A Prospective Study of Cognitive Deficits in First Episode Psychosis, and the Response thereof to Treatment with Flupenthixol Decanoate

Dr. Renata Schoeman

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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.

Dr Renata Schoeman

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Abstract

Contemporary research has confirmed the presence of cognitive deficits as a core feature of schizophrenia that has a definite and adverse impact on functional outcome.

Cognitive functioning can be improved by psychopharmacological intervention, with evidence supporting the superiority of second generation antipsychotics over their first generation predecessors. Despite evidence that cognitive impairment contributes to medication non-adherence and that depot antipsychotics are able to enhance treatment compliance whilst decreasing relapse rates, depot preparations remain less frequently prescribed than their oral counterparts, especially in patients with first episode psychosis (FEP). The aims of this study were primarily to investigate cognitive deficits in patients with FEP, and to then describe the response of these impairments to treatment with a very low dose flupenthixol decanoate.

This was a prospective, non-randomized, single arm, open-label, longitudinal study of 58 participants with FEP treated according to a fixed protocol over a period of 12 months. There was a wash-out phase of up to seven days during which all psychotropic medications were discontinued. There was an initial treatment period of one week with oral flupenthixol 1mg/day, after which flupenthixol decanoate was initiated at 10mg intramuscular depot injection every fortnight. Dose increases, in cases of poor or inadequate

response, were allowed at 6-weekly intervals and in increments of 10mg per injection, up to a maximum of 30mg per fortnight.

The principal findings of the study were as follows: The majority of participants were markedly ill, with significant cognitive impairment at baseline. There was a discrepancy between subjectively reported, and objectively measured, cognitive impairment. The majority of the participants responded to, and achieved remission, on a very low dose of flupenthixol decanoate (22.48 ± 0.47mg/month). The majority of symptomatic and cognitive improvement occurred between baseline and three months, with response leveling out at six months. Social cognition did not improve significantly over time, whereas functional outcome and quality of life did improve with treatment. Flupenthixol decanoate was well tolerated and side-effects were of a mild and transient nature.

This study reconfirms that the majority of individuals with FEP experience significant cognitive impairment at baseline. It also suggests that these impairments can be successfully treated with a very low dose of flupenthixol decanoate. The use of depot flupenthixol decanoate ensures sustained treatment delivery, thereby decreasing the risk for relapse. This holds the promise of improved long-term functional outcome for those suffering with psychotic illness.

Abstrak

Onlangse navorsing het kognitiewe inkorting identifiseer as een van die kern simptoomkomplekse van skisofrenie, met toenemende bewyse vir die duidelike en ongunstige impak hiervan op funksionele uitkoms.

Kognitiewe funksionering kan deur psigofarmakologiese ingrepe verbeter word. Onlangse literatuur toon dat die tweede generasie antipsigotika relatief meer effektief is as hulle eerste generasie voorgangers. Ondanks bewyse vir die negatiewe impak van kognitiewe inkorting op behandelingsinskiklikheid, én data wat daarop wys dat die gebruik van langwerkende intramuskulere (depot) antipsigotika inskiklikheid verbeter en periodes van simptoom-terugval voorkom, word dié preparate steeds minder gereeld as hulle orale eweknieë voorgeskryf, veral by pasiënte met 'n eerste episode psigose (FEP). Die doel van hierdie studie was om kognitiewe probleme by pasiënte met FEP te beskryf, en ook om die respons hiervan op behandeling met 'n baie lae dosis flupentiksol dekanoaat, te ondersoek.

Die studie was 'n prospektiewe, nie-ewekansige, enkel middel, oop studie van 58 deelnemers met FEP, wat oor ‘n tydperk van 12 maande volgens 'n spesifieke protokol behandel is. Daar was 'n uitwas periode van 7 dae, waartydens alle psigotrope medikasie gestaak is. Hierna is behandeling met orale flupentiksol 1mg/dag begin vir een week, waarna flupentiksol dekanoaat geinisieer is teen 10mg intramuskulêr elke 2de week. Dosisverhogings, in geval van onvoldoende respons, was toelaatbaar met

6-weeklikse tussenposes, in inkremente van 10mg per inspuiting, tot 'n maksimum van 30mg elke 2de week.

Die vernaamste bevindinge van die studie was soos volg:
Die meerderheid van die deelnemers was ernstig siek, met beduidende kognitiewe inkorting tydens basislyn evaluasie. Daar was 'n verskil tussen subjektief-gerapporteerde en objektief-meetbare kognitiewe inkorting. Die meerderheid van die deelnemers het goed reageer op behandeling en het ook remissie op 'n baie lae dosis flupentiksol dekanoaat (22.48 ± 0.47mg/maand), bereik. Die meerderheid van simptomatiese en kognitiewe verbetering het plaasgevind binne die eerste 3 maande, met afplatting in die tempo en hoeveelheid van verbetering vanaf 6 maande. Sosiale kognisie het nie beduidend gedurende die studieperiode verbeter nie. Funksionele uitkoms en lewenskwailiteit van deelnemers het ook met behandeling verbeter. Flupentiksol dekanoaat is goed verdra en die newe-effekte, indien dit teenwoordig was, was van ligte graad en verbygaande aard.

Hierdie studie herbevestig dat individue met FEP beduidende kognitiewe inkorting by basislyn ervaar, maar dat hierdie inkortings effektief met 'n baie lae dosis van flupentiksol dekanoaat behandel kan word. Die gebruik van depot flupentiksol is 'n suksesvolle manier om volgehoue behandeling te verseker en sodoende die risiko vir terugvalle te verminder. Dit verstewig dus die hoop op beter langtermyn funksionering vir persone met psigotiese siektes.

CONTENTS

CHAPTER 1

INTRODUCTION

Mental health refers to “a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community” [1].

Throughout human history, mental illness has been surrounded by stigmas founded in ignorance. The general public frequently considers mental illnesses as character flaws, or a lack of willpower[2]. Patients are often viewed as “crazy”, or “psycho”[3], and their illnesses are not considered as real, treatable, biologically-based brain disorders[4]. The stigmas, myths, and misconceptions surrounding mental illness frequently prevent individuals from seeking timely help, intervention, support and treatment; thus adversely affecting potential recovery, productivity and social functioning[5].

