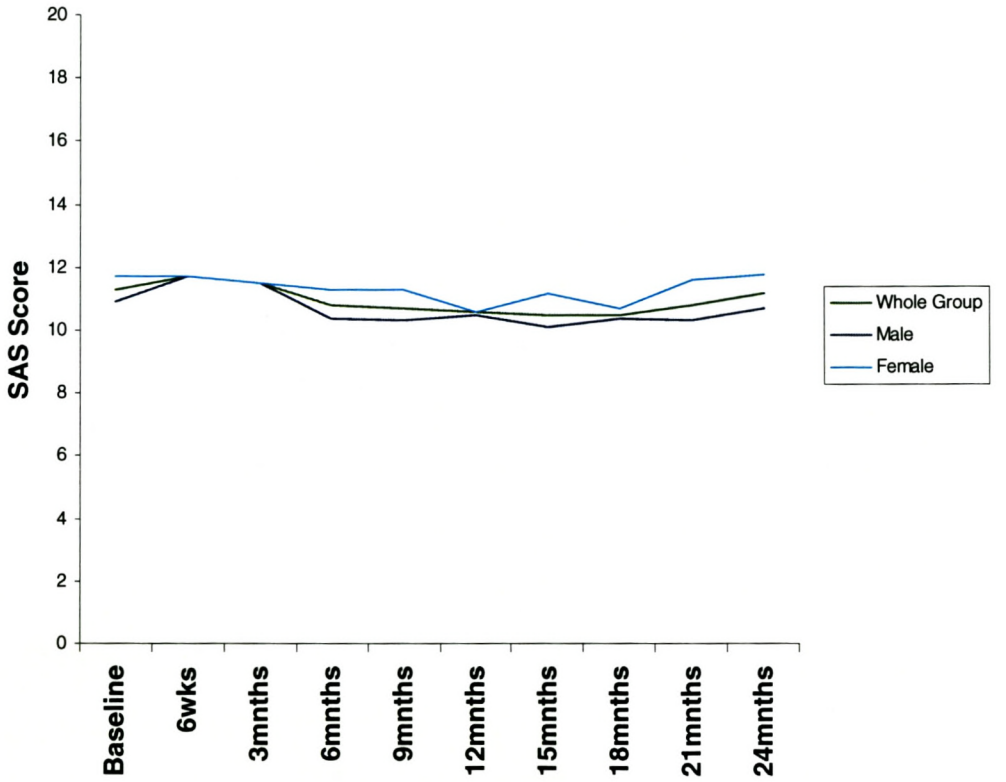
Mean scores on Simpson-Angus Rating Scale over 24 months

Group	Time	Mean	Standard Deviation
Total	Baseline	11.3	2.4
	6 Weeks	11.7	3.5
	3 Months	11.5	2.2
	6 Months	10.8	1.8
	9 Months	10.7	1.2
	12 Months	10.6	1.2
	15 Months	10.5	1.3
	18 Months	10.5	1.0
	21 Months	10.8	1.9
	24 Months	11.2	2.4
Males	Baseline	10.9	1.5
	6 Weeks	11.7	3.4
	3 Months	11.5	2.2
	6 Months	10.4	0.6
	9 Months	10.3	0.7
	12 Months	10.5	1.4
	15 Months	10.1	0.2
	18 Months	10.4	0.8
	21 Months	10.3	0.6
	24 Months	10.7	1.8

Females	Baseline	11.7	3.0
	6 Weeks	11.7	3.5
	3 Months	11.5	2.2
	6 Months	11.3	2.5
	9 Months	11.3	1.4
	12 Months	10.6	1.0
	15 Months	11.2	1.9
	18 Months	10.7	1.3
	21 Months	11.6	2.8
	24 Months	11.8	3.1

Figure 13.10

Mean scores on Simpson-Angus Rating Scale over 24 months



Akathisia

Ratings for the Barnes Akathisia Rating Scale at different time points are tabulated below. None of the changes were statistically significant:

Table 13.13

Mean Scores for Barnes Akathisia Rating Scale

Group	Time	Mean	Standard Deviation
Males	Baseline	0.04	0.18
	12 Months	0.00	0.00
	24 Months	0.11	0.46
Females	Baseline	0.03	0.19
	12 Months	0.00	0.00
	24 Months	0.00	0.00
Total	Baseline	0.04	0.19
	12 Months	0.00	0.00
	24 Months	0.07	0.37

Dyskinesia

No subjects had a positive score on any of the AIMS ratings at baseline. Seven subjects (12.3%) developed tardive dyskinesia according to the Schooler and Kane criteria within the 12-month follow-up period (see Table 13.14).

Table 13.14

Details of the seven patients who developed TD in the first 12 months

Age	Sex	Schooler/Kane classification	AIMS Score Baseline	AIMS Score 6 Months**	AIMS Score 9 Months	AIMS Score 12 Months
49	F	Persistent	0	4	4	5
42	F	Probable	0	0	0	2*
47	F	Persistent	0	3	3	8
30	F	Persistent	0	4	3	4
37	M	Probable	0	0	0	2*
30	M	Persistent	0	5	3	3
25	M	Probable	0	0	0	2*

* These ratings were reconfirmed within 1 week
** No subjects developed involuntary movements before 6 month rating.

Table 13.15

Details of subjects who developed TD from 12 to 24 months

Subject	Sex	Schooler/Kane Classification	Area/s affected	Time of first report
8	M	Persistent	Lips, peri-oral, right thumb	18 months
9	F	Persistent	Lips, jaw	18 months
10	F	Probable	Tongue	24 months
11	M	Probable	Lips, jaw	24 months

No subjects displayed signs of spontaneous dyskinesia at baseline, while 7 (12.3%) met Schooler and Kane criteria for persistent or probable TD at 12-months follow-up. Details of these seven subjects are given in Table 13.14. At

the end of 24 months, 11 subjects (19.3%) met criteria for persistent or probable TD (LOCF data).

We compared the subjects with TD to the rest of the group, and found no significant differences with regard to gender (Fisher exact p = .12), race (Fisher exact p = .63), and duration of untreated psychosis (p = 0.5).

We did, however find differences between the groups with and without TD in terms of the following variables:

Mean dose of haloperidol at 12 months: The mean dose of haloperidol at 12 months for subjects with TD by 12 months was 2.8mg/day (±1.64mg) versus 1.39mg/day (±0.69mg/day) for those without TD at 12 months (t = -3.13; df = 25; p = 0.004).
If we consider the haloperidol dose at **12 months** for subjects who developed TD by **24 months**, results are virtually identical (p = 0.004).

Age at inclusion into the study: The mean age of subjects who developed TD within the first 12 months was 37.14 years (±9.23 years) versus 27.30 years (±8.09 years) for those who did not develop TD (t= -2.77; df = 30; p = 0.01). The same comparison over 24 months yielded similar results (t =-2.96; df = 55; p = 0.005).

Symptoms of EPS as measured on the Simpson-Angus Scale at 9 months:

The mean score on the SAS for subjects with TD by 12 months was 12.00 (± 1.83) versus 10.32 (±0.63) for subjects who did not develop TD by this time (t = -3.97; df = 30; p = 0.0004). This difference remained significant at 24 months (p = 0.006).

Symptoms of EPS as measured on the Simpson-Angus Scale:

The mean score on the SAS for subjects with TD was 11.86 (±1.95) versus 10.20 (± 0.65) for subjects who did not develop TD by one year (t = -3.70; df = 30; p = 0.0009). This difference also remained significant at 24 months (p = 0.01).

Mood symptoms as measured by the depression factor of the PANSS[28]:

The difference in mean score was only statistically significant at 6 months (i.e. in the post-psychotic phase), with mean score for subjects who developed TD at 7.43 (± 3.21) versus 5.38 (± 1.69) for subjects who did not develop TD (t = -2.28; df = 29; p = 0.03). We did not, however find any differences between subjects who developed TD by either 12 or 24 months and those who did not in terms of ratings on the Calgary Depression Rating Scale at any time.

In the initial statistical analysis, we did not find any significant differences between the two groups in terms of symptom severity and changes in psychopathology as rated on the PANSS, although percentage change in

negative symptoms and PANSS total score did approach significance (see table 13.16)

Table 13.16

Changes in psychopatholgy over 12 months: Subjects with TD versus subjects without TD

PANSS Score	No TD	With TD	t-value	df	p
Positive Score Baseline	25.36 (±3.45)	24.29 (±4.92)	0.66	30	0.513
Negative Score Baseline	24.24 (± 7.95)	22.43 (±6.27)	0.55	30	0.584
General Baseline	45.44 (± 9.54)	38.14 (± 7.40)	1.86	30	0.072
Total Baseline	95.04 (± 18.03)	84.86 (± 13.30)	1.39	30	0.176
Positive 12months	10.24 (± 5.13)	12.57 (± 5.74)	-1.04	30	0.308
Negative 12 months	15.56 (± 6.21)	19.29 (± 7.20)	-1.36	30	0.185
General 12 months	25.96 (± 7.79)	25.29 (± 4.54)	0.22	30	0.829
Total 12 months	51.76 (± 16.27)	57.14 (± 13.64)	-0.80	30	0.431
% Change Pos Scale	59.12 (± 20.38)	44.76 (± 32.82)	1.43	30	0.162
% Change Neg Scale	31.42 (± 28.96)	6.93 (± 41.76)	1.79	30	0.083
% Change General Scale	41.35 (± 18.42)	30.97 (±20.02)	1.29	30	0.205
% Change Total Score	44.46 (± 17.41)	30.27 (± 21.66)	1.81	30	0.081

Table 13.17

Changes in psychopatholgy over 24 months: Subjects with TD versus subjects without TD

PANSS Score	No TD	With TD	t-value	df	p
Positive Score 24 mnths	12.53 (±6.73)	10.64 (±4.37)	0.89	54	0.379
Negative Score 24 mnths	17.44 (±7.89)	16.27 (±7.23)	0.45	54	0.656
General 24 mnths	27.84 (±9.81)	23.91 (±7.05)	1.25	54	0.217
Total 24 mnths	57.82 (±21.93)	50.82 (±16.19)	0.99	54	0.326
% Change Positive Scale	49.33 (±26.89)	55.96 (±21.74)	-0.76	55	0.451
% Change Negative Scale	22.18 (±30.48)	21.24 (±38.25)	0.09	55	0.931
% Change General Scale	35.39 (±23.79)	39.26 (±18.66)	0.50	55	0.617
% Change Total Score	37.36 (±23.06)	40.53 (±9.65)	-0.42	55	0.676

In the second analysis, when we applied the proportional hazards method (Cox regression) to investigate the effects of different predictor variables, we found the following:

EPS ratings and mood symptoms were no longer significant predictors of risk for TD. The following three variables were found to be significant predictors of risk

for developing TD in the first year: age at inclusion, percentage change in negative symptoms and dose of medication at 12 months.