Furthermore, discrimination of such a nature has impacted harshly on the health care delivery system. Psychiatry remains the most poorly funded medical speciality[6] within the South African medical aid funds structure, with exclusion criteria, or restricted benefits, available for treatment[7] – a situation exacerbated by an ineffectual portion (2.5%)[8] of the country’s health budget being spent on mental health[6]. Historically regarded as ‘low priority’ by policy makers, mental health is now one of the four priority programs in the Reconstruction and Development Program’s health section[9-11].

Recent decades have seen rapid development in technology (including brain imaging techniques, and psychopharmacological developments) which has helped to shift the opinion from mental illnesses being ‘all in the mind’, to ‘all in the brain’. Contemporary treatments for serious mental illnesses are highly effective; with 70% to 90% of patients having a significant reduction in symptoms, and improved quality of life, with combined pharmacological and psychosocial interventions.

One in 4 people worldwide will suffer from a mental or behavioral disorder during his or her lifetime[12]. According to the South African Stress and Health study, the first large population-based mental health epidemiological survey in South Africa, the lifetime prevalence for any mental disorder is currently 30.3%, with a 47.5% projected lifetime risk of any such disorder[13].

Disabling in nature, often lasting for many years, and with a characteristic onset in early adulthood, mental illnesses greatly diminish an individual’s role and productivity in the community. These disorders greatly affect the emotional and socio-economic capabilities of relatives who care for the affected individual, particularly when health systems are unable to offer the necessary treatment and support. Yet, without treatment, the direct and indirect costs to the individual, and society as a whole, are staggering.

The North American mental health sector experienced the largest increase in expenditure of all the health conditions, between 1996 and 2006. Figures rose from $35.2 billion (1996 dollars) to $57.5 billion (2006 dollars); with a

near doubling in number of individuals with mental disorders (19.3 million to 36.2 million) [14]. Neuropsychiatric conditions currently account for 14% of the global burden of disease. Within the category of non-communicable diseases mental disorders account for 28% of the disability adjusted life years, this figure surpasses both cardiovascular disease, and cancer[15]. When taking the direct, indirect and indeterminate costs into account, schizophrenia is the most costly illness that psychiatrists treat; ranking as the world's 9th most important cause of disability[16].

It is quite possible that patients suffering from schizophrenia have been stigmatised and discriminated against more so than any other 'group', with or without illness[17]. Throughout history, prevailing misconceptions have led to the ostracism and institutionalization of those afflicted with this disorder. Sadly, these ignorant concepts remain prevalent in modern society. Schizophrenia is, invariably, synonymous with a 'split-personality', and patients who are considered dangerous[18]. These individuals are seen as having factitious disorders, or psychological 'hang-ups' from childhood parental abuse. This lack of public awareness, combined with inadequate treatment and care facilities, has resulted in the marginalization of these patients. Evidence suggests that this "de-humanization" of individuals with schizophrenia has led to the abuse of basic human rights, particularly in developing countries[19].

With its early onset, devastating effects, and typically lifelong course, schizophrenia has been referred to as "youth's greatest disabler" [20].

Schizophrenia will affect almost 1% of the population at some point in life, with the course of the illness being marked by frequent relapses, re-hospitalizations, suicidality, and prominent impairment in social and occupational functioning[15].

Extrapolated figures for the prevalence of schizophrenia in South Africa estimate that 1 in every 124 South Africans (0.81%) are affected with schizophrenia[21]. Further estimates indicate that 80% percent of these individuals are unemployed; and 50% will attempt suicide - 10% of the latter will be successful. It is not unrealistic to propose that the direct costs (e.g. medication, hospitalization), indirect costs (e.g. loss of earnings, financial and social burdens on informal caregivers), and indeterminate costs in South Africa likely amount to billions of Rand annually.

The assessment and management of schizophrenia has, however, undergone important new developments, with the emergence of improved diagnostic precision and more effective treatment options. These recent developments provide the potential for improved outcome *vis-á-vis* reduced functional impairment, better quality of life, and reduced emotional distress for patients and their families.

Cognitive impairment is well documented in schizophrenia, and has been significantly correlated with poor functional outcome[17]. Cognitive impairment is possibly the more common of the symptoms of schizophrenia and a major barrier to functional recovery, with up to 79% of the variance in improvement

in work habits ascribable to neurocognitive functioning[22]. A comprehensive neuropsychological assessment by Palmer et al. indicated that 85% of the patient group was cognitively impaired by comparison to 5% of healthy volunteers[23]. A review by Green indicates that the relationship between cognitive symptoms and social and vocational impairments is particularly strong, suggesting that improving cognition may be the most direct pathway to improvement in functional outcome[24].

Neuropsychological domains affected in schizophrenia include attention, memory, executive function, motor function and language[25]. The National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) initiative identified 7 domains that were included in their consensus cognitive battery, namely: working memory; attention and vigilance; verbal learning and memory; visual learning and memory; reasoning and problem solving; speed of processing and social cognition[26].

Given the heterogeneity of schizophrenia, it has been proposed that cognitive approaches hold the most promise for understanding variability in the neurobiological substrates of the disorder[27]. There is evidence for cognitive symptoms being a core feature of schizophrenia, as these impairments have been observed in patients before the onset of other clinical features[28,29]. First degree relatives without any psychotic features demonstrate similar deficits, suggesting that there might be a genetic vulnerability to schizophrenia[30]. Byrne et al. linked enhanced genetic risk for

schizophrenia to neuropsychological impairment and symptoms, thereby indicating that what is inherited by the patient due to genetic liability is not the disease itself, but a state of susceptibility due to a spectrum of neuropsychological impairments[31]. Supporting this work are findings that patients with velocardiofacial syndrome with neuropsychological impairment, are significantly more likely to develop schizophrenia than those without neuropsychological impairment[32].

Subjective experiences of cognitive dysfunction, as measured by cognitive complaints, are increasingly acknowledged as important in assessment of quality of life[33]; while cognitive dysfunction has also been reported to be a strong predictor of long-term symptomatic deterioration[34].

“First Episode Psychosis” (FEP) refers to the developmental stage at which full threshold psychotic symptoms are reached[35] in one of the schizophrenia spectrum disorders. These disorders include schizophrenia, schizo-affective disorder, and schizophreniform disorder[36]. The relationship of the neuropsychological deficits to negative symptoms, disorganization, and lack of insight, has important implications for treatment, prevention of relapse and rehabilitative strategies in FEP. The correlations between subjective complaints of cognitive dysfunction, objective impairment in neurocognitive function, and clinical outcome still remain largely unexplored.

Psychopharmacological treatment can improve cognitive functioning, with evidence supporting second generation antipsychotics (SGAs) superiority

over first generation antipsychotics (FGAs). It is not clear if this is due to true pro-cognitive effects or reduced cognitive liability of the SGAs[37], and should therefore be further explored.

Patients with schizophrenia are generally severely impaired; frequently requiring lifelong supervision and support; and they remain vulnerable to exploitation by others in society. In many cases the outcome can be substantially improved by better identification of these cognitive deficits, and adjustment to treatment.

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CHAPTER 2

SCHIZOPHRENIA

The first known treatment of mental illness has been dated to the Neolithic era. Archaeological evidence indicates that a medical intervention known as trepanning (making a burr hole), has been used in the treatment of migraines, epileptic seizures and mental disorders since 9500 BCE[1]. This theory was supported by the renowned French physical anthropologist, Paul Broca[2].

Schizophrenia has travelled through the millennia under a number of different guises. Early historical accounts that make strong arguments for incidents of psychosis, if not schizophrenia, are the 7 years of madness suffered by King Nebuchadnezzar (634 BCE - 562 BCE)[3]; and the contemporary reports of the insanity of the Roman Emperor Caligula (12 CE - 41 CE)[4].

During the Graeco-Roman period Hippocrates ascribed mental illness to an internal imbalance of the four bodily humors[5]. Galen of Pergamum (129-199 CE), the prominent Roman physician, mentioned spirits and temperature imbalances as the causes[6]; while the Greek physician, Aretaeus of Cappadocia (circa. 1st century CE) was the first to use the expression "insanity"[7]. It was not until the 18th century that the French physician, Phillipe Pinel, arrived at the understanding that mental illness is a disease of the central nervous system[8].

The first fully documented case of schizophrenia is the intriguing instance of James Tilly Matthews, a London tea broker, who was admitted to the Bethlem psychiatric hospital (notoriously known as 'Bedlam') in 1797, and was kept there at the whim of the apothecary, John Haslam, until 1814[9].

Benedict Morel first used the term "*demence precoce"* in 1860 to refer to patients with a cognitive disorder, with onset during early adulthood[10]; this term was subsequently translated into Latin "*dementia praecox"* by Arnold Pick in 1891[11]. In 1911 Paul Eugen Bleuler introduced the term "schizophrenia" into medical vernacular to describe his view of the condition as a schism between emotion, behavior and thinking, thus earning himself the title: "the father of schizophrenia"[12].

The diagnosis and concept of schizophrenia varied over the years until the introduction of the Diagnostic and Statistical Manual of Mental Disorders (DSM), in 1952. This publication had as its goal the establishment of reliable, standardized criteria, or prototypes, with which to diagnose the presence of mental disorders. This helped to establish diagnostic accuracy for the clinical management of patients, as well as research. The current edition of the DSM, the DSM-IV-TR, does, however, state that: "…there is no assumption each category of mental disorder is a completely discrete entity with absolute boundaries..." (pg xxxi)[13]. See table 2.1 for the DSM-IV-TR Manual criteria for schizophrenia.

Table 2.1: DSM-IV-TR Diagnostic criteria for schizophrenia	
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): • delusions • hallucinations • disorganized speech (e.g. frequent derailment or incoherence) • grossly disorganized or catatonic behavior • 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 behavior 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 (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
C. Duration	Continuous signs of the disturbance persist for at least 6 months. This 6 month period must include at least 1 month of symptoms (or less if successfully treated) 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 present in an attenuated 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 episode, manic episode, or mixed episode 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:	The 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 made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Epidemiology

A meta-analysis of 55 studies across 33 countries, spanning the period 1965-2001, concluded that schizophrenia affects roughly 1% of any given population, with a prevalence rate of 15.2 in every 100 000 individuals per year[14]. Schizophrenia has a similar prevalence in all areas of the world, and in all population groups[15]. However, the incidence of schizophrenia has an association with social factors, being increased in urbanicity[16], migration[17], and the male gender[18]. Schizophrenia generally presents in late adolescence and early adulthood, with the onset in men occurring one decade earlier than in women[19]. As schizophrenia has its onset in early adulthood and follows a lifelong, debilitating course, it consumes a far larger portion of health expenditure, as discussed in Chapter 1, than its prevalence would suggest.

Etiology

Schizophrenia is a heterogeneous, polygenic, multi-factorial disease[20]. Whereas the neurobiological basis of schizophrenia has been suspected for more than a century, the precise understanding of the pathogenesis of the disorder remains elusive, thus leading to the existence of multiple theories of the pathophysiology of schizophrenia.

- Non-Biological theories

Psychological theories: Psychoanalytic thinking predominated psychiatry during the 18th and 19th centuries. These disciplines theorized that serious inadequacies in the 'caretaking person' during the child's preverbal period can result in impairments of: early object relations; the development of psychic structure; and basic ego functions[21]. Yet this ego defect and ego disintegration hypotheses, with regression in response to conflict and frustration in the absence of underlying biological abnormalities, did not stand the test of time[22]. Technological advances in brain imaging, psychopharmacology, and neuropathology, have confirmed the biological underpinnings of schizophrenia.

Social causation hypothesis: A review by Elizabeth Cantor-Graae reported on the strong evidence for the role of social factors in the development of schizophrenia[23]. This review reminded us of the markedly increased incidence of schizophrenia in second generation migrants, those of urban birth and/or upbringing, and people exposed to social adversity during childhood. Whether the social environment influenced the development of schizophrenia (causation), or the individuals at risk aggregated in adverse social environments (selection), is an ongoing debate[24]; as is the mechanism by which these social factors contribute to the development of schizophrenia. There is an established relationship between stress, cortisol, and psychosis, as documented by stress-induced, psychotic episodes[25]. Patients with psychosis have an elevated measurement of urinary cortisol[26]; and non-

suppression on the dexametasone suppression test. These conditions are suggestive of hypothalamus-hypohysis-adrenal (HPA) axis overactivity[27]; and anatomical changes, such as enlarged ventricles, and structural changes in the hippocampus that are associated with greater severity and cognitive impairment[28,29]. Animal experiments also support dopamine dysregulation or sensitization due to social defeat[30], or social exclusion[31].