Table 13.18

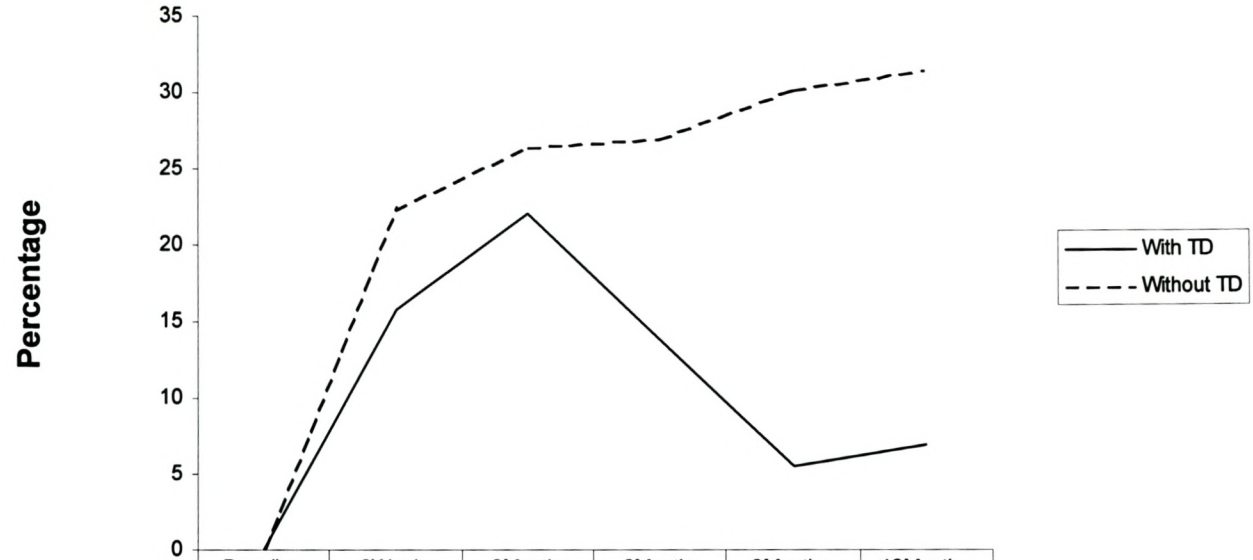
Significant risk factors for TD by 12 months (Cox Regression Analysis)

Parameter	Estimate	95% CI	S. Error	t- ratio	p
Age	0.197	0.019-0.376	0.091	2.163	0.031*
% Change Neg. Scale	-0.035	-0.067 – 0.004	0.016	-2.199	0.028*
Dose	1.289	0.236 – 2.341	0.537	2.399	0.016*

*Significance at 0.05 level

Figure 13.11

Percentage change in negative symptoms over 12 months



	Baseline	6Weeks	3Months	6Months	9Months	12Months
——— With TD	0	15.8	22	13.9	5.5	6.9
- - - - Without TD	0	22.3	26.4	26.9	30.1	31.4

We also compared the group of subjects who developed TD within the first 12 months to those who developed TD later. Although the numbers are very small, there are some interesting trends evident:

Table 13.19

Comparing subjects who developed TD within 12 months to those who developed TD between months 12 and 24

	Year 1 (n=7)	Year 2 (n=4)	T	df	p
% Change Pos Scale	50.79(±24.66)	65.00(±13.74)	-1.05	9	0.322
% Change Neg Scale	5.25(±37.77)	49.22(±19.57)	-2.14	9	0.061
% Change Gen Scale	35.16(±15.39)	46.44(±24.05)	-0.96	9	0.362
% Change Total Score	33.58(±17.33)	52.70(±19.41)	-1.70	9	0.125

Serious adverse events

We encountered only one adverse event that was rated as serious. This was a 19-year old female subject on phase I of the study who committed suicide.

This subject was born on 18-3-1979 and was included in the study on 6-01-2000 after a very brief period of psychosis. The subject had had a sudden onset of psychosis with no noticeable prodrome.

She had no previous history of severe medical or psychiatric illness. She had no family history of psychiatric illness, although her mother suffered epilepsy.

At baseline, she was rated as "Markedly Ill", with prominent paranoid delusions and auditory hallucinations. Her initial diagnosis was noted as Schizophreniform Disorder. Her medical work-up was unremarkable. What is notable is that she also had a rating of 6 on the Calgary Depression Rating Scale at baseline.

On inclusion into the study she had already been on antipsychotic medication for three days, with the result that she had signs of EPS, with a Simpson-Angus Score of 23. There were, however, no signs of akathisia or dyskinesia present. She responded very well to 1mg of haloperidol and was already rated as "much improved" after one week. At visit 4 /week 4 she was rated as apsychotic.
She was compliant on medication and attended follow-up regularly. She never displayed any symptoms or signs of mood disturbance again.
Her last consultation was on 31-3-2000. At this time, she had been on the study for 3 months and was again rated apsychotic. No mention is made in the notes or any of the rating scales of any mood disturbance. At this consultation, her medication dose was reduced to 0.5 mg per day. This was due to the fact that she complained of sedation and stiffness. Her Simpson-Angus Rating Scale

Score at the time was 13. There were no signs of either akathisia or dyskinesia present.

The subject committed suicide on 2-06-2000 by taking an overdose of oral anti-asthma medication (her mother's medication). Her mother did not report any exacerbation in her psychosis or any obvious mood disturbance in the time before the incident.

Chapter 14

Results: Phase II

Forty subjects were included in the double-blind phase of the study, 20 subjects in each treatment arm.

To evaluate the effect of randomization, we compared the two treatment groups at baseline in terms of a number of variables. We found no statistically significant differences between the two groups in any of the variables tested. Results are presented below in table 14.1.

Table 14.1

Comparison of two treatment groups (2mg/day vs 8mg/day) at baseline

Parameter (baseline)	2mg Group	8mg Group	X^2	t; df	p
Gender M:F[a]	14 : 6	10 : 10	1.7		0.20
Ethnic group M : W : B[b]	17 : 2 : 1	14 : 2 : 4	2.1		0.35
Marital history E : N[c]	1 : 17	5 : 13			0.18[d]
Age at inclusion (years)	26.8 (±7.3)	28.9 (±8.1)		0.8; 34	0.42
PANSS Positive Scale	27.0 (±5.7)	27.3 (±3.9)		-0.19; 38	0.85
PANSS Negative Scale	25.6 (±10.0)	23.9 (±6.4)		0.64; 38	0.53
PANSS General Scale	47.6 (±9.5)	44.6 (±8.2)		1.05; 38	0.30
PANSS Total Score	100.1 (±19.3)	95.7 (±13.0)		0.84; 3.0	0.41
Simpson-Angus Score	10.5 (±1.8)	10.1 (±0.3)		0.86; 38	0.39
CGI	5.4 (±0.9)	5.2 (±0.7)		0.80; 38	0.43

a M = Male; F = Female

b M = Mixed ; W = White; B = Black

c E = Ever Married; N = Never Married

d Fisher's exact test, two tailed

Of the 40 subjects included at baseline, 11 (27.5%) did not complete the full six weeks of the study.

Of the 11 subjects who did not complete the study, 3 were in the low dose (2mg per day) group, whereas 8 were in the standard dose (8mg per day) group. The numeric difference between the two treatment groups did not, however reach statistical significance ($p = 0.08$, Fisher's exact test, two-tailed).

When we considered the reasons for subjects not completing the study, the following was found:

Six subjects were withdrawn due to EPS. All of these subjects were from the 8mg haloperidol group. This means that 33.3% of subjects in the 8mg per day group did not complete 6 weeks of treatment due to side effects. The difference in withdrawal rates due to EPS was statistically significant ($p = 0.02$, Fisher's exact test, two-tailed).

Three subjects were withdrawn due to poor response. Two of these subjects were in the 8mg per day group and one in the 2mg per day group.

One subject withdrew consent shortly after baseline evaluation based on religious grounds. He had been randomised to the 2 mg per day group.

One subject in the 2mg per day group failed to return from weekend leave after week 4 evaluation.

Table 14.2

Phase II: Subjects withdrawn from study

Subject no.	Treatment Group	Time in study (weeks)	Reason for withdrawal
6	8mg	1	EPS
7	8mg	3	EPS
9	8mg	5	EPS
16	2mg	0	Consent
17	8mg	1	EPS
22	8mg	2	EPS
29	8mg	4	Poor response
31	2mg	4	Lost
36	8mg	5	EPS
38	8mg	1	Poor response
39	2mg	5	Poor response

In phase II of the study, there were no gender differences in dropout rates (chi-square = .19; p = 0.67)

There were also no significant gender differences found in the following variables (all LOCF data):

Percentage change in PANSS Total Score and all subscale scores.

Remission rates.

EPS (as measured on the Simpson-Angus Scale or the ESRS).