- Biological Theories

Evidence for the biological underpinnings of schizophrenia was noted by the French physician and neurosurgeon, Henri Laborit (1914-1995), who used chlorpromazine, an antihistamine, to calm patients prior to surgery. His observation of the calming effect of the drug led him to use it as treatment for patients with schizophrenia. Subsequent studies have proven the efficacy of antipsychotic medication in the treatment of the disorder[32].

The current concept of the etiological pathways of schizophrenia, known as the “double-hit” or stress-diathesis model, is as follows: an individual has a genetic predisposition to develop schizophrenia with early environmental insults leading to neurodevelopmental abnormalities (the “first hit” or diathesis). Later environmental insults, such as stressors, can cause further brain dysfunction (the “second hit”) with the onset of psychosis and the clinical picture of schizophrenia, followed by neurodegeneration[33].

Genetic Factors: Early evidence, suggestive of a genetic underpinning of mental illnesses resembling schizophrenia, is reports of familial aggregation of the disease. Examples of this genetic connection are found in historical documentation of the French Duke of Bourbon, Peter I; Joan of Bourbon; Charles VI of France; and Henry VI of England; this being the lineage of father, daughter, grandson, and great grandson. The risk of developing schizophrenia increases as the degree of genetic affinity with the proband increases[34]; this means that the risk in the general population is 1%; in siblings 9%; in fraternal twins 17%; and in monozygotic twins 48%[35]. Adoption studies have shown that an 'adopted-away' offspring's risk of developing schizophrenia is due to the presence of the illness in the biological parents, not the adoptive parents[36]. Studies of twins confirmed the heritability of the disease as 80%[37]. Subsequently, various chromosomal abnormalities were implied, such as: chromosome 22q11 deletion (velocardiofacial syndrome), a balanced reciprocal translocation of chromosomes 1q42/11q14; and loci on the X chromosome[38].

In a meta-analysis of 20 genome scans, Lewis et al. found that linkage analysis implied more than 4000 genes, with clusters on chromosomes 8p, 22q, 2p, and 5q, amongst others[39]. Tandon et al. summarized association studies that examined the relationship between specific gene variants and the risk of developing schizophrenia, and documented the following: Neuroregulin 1 (NRG1); Dysbindin (DTNBP1); dopamine receptors (DRD_{1-4}); "Disrupted in schizophrenia 1" (DISC1); Catecholamine-O-methyl-transferase (COMT); and the metabotropic glutamate receptor (GRM3). The

results of this analysis concluded that none of the genes appeared to be a prerequisite for the development of schizophrenia[40].

Current approaches include the study of intermediate phenotypes, and endophenotypes[41], which seek to identify very specific aspects, or syndromes, of a disorder; with a view to linking these aspects to candidate genes, and the breaking down of the complex phenomenon into smaller, salient units, to enable more rigorous scientific investigation.

Neurodevelopmental Hypothesis: Advocates for the neurodevelopmental hypothesis of schizophrenia find support in evidence of early environmental insults that increase the risk for the development of schizophrenia with an odds ratio of 2.0 (95% CI 1.6-2.4)[42]. These risk factors include being born both during the winter and in urban areas; maternal infections such as influenza and rubella; prenatal stressors such as famine, bereavement, and maternal deprivation; and obstetric complications such as Rh incompatibility, hypoxia, central nervous system damage, low birth weight and pre-eclampsia[43]. The common underlying mechanisms for increasing the risk for the development of schizophrenia appear to be hypoxia-ischemia[44], inflammation and infection[45], malnutrition[46], and the stress response[47]. Later developmental insults include any emotional stressors, physical stressors and abuse of substances such as cannabis. According to Andreasson et al., regular cannabis use increases the incidence of schizophrenia as much as 6 times[48].

Further support for the neurodevelopmental hypothesis has been summarized by Murray and Lewis, who documented the presence of developmental abnormalities in a significant number of patients. These anomalies include corpus callosum agenesis, aqueduct stenosis, cavum septum pellucidum, cerebral hamartomas, and arteriovenous malformations[49]. Abnormal cytoarchitecture, such as neuronal displacement indicative of failure of neuronal migration in the second trimester[50], and a reduction in neuropil and dendritic spines in the prefrontal cortex[51], were also found. These non-progressive abnormalities are present at first onset of psychosis, and markers of neurodegeneration, such as glial response, are absent[52]. A number of patients also have dermatoglyphic abnormalities, some minor physical abnormalities, and neurological soft signs displaying problems with sensory integration, motor coordination, motor sequencing, and primitive reflexes[53,54].

Neurodegenerative Hypothesis: Supporters of the neurodegenerative hypothesis, such as DeLisi et al.[55] and Lieberman et al.[56] mention the progressive nature of structural changes in a subgroup of patients, cognitive deterioration, and the influence of the duration of untreated psychosis (DUP), as evidence in support of the neurodegenerative hypothesis. On a neuropathological level synaptic integrity was disturbed, and proposed to be related to excessive apoptosis[57].

Integrative Hypothesis: Current evidence seems to favor the integrative hypothesis. This represents a combination of neurodevelopmental and

neurodegenerative mechanisms. In a meta-analysis of the time course of brain volume reduction, Woods et al. found significant whole brain volume loss both prior to, and after, attainment of maximal brain volume[58]. Reduced brain weight and volume, ventricular enlargement and loss of asymmetry[59] and structural loss in the hippocampus[60] was confirmed in post mortem studies.

Pathophysiology

Neurochemistry: Neurotransmitter abnormalities led to the proposal of the dopamine excess theory[61,62], and the glutamate hypothesis[63]. Three factors that support the dopamine excess hypothesis are: an increased striatal dopamine release in response to an amphetamine challenge associated with acute psychosis[64]; post mortem studies, and positron emission tomography (PET) studies that demonstrated increased dopamine receptor type 2 (D_2) binding in the brains of patients with schizophrenia[65]; and hypofrontality , with a resultant hyperactive mesocortical dopamine system[66].

Evidence has been documented for glutamatergic dysregulation in phencyclidine (PCP)[63] and ketamine induced psychosis[67], and postmortem studies have shown reduced expression of N-methyl-D-aspartic-acid (NMDA) receptors in the prefrontal cortex and hippocampus[68]. These data lend credence to the glutamate hypothesis of Kim et al. which states that schizophrenia patients have a deficiency in glutamatergic function and/or an increase in dopaminergic function[63].