Psychopathology

Table 14.3

Psychopathology Scores in Phase II

PANSS Subscale	All Baseline	2mg Baseline	8mg Baseline	All Endpoint	2mg Endpoint	8mg Endpoint
Positive	27.0 (±4.8)	27.0 (±5.7)	27.3 (±3.9)	16.9 (±7.6)	17.4 (±8.3)	16.6 (±7.0)
Negative	24.7 (±8.4)	25.6 (±10.0)	23.9 (±6.4)	20.9 (±9.6)	20.3 (±10.8)	21.5 (±8.5)
General	46.1 (±8.9)	47.6 (±9.5)	44.6 (±8.2)	36.4 (±17.3)	34.6 (±12.9)	38.1 (±20.9)
Total	97.9 (±16.4)	100.1 (±19.3)	95.7 (±12.8)	74.2 (±30.9)	72.3 (±29.8)	76.1 (±32.6)

Table 14.4

Percentage changes in psychopathology from baseline to endpoint

PANSS Subscale	Total Group	2mg Group	8mg Group
Positive	37.3 (±26.9)	36.0 (±27.6)	38.6 (±26.8)
Negative	15.2 (±31.4)	21.8 (±31.0)	8.9 (±31.3)
General	20.1 (±38.4)	27.2 (±22.9)	13.4 (±48.6)
Total	24.7 (±29.1)	28.9 (±23.9)	20.7 (±33.4)

PANSS Total Score

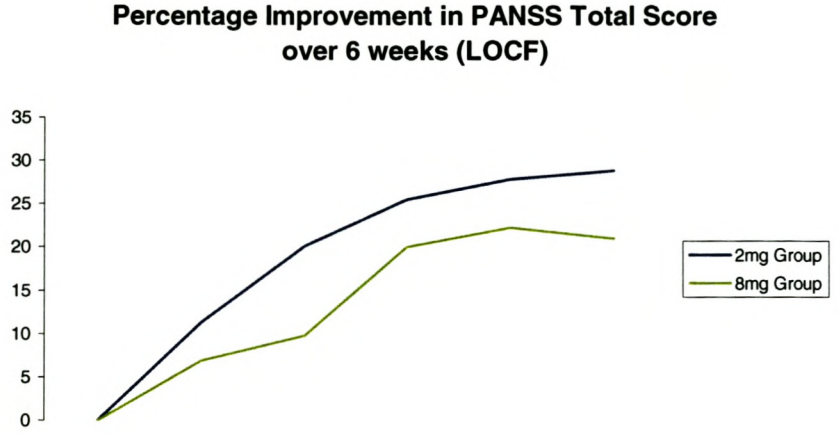
Although there was a numerical difference in improvement in PANSS Total Score, this was not statistically significant at any evaluation point. Data is presented below in table 14.5 and figure 14.1.

Table 14.5

Percentage change in PANSS Total score over 6 weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Week 1	11.4 (±15.9)	6.8 (±14.3)	0.9	36	0.361
Week 2	20.1 (±18.4)	9.8 (±16.8)	1.8	37	0.078
Week 3	25.5 (±21.6)	19.5 (±21.2)	0.9	37	0.390
Week 4	27.8 (±24.0)	22.3 (±22.3)	0.7	37	0.460
Week 6	28.9 (±23.9)	20.7 (±33.4)	0.9	37	0.389

Figure 14.1



PANSS Positive Subscale

Percentage improvement for the two groups was similar throughout. Data (all LOCF) are presented below in table 14.6 and figure 14.2.

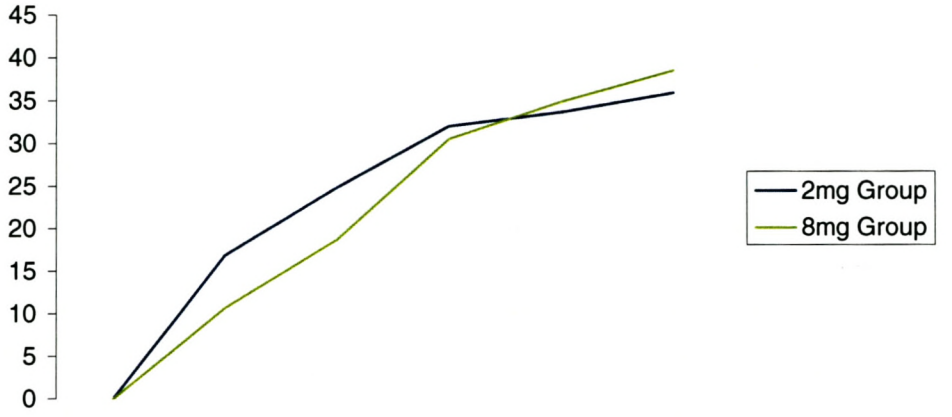
Table 14.6

Percentage change in PANSS Positive Subscale score over 6 weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Week 1	16.9 (±25.7)	10.8 (±15.4)	0.9	37	0.38
Week 2	24.9 (±19.9)	18.8 (±18.2)	1.0	37	0.32
Week 3	32.1 (±26.2)	30.6 (±23.2)	0.2	37	0.86
Week 4	33.7 (±27.4)	35.0 (±25.3)	-0.2	37	0.88
Week 6	36.0 (±27.6)	38.6 (±26.8)	-0.3	37	0.77

Figure 14.2

Percentage improvement in PANSS Positive Subscale over 6 weeks (LOCF)



PANSS Negative Subscale

There was a large numerical difference in PANSS negative symptom subscale scores throughout, although this only reached statistical significance at week 2. The data (all LOCF) are presented below in table 14.7 and also in figure 14.3.

Table 14.7

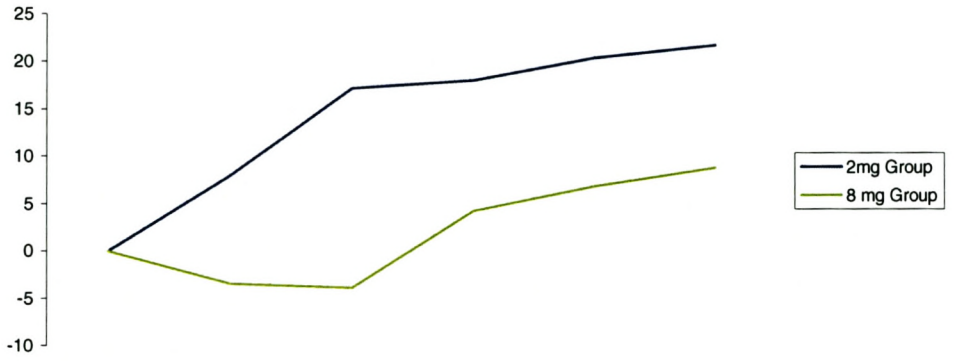
Percentage change in PANSS Negative Subscale score over 6 weeks

Group	2mg	8mg	t-value	df	p
Week 1	8.0 (±16.4)	-3.4 (±27.8)	1.5	36	0.14
Week 2	17.2(±22.6)	-3.8 (±26.1)	2.7	37	0.01*
Week 3	18.1 (±29.2)	4.3 (±27.2)	1.7	37	0.10
Week 4	20.4 (±29.8)	6.9 (±27.8)	1.5	37	0.15
Week 6	21.8 (±31.0)	8.9 (±31.3)	1.3	37	0.20

*Significance at the 0.05 level

Figure 14.3

Percentage improvement in PANSS Negative Score over 6 weeks (LOCF)



PANSS General Psychopathology Subscale

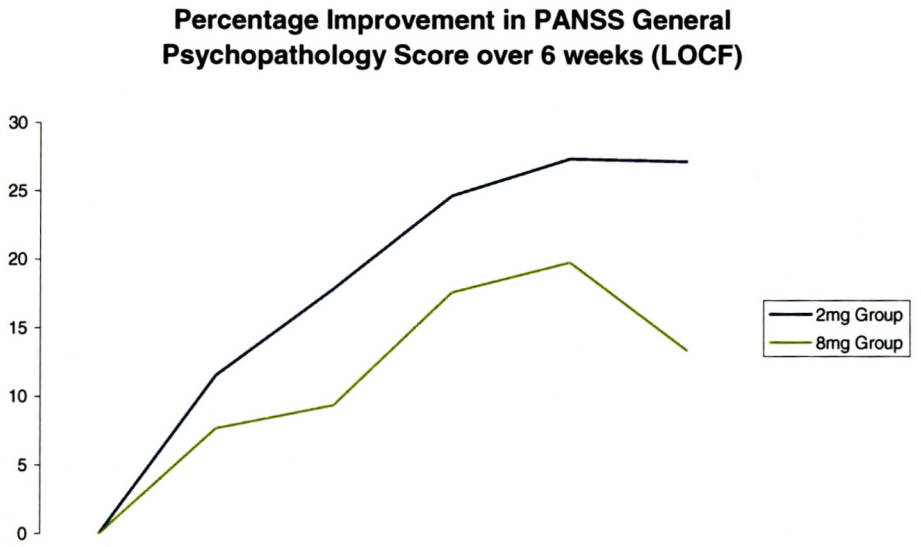
Once again, there was a large numerical difference between the two groups. However, this did not reach statistical significance at any point. Results are presented in table 14.8 and figure 14.4.

Table 14.8

Percentage improvement in PANSS General Psychopathology Subscale over 6 weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Week 1	11.6 (±17.6)	7.7 (±14.1)	0.7	36	0.46
Week 2	17.9 (±18.6)	9.4 (±18.5)	1.4	37	0.16
Week 3	24.7 (±20.5)	17.6 (±25.0)	1.0	37	0.34
Week 4	27.4 (±23.1)	19.8 (±25.9)	1.0	37	0.34
Week 6	27.2 (±22.9)	13.4 (±48.6)	1.1	37	0.27

Figure 14.4



Mood Symptoms

Mood symptoms were measured with the Calgary Depression Rating Scale. There were no significant differences found between the two treatment groups. Results are presented below in table 14.9 and figure 14.5.