Further evidence of neurotransmitter dysfunction suggests reduced gamma-amino-butyric acid (GABA) expression in the prefrontal cortex[69], deficits in muscarinic activity[70], and serotonergic deficits[71].

Changes suggestive of a reduction in neuronal, and membrane integrity (e.g. reduced N-acetyl aspartate (NAA) in the prefrontal cortex and hippocampus), were the result of *in vivo* metabolic studies with magnetic resonance spectroscopy[72]; as were the observations of decreased phosphomonoesters (PME) in the prefrontal region[73].

Structural Imaging: In a review of fifteen voxel-based morphometric studies of patients with schizophrenia, significant volume deficits and reduced grey matter were present in the left medial temporal lobe, correlating with memory deficits. Significant volume deficits and decreased density of grey matter were also present in the left superior temporal gyrus correlating with the presence of positive symptoms [74]. In a meta-analysis of 58 studies, the absolute regional brain volumes, and volume of ventricular structures, of 1588 patients with schizophrenia were compared to those of healthy comparison subjects. The mean cerebral volume of the group with schizophrenia was 98% of the healthy group (effect size 0.25), while the mean total ventricular volume were 126% of the comparator group (mean effect size 0.49). Other important differences were noted for the hippocampi-amygdalae structures, and the superior temporal gyri[75].

Fractional anisotropy is a measure used in diffusion tensor imaging studies to reflect fibre density, axonal diameter, and myelination in white matter. A lower value (approaching zero) reflects isotropic diffusion, i.e. diffusion which is unrestricted in all directions, while a higher value (approaching one) is indicative of diffusion occurring along one axis only, such as occurring along axons[76,77]. Reduced fractional anisotropy in various white matter tracts, including the corpus callosum, the cingulum, arcuate fasciculus, and the uncinate fasciculus reflecting reduced white matter integrity[78]. A meta-analysis of fractional anisotropy studies by Ellison-Wright and Bullmore identified two consistent locations of reduction in fractional anisotropy in schizophrenia: in the deep white matter of the left frontal lobe, and in the deep white matter of the temporal lobe[79]. These white matter changes are thought to be related to glial integrity[80] influenced by neuregulin[81]; thereby lending support for the glutamatergic developmental model of schizophrenia.

Functional Imaging: Functional imaging studies report conflicting results with regard to prefrontal activation in response to cognitive tasks. Berman & Meyer-Lindenberg demonstrated hypofrontality with a lack of activation of the dorso-lateral prefrontal cortex (DLPFC)[82], while a meta-analysis by Hill et al. showed moderated effect sizes for both activated (0.42), and resting (0.55), hypofrontality[83]. When controlling for performance differences, it was demonstrated that patients show more prefrontal activity than normal controls[84]. It would therefore appear that inefficient information processing is present, and it is assumed that the increase in subcortical dopamine is secondary to this hypofrontality[85]. This supports the dopamine theory's

connection to the etiology of schizophrenia whereby an excess of dopamine causes psychosis[86].

Neurophysiology: Neurophysiological studies have centered on event-related potentials including mismatch negativity (MMN), P300 event-related potentials, P50 gating deficits, and changes in pre-pulse inhibition. MMN refers to the brain's response to standard and anomalous sounds; this is the pre-attentive stage of auditory information processing. Patients with schizophrenia were observed to have a reduction in the amplitude of MMN[87]; particularly in the primary and secondary auditory cortices, as well as the DLPFC, which relates to prolonged illness duration and impairments in sensory memory.

Additionally, an increased latency for and amplitude reduction of the P300 wave was demonstrated in the superior temporal gyrus, the inferior parietal lobe, frontal lobe, hippocampus, and thalamus[88]. The P300 wave is linked with higher cognitive functions, and these changes were also present in ‘at risk’ individuals.

The P50 gating deficit noted in patients is symptomatic of frontal-hippocampal mismatch communication[89], and has been linked to chromosome 15q14 - the alpha$_7$-nicotinergic receptor gene[90]. Abnormal pre-pulse inhibition serves to further confirm the presence of sensori-motor gating deficits, most noticeably in the striatum, hippocampus, thalamus, frontal, and parietal regions[91].

Further evidence of neurophysiological changes in schizophrenia includes abnormal eye movements, changes in sleep patterns and architecture, and electroencephalogram (EEG) abnormalities. Abnormal anti-saccade and tracking eye movement[92] has been linked to failure of the frontal-striatal saccade suppression mechanism[93] with a 91% incidence of inheritability[94]. Decreases in total and non-rapid eye movement (NREM) sleep and sustained waking time have been documented[95]. Evidence for thalamocortical integration dysfunction[96] are indicators of perceptual anomalies that include the presence of gamma-band abnormalities and variations in synchronicity on EEG[97].

Clinical Presentation

In the 20th century schizophrenia became synonymous with the presence of positive symptoms such as hallucinations and delusions. However, when we carefully consider the diagnostic criteria, it becomes clear that these are neither necessary, nor sufficient for the diagnosis. Bleuler was the first to talk about the “abnormal A’s” of schizophrenia, later be known as the negative symptoms of schizophrenia: abnormal affect, abnormal thoughts and speech, alogia, avolition and anhedonia. Other symptoms include apathy, asociality and poor attention[98]. Factor analysis also revealed the presence of separate mood symptoms and aggression/hostility clusters[99].

Although the earliest researchers of schizophrenia recognized cognitive impairment in schizophrenia and named it *“dementia praecox”* (dementia

with early onset), the focus has only recently shifted to cognitive symptoms as a separate symptom cluster. The importance of cognitive impairment, the affected domains, the course, relationship to outcome, and treatment thereof, will be discussed in the following chapter.

Prognosis

The course of life and outcome of patients with schizophrenia has been the subject of numerous longitudinal studies conducted by a host of medical professionals, beginning with Bleuler in 1911[100], through to present day studies. The findings of these studies show that approximately 10% of patients succumbed to suicide; 50% had a chronic, unremitting and debilitating course; 10% recovered after a single psychotic episode; and 25% significantly improved, and functioned well between episodes.

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CHAPTER 3

COGNITION

Defining cognition

Cognition (L: *cognoscere*, “the action or faculty of knowing including perceiving, and conceiving”) is a general term embracing the mental activities associated with thinking, learning, and memory; or any process by which one attain knowledge[1].