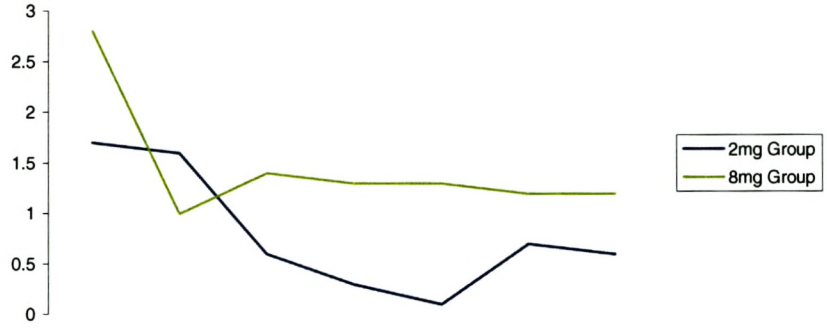
Table 14.9

Mood Symptoms as rated on Calgary Depression Rating Scale over 6 weeks (LOCF)

Group	2mg Group	8mg Group	t-value	df	p
Baseline	1.7 (±3.8)	2.8 (±4.5)	-0.83	38	0.4
Week1	1.6 (±4.1)	1.0 (±2.4)	0.56	36	0.6
Week2	0.6 (±1.5)	1.4 (±3.3)	-1.00	37	0.3
Week3	0.3 (±1.0)	1.3 (±3.0)	-1.28	37	0.2
Week4	0.1 (±0.5)	1.3 (±3.0)	-1.72	37	0.1
Week5	0.7 (±3.0)	1.2 (±3.0)	-0.49	37	0.6
Week6	0.6 (±1.4)	1.2 (±3.0)	-0.76	37	0.5

Figure 14.5

Change in Score on Calgary Depression Rating Scale over 6 weeks (LOCF)



In this phase of the study, due to the relatively short duration, we did not find any correlation with outcome in terms of PANSS negative symptoms as we did in the first phase. However, there was a significant correlation between mood symptoms at baseline (as measured on the Calgary Depression Scale) and the duration of hospitalization (see table 14.10 and figure 14.6.)

Table 14.10

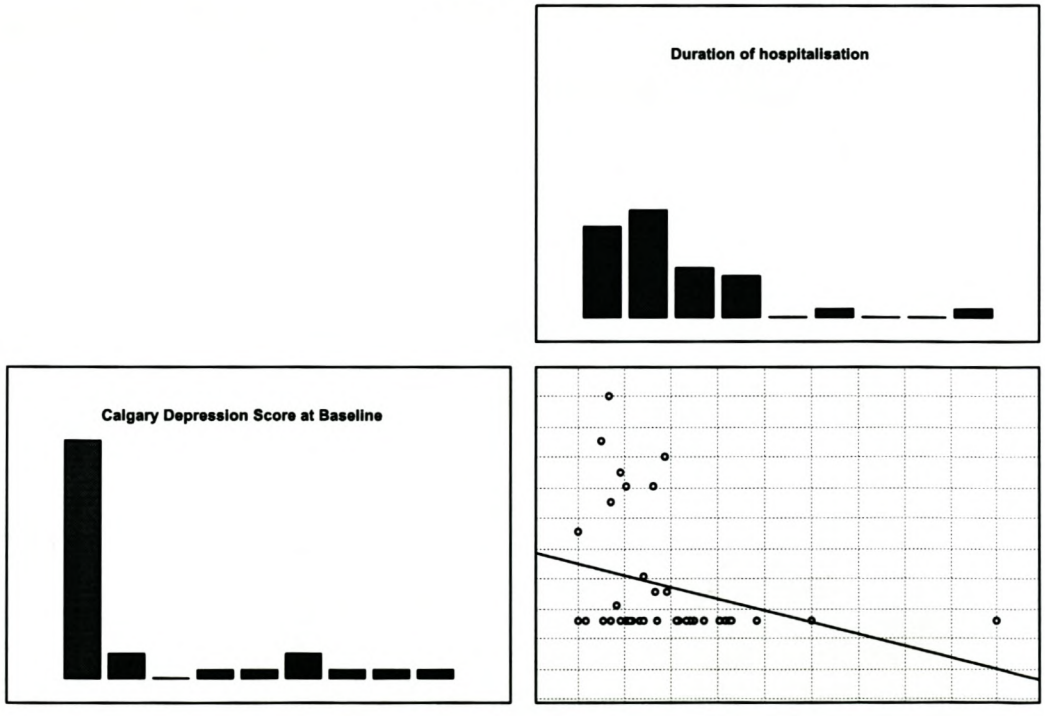
Correlation between depressive symptoms at baseline and duration of hospitalization

N	Spearman R	t	p-value
37	-0.4	-2.6	0.01*

*Significance at the 0.05 level

Figure 14.6

Correlation between mood symptoms at baseline and duration of hospitalisation



Clinical Global Impression

Ratings over six weeks for the two groups on the Clinical Global Impression Scale are presented below in table 14.11.

Table 14.11

Changes in Clinical Global Impression (CGI) Rating over 6 weeks

Group	2mg	8mg	t-value	df	p
CGIB	5.4 (±0.9)	5.2 (±0.7)	0.8	38	0.431
CGI1	4.8 (±1.3)	4.8 (±1.0)	-0.0	37	0.983
CGI2	4.3 (±1.5)	4.4 (±1.3)	-0.2	37	0.850
CGI3	4.0 (±1.8)	3.8 (±1.4)	0.3	37	0.771
CGI4	3.8 (±1.7)	3.6 (±1.5)	0.4	37	0.718
CGI5	3.7 (±1.6)	3.7 (±1.5)	0.2	37	0.863
CGI6	3.5 (±1.7)	3.3 (±1.7)	0.2	37	0.822

Side effect Ratings

As stated in the "Methods" section, subjects were evaluated for EPS with a variety of instruments. These included the ESRS, Simpson-Angus Rating Scale, AIMS and Barnes Akathisia Rating Scale.

Global Assessment of Side effects

This was rated with the total score (Items 1- 55) of the ESRS. Results are presented below in table 14. 12 and figure 14.7.

Table 14.12

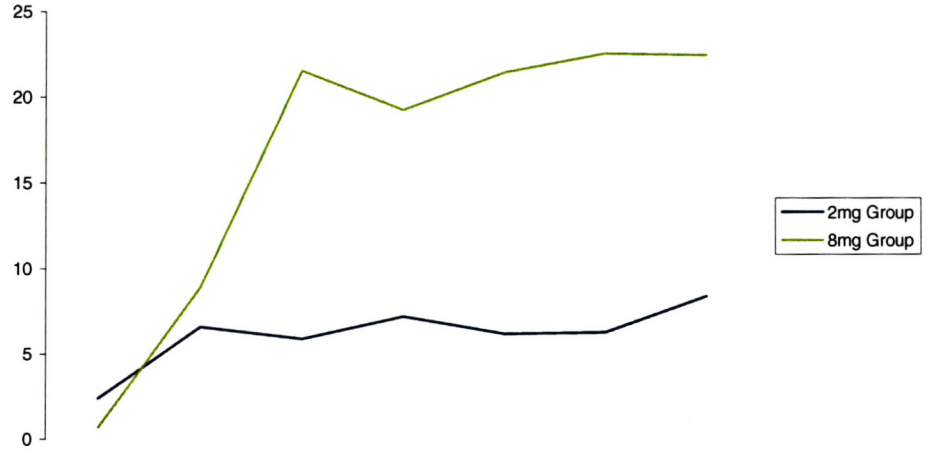
Changes in ESRS Total Scores over 6 Weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Baseline	2.4 (±4.8)	0.7 (±1.5)	1.6	38	0.126
Week 1	6.6 (±13.6)	8.9 (±19.3)	-0.4	37	0.668
Week 2	5.9 (±12.8)	21.6 (±27.2)	-2.3	37	0.028*
Week 3	7.2 (±13.6)	19.3(±20.5)	-2.2	37	0.037*
Week 4	6.2 (±8.3)	21.5 (±22.6)	-2.8	37	0.008*
Week 5	6.3 (±8.3)	22.6 (±23.7)	-2.8	37	0.007*
Week 6	8.4 (±11.0)	22.5 (±23.8)	-2.4	37	0.024*

*Significance at the 0.05 level

Figure 14.7

Change in ESRS Total Score over 6 Weeks (LOCF)



Parkinsonism

Parkinsonism was evaluated using two different scales. Firstly, we used the Simpson-Angus Rating Scale and secondly, the parkinsonism subsection of the ESRS.

Simpson-Angus Rating Scale

There were clear, statistically significant differences between the two groups from week two onwards. Data is presented below in table 14.13 and figure 14.8.

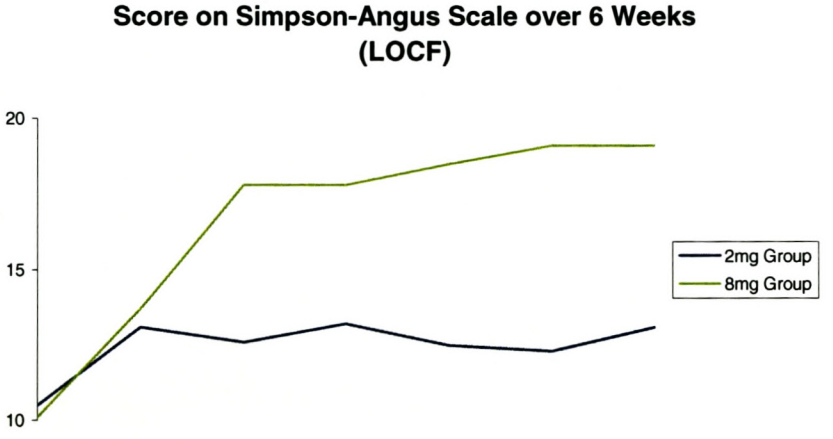
Table 14.13

Ratings on Simpson-Angus Scale for the two groups over 6 weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Baseline	10.5 (±1.8)	10.1 (±0.3)	0.9	38	0.394
Week 1	13.1 (±6.6)	13.7 (±6.7)	-0.3	36	0.767
Week 2	12.6 (±5.6)	17.8 (±8.5)	-2.3	37	0.030*
Week 3	13.2 (±6.0)	17.8 (±7.6)	-2.1	37	0.046*
Week 4	12.5 (±3.2)	18.5 (±8.0)	-3.1	37	0.004*
Week 5	12.3 (±3.1)	19.1 (±8.8)	-3.2	37	0.003*
Week 6	13.1 (± 3.9)	19.1 (±8.8)	-2.7	37	0.010*

*Significance at the 0.05 level.

Figure 14.8



Parkinsonism subsection of the ESRS

This subsection consists of items 13 – 30 of the ESRS. Our findings on this scale were very similar to those on the Simpson-Angus Scale. Results are presented below in table 14.14 and figure 14.9.

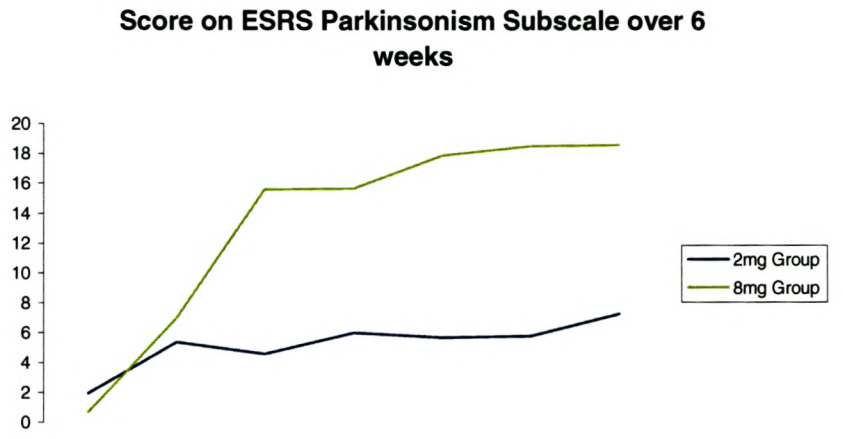
Table 14.14

Ratings on Parkinsonism subsection of the ESRS for the two groups over 6 weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Baseline	1.9 (±3.1)	0.7 (±1.5)	1.6	38	0.126
Week 1	5.4 (±11.3)	7.0 (±14.7)	-0.4	37	0.709
Week 2	4.6 (±10.2)	15.6 (±17.5)	-2.4	37	0.023*
Week 3	6.0 (±11.1)	15.7 (±16.0)	-2.2	37	0.035*
Week 4	5.7 (±7.1)	17.9 (±17.2)	-2.9	37	0.007*
Week 5	5.8 (±7.4)	18.5 (±18.2)	-2.8	37	0.008*
Week 6	7.3 (±8.7)	18.6 (±18.2)	-2.5	37	0.019*

*Significance at the 0.05 level.

Figure 14.9



What is also important, however, is that, for both treatment groups, there was a statistically significant change in ESRS rating from baseline to endpoint:

2mg Group: t = -2.9; df = 18; p = 0.009 (paired t-test)

8mg Group: t = -4.7; df =19; p = 0.0002 (paired t-test)

Dystonia

Acute dystonia was measured by means of items 31 – 39 of the ESRS. There were 8 subjects who developed dystonic reactions at some point during the study (after baseline). Of these 8 subjects, 2 were in the 2mg haloperidol group and 6

were in the 8mg haloperidol group. This was not a statistically significant difference ($p = 0.13$; Fisher's exact test, two-tailed).

Once again, however, it is important to notice that one third of subjects in the 8mg per day group had a dystonic reaction.

As a result of the short duration of the study, there were no cases of tardive dystonia.

Tardive Dyskinesia

There was one subject who clearly had abnormal movements at baseline and a score of 7 on the AIMS. These abnormal movements persisted throughout the 6 weeks of the study. One other subject scored 1 on the AIMS at baseline. This second subject did not, however, display any signs of abnormal involuntary movements after the baseline evaluation.

At the end of the study period, two more subjects had some signs of abnormal movements: One subject developed abnormal involuntary movements from week 4. These persisted for the next three evaluations, but achieved a score of only 2 on the AIMS.

The other subject had a score of 8 on the AIMS at the last evaluation (week 6), but no signs of abnormal movements at any of the other evaluations. Both of these subjects were in the 8mg haloperidol group.

There were no statistically significant differences found between the two groups in terms of AIMS score ($t = 0.04$; $df = 37$; $p = 0.97$)

Akathisia

Eleven subjects (28%) were judged to have developed akathisia at some point during the study. Of these subjects, 3 were in the 2mg per day group and 8 were in the 8mg per day group. This numerical difference did not reach statistical significance (p = 0.16, Fisher's exact test, two-tailed). However, it should be noted that 40% of subjects in the 8mg per day group developed akathisia.

There was also a significant difference in risk for dystonia between the group of subjects who developed akathisia and those who did not (p = 0.028, Fisher's exact test, two-tailed).

Table 14.15

Risk of dystonia in subjects who developed akathisia

Group	No Dystonia	Dystonia	Row Totals
No Akathisia	25	3	28
Akathisia	6	5	11
Totals	31	8	39

Concomitant medications

In this phase of the study, concomitant medications were monitored closely. All concomitant medications, as well as the cumulative weekly dose of each, were recorded at each visit for the preceding week.

Four medications used are discussed here: Lorazepam, orphenadrine, biperidine and fluoxetine.

Lorazepam

The mean dose of lorazepam used did not differ significantly between the two groups. Mean doses for the two groups are presented below in table 14.16.

Table 14.16

Mean doses of lorazepam used for the two groups over 6 weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Dose	48.7mg (±55.2mg)	49.0 (±58.2)	-0.01	37	0.99

Orphenadrine

There was a significant difference in the mean total dose of orphendrine used between the two groups. Mean total doses over 6 weeks are presented below in table 14.17.

Table 14.17

Mean total doses of orphenadrine used over 6 weeks (LOCF)

Group	2mg	8mg	t-value	df	p
Dose	555.3mg (±943.5)	1967.5mg (±2261.9)	-2.5	37	0.016

Biperiden

Three subjects had to have injections with biperiden for the treatment of acute dystonia. In two of the three cases, the incident happened within the first week and in the third case it happened in the second week of double-blind treatment.

Fluoxetine

Four subjects (10%) received concomitant treatment with fluoxetine during the 6 weeks. Of these, 2 were male and two female. Three of the subjects were from the low-dose group and one from the 8 mg group. This was not statistically significant ($p = 0.9$, Fisher's exact test, two-tailed).

There were no differences in terms of ratings of psychopathology, side effects or outcome between the group who took fluoxetine and those who did not.

Prolactin

As a result of problems with the laboratory and collection of samples, we were able to collect reliable information on only a limited number of subjects. However, we still found a statistically significant change in prolactin levels for the whole group from baseline to endpoint, as well as for the 8mg group, but not for the 2mg group (see table 14.18.)

Table 14.18

Change in mean prolactin level for whole sample

Group	Baseline	Endpoint	t	df	p
Whole	14.1 (±9.5)	34.3 (±31.2)	-2.9	20	0.01*
2mg	14.1 (±10.1)	15.5 (±8.4)	-0.38	9	0.70
8mg	14.1 (±9.5)	51.4 (±34.8)	-3.49	10	0.006*

*Significance at 0.05 level

As can be expected, this was also reflected in a statistically significant difference between the low dose and standard dose groups in prolactin levels at endpoint as well as the change in prolactin levels from baseline to endpoint:

Table 14.19

Mean prolactin levels at endpoint

Group	2mg	8mg	t-value	df	p
Level (ng/ml)	15.5 (±9.5)	51.4 (±34.8)	-3.2	19	0.005

Table 14.20

Change in mean prolactin levels between baseline and endpoint

Group	2mg	8mg	t-value	df	p
Level (ng/ml)	0.7 (±10.8)	36.7 (±33.9)	-3.4	21	0.003

Table 14.21

Prolactin levels at endpoint for male subjects

Group	2mg	8mg	t-value	df	p
Level (ng/ml)	17.3 (±8.3)	30.8 (±9.8)	-2.5	10	0.03

Table 14.22

Prolactin levels at endpoint for female subjects

Group	2mg	8mg	t-value	df	p
Level (ng/ml)	8.3 (±4.9)	63.2 (±37.9)	-1.9	7	0.1

Chapter 15

Discussion

General

This is, to our knowledge, the largest study to date of first episodes of psychosis in a South African population. It offers unique information on the demographics, clinical presentation, response to treatment and outcome in a population that is markedly different from North American and European populations. There is good reason to believe that patients from different parts of the globe may present and respond differently to treatment[8], however this has not been studied extensively and more studies are needed to provide comparable data. Our study confirmed many of the findings of previous first-episode studies, while also presenting data that is new.

Gender

There have been suggestions in the literature before that schizophrenia may be a less severe disorder in women than in men[59;100]. Our study provided mixed findings in this area:

Female subjects in our study were considerably older than male subjects at inclusion. Other studies have also found earlier onset in males, with later peaks for females[227]. Females from our group were more likely to be married and also more likely to have produced offspring. Our findings in this regard are similar to that of studies from other parts of the world, which showed women to have higher overall premorbid functioning, more likely to be in stable relationships and more likely to be parents [228].

It is somewhat questionable though, if in a fairly traditional society like South Africa, the increased likelihood of being married and having produced offspring are, in fact indicators of higher social functioning. Women often have limited rights in society and are more likely to be passive participants in courtship, marriage and sexual relationships. Marriage could therefore not be considered as a reliable measure of social functioning. The fact that the women were older at inclusion than the men could also confound other variables, such as marriage and fertility. In contrast to the finding that women were older than men at inclusion, we did not find any significant difference in duration of untreated psychosis, suggesting that the onset for female subjects was in fact later and not a result of delayed help-seeking.

On most other demographic measures as well as measures of outcome that we had available, we did not find any difference between the genders. In fact, we were surprised that there was no difference in the level of schooling between male and female subjects.

The one very significant difference between the genders that remains difficult to explain is the dropout rate in phase I. Fourteen female subjects dropped out of the study in the first year alone, compared to only 4 male subjects. The difference remained significant at two years. The fact that women have a later onset of illness and are more likely to have a family of their own seems to be the most likely cause. Factors such as pressure to return to work and caring for the family – in particular the children – seemed to have played a major role here. In the shorter, phase II study, we did not find a similar problem with drop-out rates.

Unlike other studies, we did not find poorer outcome for male subjects on clinical measures. This finding may have been confounded to some extent by the high initial drop-out rate for female patients in phase I, as the LOCF data for females may therefore reflect more severe psychopathology at endpoint. However, in the phase II study, where there were no gender differences of note in drop-out rates, outcomes were also similar in terms of clinical measures.