Cognition can be conscious or unconscious, and is in close relation to abstract concepts describing capabilities of the mind, such as reasoning, perception, intelligence, and learning. Cognition is considered an abstract property of advanced living organisms, and is studied as a direct property of a brain at the factual and symbolic levels, particularly mental processes such as perception; memory and learning; thinking, and expressive functions[2].

Thomas Aquinas (1225 – 1274), the medieval empiricist, divided the study of behavior into two broad categories, namely: cognition (how we know the world), and affect (feelings and emotions). Subsequently, mental processes described as “cognitive” have been largely influenced by research which has successfully used this “time-tested” paradigm[3].

The history of cognition in schizophrenia

Although impaired cognition is not categorically listed as part of the DSM-IV-TR[4] diagnostic criteria of schizophrenia, the manual does make several references to cognitive processes in the description of this disorder, for example the presence of delusions, and disorganized speech with derailment and incoherence (which is the "visible" manifestation of underlying disorganized thought processes).

Cognitive deficits have been noted as a consistent feature of schizophrenia since early descriptions of the disorder by Benedict Morel[5], Emile Kraepelin[6] and Eugene Bleuler [7]. Morel used the term *"demence precoce"* to describe cognitive dysfunction with onset during early adulthood. Kraepelin followed by describing "a rapid yielding of will-tension" and attentional problems on calculation tasks in patients with *"dementia praecox"*.

The importance of cognitive deficits: evidence for effects on functional outcome

Cognitive impairment has been noted as a feature of schizophrenia, and has important clinical and economic implications. Long-term deficits in the domains of employment[8,9], independent living[10], and social functioning[11,12] are major causes of disability in schizophrenia. There is also a negative impact on quality of life[13], with increasing acknowledgement of self-

perception of cognitive dysfunction (as measured by cognitive complaints) attributing to a major role in quality of life[14,15].

The bulk of the literature supports the negative impact of cognitive impairment on functional outcome and recovery[16], with up to 79% of the variance in improvement in work habits ascribable to neurocognitive functioning[17]. A review and meta-analysis of 37 studies, which included both recently and chronically ill patients, demonstrated that immediate and secondary verbal memory, executive functions, and vigilance, are all significantly related to functional outcome, both in terms of social skills acquisition, problem-solving, community outcome and activities of daily living[18]. However, Stirling et al. followed 49 FEP patients over a period of 10 years and concluded that baseline cognitive scores bear no significant relationship to outcome variables (work performance, social competence, and Global Assessment of Functioning scores) 10 years later[19]. In a cross-sectional study of 78 schizophrenia patients, in the 50-85 year old age bracket, Bowie et al. found that neuropsychological performance contributed little to real life performance (interpersonal skills, work skills, and community activities - as rated by case managers) after accounting for functional capacity (as measured by performance) [20]. The discrepancies in findings reported in the above studies can be ascribed to the methodological differences between these studies, with regard to test measures used, patients included (recently versus chronically ill), and duration of the studies.

Cognitive impairment is associated with both poor premorbid, and current social functioning, with neuropsychological deficits accounting for 5-25% of the variance in social and vocational outcome after a FEP[21,22]. In a review of studies with a minimum follow-up period of 6 months, cognitive deficits correlated well with present functioning, and predicted future outcomes, with regard to job performance, job tenure, and social relations[23]. Although Addington and Addington found no relationship between neurocognitive test performance of 80 FEP patients at baseline and community functioning 2.5 years later, poor performance on cognitive flexibility tests at baseline did predict lower quality of life scores[24]. Furthermore, the attrition rate (18.75%) in their study can be seen as support of the negative impact of cognitive impairment on compliance with treatment[25], on response to health promoting interventions[26], and on the ability to acquire skills in psychosocial rehabilitation[18]; all of which have the potential to negatively impact on relapse prevention.

Fujij and Wylie evaluated the predictive validity of neuropsychological measures at baseline to functional outcome 19.7 years later in 26 patients. Verbal memory significantly predicted community functioning, while executive functioning predicted the duration of hospital inpatient stay[13]. The relationship between cognitive symptoms, specifically working memory, and functional outcome[27,28], seems stronger than the relationship between positive and negative symptoms with functional outcome[29].

Cognition: is it an independent domain?

For many years, cognitive symptoms were seen as a product of other symptom clusters of schizophrenia, namely; positive, negative, and disorganized symptoms. It has been demonstrated that there is a connection between changes in the superior temporal gyri and negative symptoms in patients with schizophrenia[30]; however, the relationships between cognitive deficits and structural differences of the brain are less well-documented.

Differences in cognitive deficits associated with clinical symptoms have been reported. Cross-sectional correlation of negative symptoms and neurocognitive impairment has been reported[31-33]. On the other hand, Bell and Mishara failed to demonstrate a relationship between negative symptoms and neurocognition[34], which might be due to measurements not distinguishing between verbal fluency, poverty of speech, and motor retardation[35]. Green and Walker found that negative symptoms were associated with more impairment in visuomotor and visuospatial skills, whereas verbal memory deficits and distractibility were more strongly associated with the presence of positive symptoms[36]. Further studies have linked deficit symptoms to frontal, and parietal lobe functions[37,38], with positive symptoms correlating to frontal lobe and encoding memory tasks[39].

Using Liddle's three-factor model, psychomotor paucity was correlated with reduced verbal fluency[40], disorganization with errors on continuous performance tasks, difficulties with set-shifting[41], and reality distortion with

widespread cognitive dysfunction[42]. Although negative symptoms have been associated with slower information processing, the relationship accounts for a meager portion of the variance in performance[41,43]. Another area of uncertainty is the relationship between poor motivation and negative symptoms[44,45]. The presence of depressive symptoms may also adversely affect cognitive functioning with impaired verbal memory, even when controlling for psychomotor retardation and speed of processing[46].

Isolated reports of a significant correlation between positive symptoms and working memory exist[47,48]. However, across different patient samples (FEP, chronic and elderly), the correlation between positive symptoms and cognitive ability is low, and the severity of psychotic symptoms not strongly correlated with the cognitive problems[32,49,50]. If neurocognitive deficits were the results of these positive symptoms of the disease, then, logically, the cognitive problems should disappear as the patient improves clinically. However, long term studies reported no significant improvement in cognitive deficits by patients recovering from an acute psychotic episode, despite clinical improvement in psychopathology[51-53]. Though SGAs do seem to lead to substantial clinical improvements, with mild improvements in cognition, the correlation between these improvements is not statistically significant[54].