Ethnicity

The ethnic distribution of our study sample does not fully reflect the racial compilation of the population of the Western Cape, but rather that of the catchment area of Stikland Hospital. The vast majority of patients who make use of the hospital facilities are of mixed racial origin (African-Caucasian). There is now considerable evidence from the literature that ethnicity may play a role in presentation, treatment response and outcome of schizophrenia[229;230]. Therefore, some of our results, particularly those pertaining to dose of medication and

tardive dyskinesia, should be considered in the light of these earlier findings. Although significant in the South African and perhaps African context, results might therefore not necessarily be valid in other population groups. Unfortunately, the numbers of subjects in this study were not large enough to compare ethnic groups in terms of presentation and treatment response.

Employment history

Subjects with first-episode psychosis are often dysfunctional for many years before the first, florid psychotic episode[231]. This is usually reflected in poor scholastic and work performance. Results from our study are somewhat difficult to interpret, as South Africa is a society with a high rate of unemployment. We did not do a survey of a similar control group to determine whether the rate of unemployment in our study group was statistically higher than that of the general population in our area. Nonetheless, the finding that more than 60% of subjects were unemployed and that only 15% were fully employed, seems much higher than the norm. Furthermore, only 50% of subjects were ever fully employed during their lifetime. This again suggests a high level of impairment from an early age.

It is true that United Nations resolution 46/119 states that every person with a mental illness has the right to live and work in the community. Sadly, this remains an unfulfilled ideal. What is positive in our study however was the finding that the majority of subjects had very close and regular contact with their families and seemed to live in family homes. Less than 10% of subjects were homeless, lived

in a shelter or a squatter camp. This may support the earlier finding that subjects with mental illness in developing countries seem to have better social support structures than their counterparts in the developed world[232].

Perhaps one of the greatest frustrations we encountered during this study was the relatively poor quality of information obtained on personal history. Because record keeping in South Africa has been so poor in the past, there were no official records to verify information against.

Duration of untreated psychosis

Most studies of first episodes of psychosis across the world have shown a marked treatment delay, that is the time from onset of frank psychosis, up to first treatment is instituted[46;48;95]. This delay is known as the duration of untreated psychosis (DUP). We found a very similar pattern in our population, where subjects were, on average, psychotic for about one year before they accessed mental health services. What is interesting to note is that the DUP in our study was not very different from that of studies in the first world[95].

Some authors have suggested that the DUP is associated with outcome on a variety of measures[46;48;68], although others have disputed this claim[72;73]. In this study, we did not find any correlation between the DUP and measures of psychopathology at baseline, doses of medication used or clinical measures of outcome over the short term. However, we did find that DUP correlated significantly with the improvement in PANSS Negative Scale over the latter part

of phase I. From the data presented in table 12.9, it seems that the correlation becomes progressively more pronounced over time. Also, we found a significant correlation between DUP and improvement in PANSS Total Score. This correlation was less robust though than the correlation with the Negative Scale, but still significant at 24 months.

It should be remembered that evaluation of the DUP is a particularly difficult task. We did not use any specific rating scales for DUP in this study, but rather used information obtained form patients and their carers to come to a consensus agreement on the DUP. It may therefore be that our data is less reliable in this regard than studies that used specific rating scales for this purpose.

Phase I

Measures of efficacy

Our study supports and extends previous work indicating that low-dose haloperidol is effective and well tolerated in patients with first-episode schizophrenia[61;62;90 233]. The degree of efficacy is difficult to ascertain from phase I, as a comparator drug was not used here. However, compared to other studies in first-episode schizophrenia, the effect appears to be at least as good. Thus, the study by Emsley et al[90] comparing risperidone and haloperidol in first-episode psychotic patients reported a mean reduction in PANSS total score of 30.9 for risperidone (mean dose at endpoint 6.1mg/day) and 29.3 for haloperidol (mean dose at endpoint 5.6mg/day) after a 6-week treatment period. At 6 weeks the

PANSS total score reduction in our study was 28.5. In the study by Lieberman et al[234] comparing haloperidol and olanzapine, the response was somewhat poorer. For olanzapine (mean dose 9.1mg/day) and haloperidol (mean dose 4.4mg/day) the reductions in PANSS total score over 12 weeks were 18.63 and 16.97, respectively. In our study the PANSS total score reduction was 38.0 at 12 weeks, 40.3 at 12 months and 36.4 at 24 months.

The improvement in negative symptoms over the course of the study is also important. It could be that low doses of haloperidol are less likely to cause the secondary negative symptoms that are often associated with the use of standard doses of traditional antipsychotics, while at the same time successfully treating negative symptoms that are secondary to positive symptoms and possibly even "core" negative symptoms[33;235].

From this study it seems that the majority of the improvement occurs within the first 6 months of treatment with haloperidol, after which improvement seems to level out, with little change over the following 18 months. It would be of great interest to see how the second generation antipsychotics perform over a similarly long period of treatment, as differences in effect size may become apparent only later in treatment.

The importance of maintaining doses at low levels for long enough to allow for maximum response has been emphasized before[88], and it has even been suggested that it may take several months for maximum response to develop[101]. In their study of low-dose haloperidol in first-episode psychosis, Zhang-Wong et

al [62] commented that, had they been able to maintain doses at lower levels for more than seven days, more patients might have responded at low doses. Our study supports this notion. In fact, an important aspect of our phase I study was that investigators were strongly discouraged from increasing the doses of medication for at least a month, thereby allowing time for the effect of the very low dose of medication to set in.

Mood symptoms

As discussed earlier, symptoms of depression are common in patients with schizophrenia. Depending on criteria applied and samples studied, depressive symptoms have been reported to be present in between 7% and 70% of patients with schizophrenia [34], with a modal prevalence rate of 25% [35].

Previously thought to be uncommon in the acute phase of the illness, it was proposed that the florid symptoms of psychosis might mask depressive symptoms that persist, and are later 'revealed' when the psychosis is successfully treated [236]. However, it is now recognized that depressive symptoms are a key feature of the acute psychotic episode, and that the majority of these symptoms resolve with antipsychotic treatment[237]. There are various explanations for depressive symptoms in schizophrenia, such as a subjective reaction to the illness and its accompanying adverse life events[238], substance abuse[239], co-morbid major depressive disorder or anxiety disorders, and

neuroleptic-induced dysphoria[240]. In the stress-diathesis context, depressive symptoms may themselves constitute a stressor that triggers a psychotic episode[35]. It has also been suggested that the depressive symptoms experienced in acute psychosis are a core feature of the illness itself [237].

There have been conflicting reports regarding the relationship of depressive symptoms to treatment outcome. However, it would appear that their presence in the acute phase of the illness might be associated with a favourable outcome [36], while persistent depressive symptoms appear to be negative prognostic indicators[37-39].

In keeping with previous studies, we found that depressive symptoms are common in first-episode psychosis (42% at baseline in this sample).
This once again does not support the notion that depression is only 'revealed' once the psychosis remits[236], as depressive symptoms were prominent at the outset and diminished substantially as the psychotic symptoms improved. Also, our findings argue against the likelihood that depressive symptoms in schizophrenia are misdiagnosed negative symptoms[241] – in which case a significant association between negative and depressive symptoms would have been expected. Finally, the baseline depressive symptoms identified in our sample are unlikely to be related to any pharmacological treatment or it's side effects[242], as the majority of subjects were medication naïve on entry to the study.

The lack of a significant association between PANSS depression factor scores and positive symptoms in our study was surprising, given the fact that such an association has often been reported[237;243-245]. The reasons for our failure to demonstrate such an association was not immediately apparent, as these symptoms are thought to co-occur in acute psychosis, and simultaneously improve with successful antipsychotic therapy[237]. However, when we analyzed the data from the Calgary Depression Rating Scale (CDRS), we found not only a more robust association with improvement in PANSS Negative Score than we did with the PANSS depression factor, but also found an association with improvement in PANSS Positive Score, General Psychopathology Score and PANSS Total Score.

These findings may be interpreted in a number of ways. Firstly, recent work indicates that depressive symptoms may also emerge independent of positive symptoms. In a 12-month prospective study of 105 subjects with schizophrenia, two course patterns of depressive symptoms were identified – those following the same course as positive symptoms during psychotic episodes, and those emerging de novo without a change in positive symptoms[34]. Another, more likely interpretation of the findings would however be that the CDRS provides a more sensitive measurement of depressive symptoms in psychotic patients, having been designed specifically for this purpose. Findings with the PANSS Depression factor should therefore be interpreted with great care and should, in our opinion be verified where possible by comparing it to data using the CDRS.

Both sets of analysis (PANSS Depression Factor and Calgary Depression Scale) identified a previously unreported inverse relationship between acute depressive symptoms and persistent negative symptoms – i.e. higher acute depression scores being predictive of fewer negative symptoms later on (or as it is stated in the results, a greater percentage reduction in PANSS Negative Symptom score). Thus, our findings suggest that the presence of depressive symptoms in the acute psychotic phase of the illness is a favourable prognostic indicator, given the well-established association between negative symptoms and poor overall outcome[51;246]. In a recent study[247] investigating relationships between depression and psychotic symptoms over the course of the illness, it was found that depressive symptoms in the acute phase were associated with positive symptoms only. However, depressive symptoms in the stable phase, in addition to being associated with positive symptoms, showed a positive correlation with negative symptoms. This finding, taken together with the results of our study, provides compelling evidence that symptoms of depression in the acute phase predict favourable outcome, while symptoms of depression that persist or emerge after the acute phase are predictive of poor outcome.

Our findings are in keeping with the theory of symptom dimensions in psychosis as proposed by Shergill et al[248]. According to these authors, a clear dichotomy between schizophrenia and mood disorders does not exist. Rather, the aetiology of psychosis can be explained by the interactive effects of two major types of risk factors: first, those conferring neurodevelopmental impairment and second, a genetic predisposition to react to adverse life events by developing psychotic symptoms. Mood symptoms tend to be more prominent at the life events/genetic

predisposition end of the spectrum, and therefore, are presumably associated with a more favourable outcome. Conversely, negative symptoms are associated with neurodevelopmental impairment, and therefore poorer outcome. Our data support this inverse relation between depressive symptoms and negative symptoms and provide a possible explanation for the previously reported positive prognostic effect of depressive symptoms in acute psychosis.