Cross-sectional correlations between neurocognitive impairment and psychopathological symptoms are undoubtedly weak and support the proposal that cognition is a separable domain, and not caused by psychosis. Only in recent years has there been an increase in evidence for, with a

movement toward, recognizing cognitive symptoms as a separate symptoms complex viewed as a potential target for therapeutic intervention[55].

With cognition being a central concept in schizophrenia, various studies have attempted to specify the neuropsychological association of the cognitive factor. Concerns regarding the validity of the Positive and Negative Syndrome Scale (PANSS) cognitive factor have been raised by Harvey et al.[56] and Good et al.[57]. With this in mind, Ehmann et al. examined the relationship between four versions of the PANSS cognitive factor; those of Bell et al.[58], Fredrikson et al.[59], White et al.[60], and Peuskens et al.[61]. The authors examined neuropsychological and intellectual functioning of 37 patients with a mean PANSS score of 88.35 (SD 19.02). Correlations among the four versions of the cognitive factor ranged from 0.84 (Bell with Peuskens' factors) to 0.92 (Fredrikson with Peusken's factors). The factor described by Bell et al. failed to show any significant correlations with any cognitive and intellectual variables. PANSS positive subscale scores were associated with performance IQ ($r=0.33$, $p<0.05$) and vocabulary ($r=-0.33$, $p<0.05$), while verbal IQ showed an inverse correlation with PANSS negative subscale ($r=-0.26$, ns). It appeared that the cognitive factor is likely to be more closely associated with verbal intellectual and memory scores, than with measures of attention, executive function, nonverbal memory and nonverbal intelligence[62].

Heinrichs and Zakzanis' review and meta-analysis of 204 studies (7420 patients with schizophrenia and 5865 controls) reported that individuals with

schizophrenia score 0.5 to1.5 standard deviations below the control mean in various neuropsychological domains, the most consistent of which are: attention, memory, verbal fluency, intelligence, motor speed, spatial ability, and executive functioning. Various studies have shown abnormal cognitive functioning to be present in patients with schizophrenia, even in the early phases of the disease. At group level, patients' cognitive function operates on comparable levels to age- and gender matched healthy controls[63].

In summary: Cognitive deficits in patients are characterized by generalized intellectual deficits, with an average of 19 IQ points below controls, representing specific abnormalities in definitive neuropsychological domains such as working memory, attention and executive functioning. With this evidence indicating the significance of cognitive disorders in schizophrenia, Keefe proposed that the diagnostic criteria for schizophrenia be revised to include "a level of cognitive functioning suggesting a consistent severe impairment, and/or a significant decline from premorbid levels considering the patient's educational, familial, and socioeconomic background" (pg 912)[64]. Furthermore, Mortimer contended that cognitive approaches hold the most promise for understanding variability in the neurobiological substrates of the disorder[65].

Cognitive deficits: a state, or trait marker of schizophrenia?

These early observations were the first among many descriptions of cognitive deficits in schizophrenia, leading to the inception of behavioral and

biological ‘markers’ (namely state markers, and trait markers), that serve as indicators for detection, treatment, and prevention of the disorder[66]. State markers typically encompass the information processing difficulties intrinsically characteristic of psychosis, and reflect the status of clinical manifestations in patients; these being the influence of positive symptoms such as hallucinations, delusions, and thought disorder, on cognitive processes.

Trait markers are considered to be present independent of the clinical state of the patient; therefore, the proviso for a cognitive deficit as a trait marker of schizophrenia, while contributing to the vulnerability for the development of the disorder, is that it should be present at all stages during the course of, and also be specific to, the illness. In addition to an association in the presence of the illness, a further requirement of a trait marker is that it correlates to illness liability; requiring the demonstration of the marker in individuals at risk for development of the illness, as well as unaffected family members.

Trait markers are primarily linked to information-processing, with an early perceptual processing deficit that leads to impairment in perceptual organization and higher cognitive skills. This means that reduced perceptual sensitivity causes erroneous early information processing, and interference between relevant and irrelevant perceptual information. As a result, excessive use of attentional resources leads to a decreased attentional capacity for task-relevant, cognitive processes. Abnormal attention level, and

increased distractibility are typical, primary problems of these trait markers. These problems present with deficits in reaction time crossover; backward masking; selective attention tasks, such as dichotic listening; serial recall tasks; sustained attention tasks; language; and span of apprehension.

The term ‘endophenotype’ is frequently used to describe a trait marker, or an enduring phenotype associated with schizophrenia, that is not immediately visible within the clinical domain[67].

Cognition as an endophenotype of schizophrenia

Nearly four decades ago the endophenotype concept was borrowed from the entomological writings of John and Lewis[68] and introduced to psychiatry by Gottesman and Shields[69]. An endophenotype is “not the obvious and external, but the microscopic and internal” (pg 720)[70], and therefore a distinctive type of biomarker that stands to play a pivotal role in the understanding of complex illnesses. The endophenotypic approach seeks to identify very specific sets of symptoms of a disorder, link them to candidate genes, and break down the more complex phenomenon into salient units that are amenable to rigorous scientific investigation[67,69]. In other words, the endophenotype concept seeks to separate behavioral symptoms into more stable phenotypes with an obvious genetic connection.

The criteria for a biomarker to be called an endophenotype are that it must be associated with illness in the population; be heritable; be state-

independent (manifests in an individual whether or not illness is active); and within families, endophenotype and illness co-segregate[71,72]. An additional suggestion to these requirements is that when present in afflicted family members the endophenotype is found in unaffected family members at a higher rate than in the general population[73].

Studies involving families, twins, and adoption scenarios have consistently supported schizophrenia as a highly heritable disorder consisting of diverse constituents. If cognitive impairments are present in both the patient, and first degree relatives who do not have schizophrenia, and if they are stable in and out of psychotic episode, then they are not closely linked to the clinical symptoms. Instead, they appear to reflect a predisposition to illness and, as such, may be valuable endophenotypes for the genetics of schizophrenia.

There is currently a growing interest in the use of different cognitive deficits as potential endophenotypes of schizophrenia liability[74]. Generalized impairments are supported by Blanchard and Neale[75], and Dickinson and Harvey[76]; while Saykin et al.[77] support the viewpoint of multiple specific selective deficits of differential magnitude.