Another aspect of these analyses is that the Calgary Depression Scale seems to yield better correlations with outcome variables than the PANSS Depression Factor score. This is interesting and suggests that the Calgary Depression Scale should probably be the instrument of choice when evaluating the depression symptoms of schizophrenia and schizophrenia-like psychoses, as it is the more sensitive instrument of the two.

Measures of tolerability

Side-effect ratings

Phase I provides mixed results in terms of tolerability. The finding that there were no significant differences on any of the rating scales for parkinsonism, akathisia or dystonia over the study period compared to baseline suggests a more

favourable EPS profile compared to even only slightly higher haloperidol doses[90;234] and seems to support PET studies[121;188;188;189] that suggest sufficient D2-occupancy and antipsychotic efficacy with haloperidol doses as low as 2mg.

The incidence of TD in this sample, however is considerably higher than expected. Considering that lower dosing strategies are reported to afford some protection against TD [155], we would have anticipated a rate below the ±5% per year of treatment reported with standard doses of conventional antipsychotics [144;145]. Even disregarding the cases of 'possible' TD, the 12 month incidence of 'persistent' TD of 5.3% in the present sample is similar to that previously reported, whereas the 24 months figure for 'persistent' TD at 15.8% is higher than would be expected. Thus, while lower doses of conventional antipsychotics have a low risk of inducing acute EPS[62;188;225] , this does not appear to be associated with a reduced risk for TD. Otherwise stated, patients do not escape the neurotoxic effects of haloperidol even when exposed to low doses of the agent. The results of this study therefore call into question earlier proposals by ourselves[225] and others[154] that haloperidol in low doses may be a reasonable alternative to the atypical antipsychotics.

It is important to note that, while the dose of haloperidol at 12 months was a significant indicator of the development of TD at both 12 and 24 months, the dose of haloperidol at 24 months was not. The reason for this is simple: the protocol allowed for a number of interventions when TD developed, such as reducing the dose of medication or withdrawing the subjects from haloperidol. Thus, subjects who developed TD in the early part of the study would have had

significant interventions by 24 months, thereby making the haloperidol data at 24 months unreliable in terms of its relationship to TD.

The finding of a relationship between the onset of dyskinesia and a worsening in negative symptoms, depressive symptoms and parkinsonism scores is of interest. While an association between TD and negative symptoms is well documented [26;249], their temporal relationship has not been described. Orofacial TD in particular, has been linked with negative symptoms. It is of interest that all of our TD subjects fell into this subsyndrome. We are not aware of a previously reported association between depressive symptoms and TD. Whereas the majority of depressive symptoms in schizophrenia occur in the acute phase, and resolve as the psychosis remits[237], there are patients with persistent depressive symptoms or those emerging *de novo* [34] that appear to be associated with poor social and vocational functioning[38;39], increased risk of relapse[238] and suicide. It is these persistent, or emergent depressive symptoms that were associated with TD in our sample.

Our study confirms that baseline clinical features are not significant predictors of TD [145], and further suggests that the acute response to antipsychotic treatment is similar in both TD and non-TD subjects. Some undefined event then appears to trigger the onset of TD in certain individuals, with the simultaneous emergence of negative and depressive symptoms, as well as features of parkinsonism. (It needs to be remembered however, that mood, negative and parkinsonistic symptoms are difficult to distinguish from one another, and may be

misinterpreted on the assessment scales.) This phenomenon could be explained on the basis of a disease-related vulnerability to TD that is manifest with drug exposure. It has been proposed that patients who are more severely ill and less responsive to treatment have increased vulnerability to TD, either due to an intrinsic aspect of the disease process, or due to greater antipsychotic drug exposure[145]. However, the fact that TD patients did not differ from non-TD patients in terms of baseline psychopathology and acute treatment response demonstrates against this. Also, TD patients did not have more persistent psychotic symptoms, as would be expected in a more severe form of schizophrenia. It would appear rather that TD emerges together with negative, depressive and parkinsonism symptoms. While exposure to antipsychotic treatment may be a necessary factor, the risk may not necessarily be dose-related. An alternative explanation for the reported association between dose and risk of TD [144 145;155] is that these negative and depressive symptoms are interpreted by clinicians as a deterioration in the patient's condition, with resultant increasing of the antipsychotic dose. This would explain our finding of a significant association between TD and drug dose only at 12 months, and not at the onset of TD. Furthermore, the increase in parkinsonism scores that we found could also be a consequence of increased antipsychotic dose.

As was the case in a number of previous studies, we found an association between age and TD development [141;142;144;250]. This was somewhat surprising, given the youthful age and limited age range of our sample, indicating that age as an independent risk factor for TD is not limited to elderly samples. Our failure to identify gender, race and acute EPS as risk factors for TD is in keeping with

the findings in a similar cohort of first-episode schizophrenia patients[145]. However, the incidence of acute EPS was extremely low in our sample, so that comparisons were difficult.

TD is likely to remain a focus of attention in the management of psychosis for a long time. The failure of low-dose haloperidol to reduce the risk of TD is disappointing, and argues strongly against its use as first-line treatment in psychosis if a choice of agents is available.

Phase II

This part of the study had a traditional double-blind design, with both the advantages and disadvantages of this type of study.

Comparing the two groups at baseline

The two treatment groups were similar at baseline in terms of both demographic variables as well as measures of psychopathology. Both groups of subjects were quite ill at admission, with PANSS Total Score around 100 and CGI ratings of >5 (Severely ill) at baseline. This is so because the patients were almost exclusively recruited from the acute, inpatient units at Stikland Hospital. By definition therefore, these patients were at the more extreme end of the spectrum in terms

of severity of illness. It could be argued that this is not a representative sample, as many patients with a first episode of psychosis may not need to be admitted and may have symptoms that are more subtle. However, for the purpose of this study, we believe that this situation has actually enhanced the generalizability of the study – the fact that the very low dose of medication was effective in even the most severe cases most likely indicates that it will be effective over the entire spectrum of severity.

Measures of efficacy

We compared the two groups of subjects, namely those on the low dose of haloperidol (2mg per day) and those on standard dose (8mg per day), on a variety of measures of outcome.

The two doses of haloperidol were both effective in treating the global symptoms of psychosis, as measured by the PANSS Total Score, in a majority of patients. This is important for a number of reasons, but most important of all, it shows that the low dose strategy is at least as effective as the so-called standard dose in the first weeks of treatment.

When we consider the effects of the two treatments on positive symptoms, we again see that there was no difference between the two groups. It is also of interest to note that, even at an early stage of treatment, for instance in the first week of treatment, subjects on lower doses responded as well as those on the higher dose.

But it is in the effect on negative symptoms that we see the most marked differences. Unfortunately, the relatively small number of patients in the study limited the power of the statistical analysis. Even so, there were large numerical differences in the effect on negative symptoms for the duration of the study. This reached statistical significance at week 2, but even at the end of the study, there was still a 13% difference in effect between the two groups. It has often been suggested that first-generation antipsychotics have a very limited treatment effect on negative symptoms and may, in fact, exacerbate these symptoms. This study gives some indication of why this is so – in many studies comparing second-generation antipsychotics to haloperidol, the mean doses of haloperidol were considerably higher than 8mg per day[153;204]. If the difference between 2mg and 8mg is this marked, one can imagine what the difference would be between 2mg/day and 15-20mg/day, a dose often used in comparator studies.

We did not find any difference between the two groups in terms of their effect on the depressive symptoms associated with psychosis. The brief duration of this part of the study also did not allow for the proper evaluation of the effect of baseline mood symptoms on longer-term outcome as we did in Phase I. However, an interesting finding that may support the findings on the effects of baseline mood symptoms in Phase I, was an inverse correlation between baseline depressive symptoms as measured on the Calgary Depression Scale and the duration of hospitalization: the more depressive symptoms a subject presented with at baseline, the shorter the time spent in hospital. This may be a

further indicator of improved outcome for those patients with depressive symptoms at baseline, albeit in an indirect way.

From the above, it is clear that haloperidol at 2mg per day is as effective in treating the first episode of psychosis as 8mg per day. There are suggestions here that the lower dose may, in fact, be more effective. This is particularly true for the negative symptoms and the general psychopathology symptoms as measured on the PANSS. We believe, as others have suggested before[83], that there is a therapeutic window effect with haloperidol, and that increasing doses may not only be ineffective in increasing the treatment response, but may also have a toxic effect and lead to poorer outcome in the long run.

Measures of tolerability

It should be kept in mind that even the so-called "standard dose" of haloperidol used in this study was a conservative one, as doses over 10mg are commonplace in general adult psychiatry. In fact, most recent guidelines suggest does between 6 – 20mg per day[176;251]. As recently as the mid-1980's to mid-1990's, subjects in the largest and perhaps most widely quoted first-episode study were receiving doses of haloperidol and other medications in dose equivalents that were much higher than 10mg per day[95].

The drop out-rate in this study was similar to that of other studies of double-blind treatment over a six-week period[90;204]. Although the difference between the two

treatment groups did not reach the statistically significant level of 0.05, there was a clear numerical difference between the two groups, with 8 subjects in the 8mg group failing to complete the study, whereas only 3 of the patients in the 2mg group failed to complete.

When we consider the reasons for withdrawal, the difference between the two groups is remarkable: 6 patients failed to complete the study due to EPS and all 6 were in the 8mg group. Despite earlier reports of doses of haloperidol below 10mg being tolerated well, this was certainly not the case in our study population. If almost 30% of subjects on 8mg/day withdrew over the first six weeks due to EPS, it is difficult to imagine that there would be an acceptable rate of compliance over the long term, particularly as EPS have been shown to be the principal cause of non-compliance[132].

The ratings of side-effects provide even more evidence in support of the poor tolerability of "standard" doses of haloperidol: on evaluation of overall scores of EPS (such as the ESRS global score) as well as on the scales that measure parkinsonism (ESRS parkinsonism subsection as well as the Simpson-Angus rating scale), there were significant differences between the two groups from the second week up to the end of the study.

It should furthermore be noted that, despite the fact that the 2mg dose was much better tolerated than the 8 mg dose, even this very low dose caused some side-effects and there was a statistically significant change in parkinsonism from baseline. It is therefore different from the phase I study, where we did not find

statistically significant differences in EPS between baseline and the later evaluations. This illustrates one of the shortcomings of the fixed- dose, double-blind design: when researching the effects of a compound with a very narrow therapeutic index such as haloperidol, this study design does not allow for "fine-tuning" of doses, as we were able to do in the Phase I design (and which one would certainly do in the clinical situation). Indeed, although it was our aim to use the dose from the Phase I study to evaluate against the standard dose, it leaves us with the interesting possibility that there may be a large enough difference between 1.7mg/day (the mean dose from the Phase I study) and 2mg/day (the dose we "rounded it off" to) in terms of receptor occupancy to "overshoot" the 70% D2 occupancy zone for antipsychotic effect as suggested by Kapur et al[109;188;189] and already exceed the EPS-causing 80% occupancy level, at least in a significant number of individuals. This is even more thought provoking when we consider the TD data from phase I – seemingly, doses below 2mg/day did not cause TD, whereas a dose above 2mg/day did.

As with the dropout rates, we found that the numerical difference in incidence of akathisia and dystonia did not translate into statistical significance. However, the results of the study in this regard are still important and again raise a number of issues:

a) More than 25% of patients in this study developed akathisia – an often-underrecognised phenomenon. A similar number (22.5%) developed dystonic reactions after initiation of treatment.

b) Forty percent (8/20) of patients in the 8mg group developed akathisia and 30% in this group had dystonic reactions. In the case of 5

subjects, the risk of akathisia and that of dystonia overlapped (i.e. the patients who were at risk for akathisia, were also the ones who developed dystonia)

c) Even at the 2mg dose, some patients developed akathisia.

d) Patients who developed akathisia, are at increased risk of having dystonic reactions, and vice versa.

This data is of great importance to us, as akathisia has been shown to be not only the single most common cause of non-compliance, but may in severe cases lead to suicide. This most uncomfortable and distressing of side effects has been described in graphic detail by Kendler[252], after taking only 1mg of haloperidol. Clinicians, unfortunately, remain poorly equipped to recognize this side effect, often ignoring the patient's subjective experience of inner restlessness and waiting for objective signs thereof. Similarly, clinicians (in particular the young and inexperienced) may misinterpret dystonia as "manipulation" by the patient, to get either medication or attention from staff.

As we expected, we did not find any significant indications of tardive dyskinesia in this short-term study.

Concomitant medications

We were encouraged that subjects in the low-dose group did not need more sedative medication (in the form of lorazepam) than those on the higher dose. Indeed, the mean doses used over 6 weeks were virtually identical (see table

14.16). This shows that the higher dose of medication is no more effective in achieving even its misguided goal of increased sedation. It is indeed encouraging to see that, despite the lowering of doses from those traditionally prescribed, subjects used on average only about 1mg of lorazepam per day of the study.

The use of antiparkinsonian medication reiterates the poor tolerability of the 8mg/day dose. The patients in this group used between three and four times as much orphenadrine as the 2mg/day group. Furthermore, despite the fact that there were no restrictions placed on the use of antiparkinsonian medications and the fact that the 8mg group used it in much larger quantities, this still did not achieve the desired goal of preventing/treating EPS successfully, as reflected in the data on these side-effects.

The data on the use of antidepressants in this group is too limited to make any deductions from. The only clinically significant finding here was that, within the first 6 weeks, 10% of the subjects became depressed enough to be treated with antidepressants.

Although our data on prolactin levels were limited due to laboratory problems, the data that we had did not show any significant increase in prolactin levels for the 2mg/day group, whereas the 8mg/day dose had a marked, significant effect on the prolactin level. It can be postulated therefore that low doses of haloperidol may hold a much-reduced risk of the potential long-term detrimental effects of increased prolactin. As discussed in the section on prolactin in the introduction, increased prolactin levels may cause a number of "down-stream" effects, some

of which may be uncomfortable (sexual dysfunction), but also others such as osteoporosis that may have severe medical implications. An interesting finding here was that the low-dose treatment had a much more profound effect on the prolactin levels of male subjects than on female subjects, whereas the higher dose affected both sexes, but with a greater mean effect in female subjects.

It is clear then, that on all measures of outcome, the 2mg dose was at least as effective as the 8mg dose. There are some indications of superiority for the low-dose group in some aspects of efficacy, particularly in terms of the treatment of negative symptoms. Whether this would be a sustained effect needs to be evaluated in longer-term studies, although data from the phase I study seems to suggest that there is a long-term effect. There can be little argument as to the tolerability of the two treatments: in fact, we were surprised at how poorly the 8mg dose was tolerated and how high the dropout rates with this treatment were.

Chapter 16

Limitations

Every study design has its limitations, and this one is no exception. We consider the following to be the major shortcomings of this study:

1. Phase I did not have a comparator group and had an open-label, algorithm based design. This may have lead to prejudice on the side of the investigators.
2. Although the 97 patients that we recruited presents a large group in terms of first episode studies, the power of the study would have been enhanced had we been able to recruit even larger numbers.
3. There was no placebo group in the study. This could not be considered, however, as it would have been an unethical practice to withhold treatment from acutely ill patients.
4. Phase II ran over only 6 weeks. Longer study duration may have yielded different results.
5. Also, it may be that our findings cannot be generalized to all ethnic groups. Previous work suggests that patients of African descent may be at particular risk for developing TD[147], and we have reported significant racial differences in treatment response to antipsychotics[229], suggesting that some groups may be more sensitive to the effects of these agents.

The principal reason for using the 2 study designs was to try and reduce the limitations of both kinds of study as far as possible. We believe that we have achieved this to some extent, gathering both short-term and longer-term data.

Chapter 17

Conclusion

"If somebody is hearing voices we don't work with them to cope with the experience and support them to go on with their lives. Instead, we isolate them and dose them up with the latest brand of sedative. The liquid straightjacket has replaced its physical predecessor. Being on such medication is like thinking through treacle. I remember wondering: How am I expected to recover from this? To put it crudely: as a society we try to turn distressed and confused people into passive drug-dependent victims. This is not to mention the hundreds of adverse effects on the body that these chemicals cause. The widespread, long-term use of powerful drugs in a heavy-handed way continues to disable permanently thousands who have sought help from psychiatry." (The Independent on Sunday, United Kingdom, Sunday 30 June 2002, page 20).

Over the past number of years, psychiatrists have been striving to improve the image of our discipline in the eyes of both the rest of the medical fraternity as well as the public. Whether we agree with the notion or not, we are seen to be capable of "controlling the minds" of those whom we serve. Yet, we often claim to be the moral guardians of ethical values in medicine. If this were to be the case, we should continually be re-examining ourselves to see whether we are meeting the standards that we set for others. Why would an article like the one quoted above appear in a highly respected, international newspaper? We could write it

off as the misguided ramblings of an obsessed fringe group. However, it may reflect the perception of the public at large.

We are certainly in a unique position within medicine: whereas a patient with cancer may choose to refuse treatment, even if we know that the choice may be wrong, the patient with psychosis in our country (and many others) has no such luxury. He/she may be incarcerated without consent, and is often treated against his/her will. This, we proclaim, is for the greater good. We have thus become both the all-powerful treating agent, whilst at the same time claiming for ourselves the title of defender of those who cannot speak for themselves. We should treat this paradoxical position with the greatest circumspection. It is a great responsibility.

Up to the middle of the previous century, psychiatry was a custodial profession, and treatment was not a real option. Today, we have a myriad of treatments available, many of which are chemical in nature. It has, in some ways, made life easier for the psychiatrist, who can now offer his patient real treatment, with the possibility of return to pre-morbid functioning. On another level, though, there may be truth in the perception that the chemical option has provided an "easy way out" and has robbed psychiatry of many of the things that it is supposed to stand for: close interaction with patients and family, empathy, warmth, unconditional acceptance. So often today, we will prescribe a pill for any disturbance in behaviour, lest a patient becomes dangerous or stays in hospital too long. We have, in many ways, not progressed from the time when "madmen" were banned from the cities of the middle ages, to live like lepers outside the

walls of civilization. The only difference is that, with so-called "defensive medicine" the only safe option available, we use chemicals to remove people from society, so-called "defensive medicine".

Does this imply that treatment with medication is bad? Certainly not, and we should guard against oversimplified and dichotomous thinking of "all good" or "all bad". These medications offer us magnificent, but limited options. Like all medications, be they painkillers or antibiotics, they have a therapeutic window. As long as we stay within this window, the medication is, for most people, a godsend that will relieve their suffering. However rampant, unrestricted use of huge doses of psychiatric medication will have the same effect as with any other medication: side effects and toxicity.

Antipsychotic medication is one of the wonders of modern medicine. We should treat it with the respect it deserves and use it with great care. There is now ample evidence that these medications may be harmful if given unnecessarily or in excessive doses. The first rule of medicine remains: First, do no harm.

We believe that the value of the study lies therein that it neither vilifies nor glorifies haloperidol – it shows it for what it is: a chemical compound with excellent, but limited treatment abilities. When used carefully and in appropriate doses, it may help many people achieve better quality of life. But in doses that are even slightly too high, it turns into a toxic compound that causes parkinsonian side effects, dystonia, akathisia, hyperprolactinaemia and tardive dyskinesia.

It seems that patients from our population may be even more susceptible to the side effects of this medication. Achieving these "perfect" doses therefore requires a considerable amount of time, but more particularly, skill. Unfortunately, most people who prescribe these medications possess neither. It is therefore a great irony that the very people who could perhaps benefit the most from the second-generation antipsychotic medications are the ones who are denied access to them.

While we have, for various reasons, no access to the second-generation antipsychotics, it is imperative that we use the medications at our disposal with the utmost care, particularly in patients who have a first episode of psychosis. We believe that we have provided considerable evidence that, at ultra-low doses (below 2mg/day), haloperidol is an effective and well-tolerated antipsychotic for the majority of subjects with a first psychotic episode. Even slightly higher doses hold risks that our patients should not be exposed to.

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