In a study by Keefe et al., 147 out of 150 patients (98.1%) with schizophrenia performed significantly worse on cognitive tests than would be predicted by their parents' educational level[78]. In a monozygotic twin study, affected twins performed significantly worse than their unaffected siblings[79], demonstrating the presence of a general cognitive deficit in schizophrenia. Although 63.6%

of the variance in cognitive performance was approximated to be due to the general cognitive factor, verbal memory and processing speed also demonstrated direct effects, of 13.8% and 9.1% respectively[80].

Genome-wide searches have revealed possible susceptibility genes for the disorder in relatively broad regions of multiple chromosomes[81], with meta-analysis of the data providing some support for chromosomes 6p, 8p, 10p, 13q, 15q, 18q and 22q[82]. A number of studies have successfully linked genes with neuropsychological performance, for example; it has been established that individuals with velocardiofacial syndrome (VCFS) and schizophrenia perform significantly worse in terms of spatial working memory, visual recognition, and attentional tasks, in comparison to individuals with VCFS, but without schizophrenia[83].

An indication of cognition as a cognitive endophenotype is the cognitive deficits present in ‘at risk’ individuals; that is to say, individuals with a family history of schizophrenia, and/or manifestations of mild symptoms, and signs of the early onset of the illness [84]. Neuropsychological deficits are detectable in genetically at risk, but otherwise healthy, first degree relatives of probands with schizophrenia[85]. Studies have identified the following cognitive impairments as valid endophenotypes for schizophrenia: IQ[86], verbal memory[87], visual memory[88], attention[89], executive function[90], language[91], and psychomotor speed[92].

In a meta-analysis by Sitskoorn et al.[93], of 37 studies encompassing 1639 relatives of schizophrenia patients and 1380 healthy controls, differences in cognitive performance between the groups were documented. Patients were more impaired than their relatives; while their relatives showed attenuated cognitive deficits when compared to healthy controls. Yet, despite a 65% overlap between relatives and controls, no test adequately discriminated between the two groups. The cognitive performance of first degree relatives was more than half of a standard deviation below that of healthy controls; with these deficiencies being more pronounced in the domains of memory, executive functioning and attention. These functions are deemed to be related to frontal and temporal lobe dysfunction[94,95].

The course of cognitive impairment in schizophrenia

Even though several decades of research have been invested in the temporal trajectory of cognitive impairment, the net yield of results is laced with incongruities; and both the timing and course of this disorder remain tantalizingly elusive. Relative and successful comparison of studies such as these has proven to be a problematic issue due to the methodological differences of the tests, and dissimilar categories of the test subjects themselves (e.g. chronic patients, and first episode patients). A representative sample of such discrepancies are the conflicting reports by Yung & McGorry[84], who noted cognitive dysfunction during the prodromal period; and Moritz, who observed it to be a strong predictor of long term symptomatic deterioration[96].

The trajectory of cognitive impairment in relation to the lifespan of schizophrenia is not clear. As next discussed, there is evidence for three distinct groups of patients: a small group, who remain cognitively preserved; those who are premorbidly compromised; and those with cognitive deterioration, specifically during the first 3 to 5 years after onset of illness.

- Cognitive preservation

The group of patients in which the integrity of cognitive functions remain preserved are high functioning individuals (IQ 120-140) demonstrating no cognitive impairment, nor decline, and account for between 25% and 31% of all patients[97-101]. This 'cognitively preserved' group demonstrates executive dysfunction suggestive of prefrontal cortex involvement[102].

- Cognitive aberration

Long-term studies, as well as retrospective reviews of academic records, provide more than enough evidence for cognitive impairment to be a neurodevelopmental abnormality that is present before the onset of the first psychotic episode[103-106]. IQ deficits with scores below 84, predating the onset of psychosis, were reported[107]. A higher incidence of consequent development of schizophrenia was found in a group of individuals with pre-morbid IQs below 96[108]. These observations correlated with similar findings of an earlier meta-analysis[109]. A small group of individuals with

schizophrenia displayed severe cognitive impairment, prior to the first psychotic episode[110-112].

A meta-analysis of 18 studies determined premorbid IQ in subjects who were subsequently diagnosed with schizophrenia, schizo-affective disorder or schizophreniform disorder. A mean effect size (MES) of -0.54 was calculated; being suggestive of a medium sized deficit in global cognition prior to the onset of schizophrenia[113]. This equates to a mean premorbid IQ estimate of 94.7 (0.35 of a SD below the mean and at the lower end of the average range).

A 1994 birth cohort study by the UK National Survey of Health and Development, based on the examination of childhood data from 5362 adult patients who developed schizophrenia, reported a wide range of cognitive and behavioral differences from those of the general population. This included differences in educational achievement, and slower attainment of neurodevelopmental and motor developmental milestones. Lower verbal, non-verbal, and mathematics educational test scores, at all ages, were documented for the afflicted group[114].

The data of 61 schizophrenia patients, drawn from the 1966 North Finland Birth Cohort, compared to 104 healthy individuals, demonstrated associations between delayed motor developmental milestones at 12 months with impaired neurocognitive measures at ages 33 to 55. This is seen as evidence that infant motor developmental delays and adult cognitive

deficits are age dependent manifestations of the same underlying neural process[115].

A study of 44 FEP patients (all of who underwent premorbid cognitive assessments at age 16 to 17 years, as part of the compulsory Israeli Draft Board aptitude evaluations) found that the majority of cognitive impairment occurred prior to, and was exhibited at, the first psychotic episode[116].
It would therefore appear that up to approximately 50% of patients can be considered "premorbidly impaired". These patients are impaired in all domains, including attention, memory, executive functioning, language, oculomotor speed and visuospatial perception, and display a high frequency of hallucinations. There is evidence for increased parietal and temporal cortical dysfunction (thus explaining the semantic memory and visuospatial deficits), though frontal lobe dysfunction is also present[117].

- Cognitive deterioration

The first reports of declines in IQ from pre- to post-FEP dates back to the 1950s, when Rappaport and Webb found an average decrease of 33 IQ points[118]; and Lubin et al. observed declines in IQ from premorbid levels between 0.17 and 0.3 standard deviations[119]. Kolb and Wishaw[120] used a variety of tests, developed at the Montreal Neurological Institute, that were sensitive to left or right frontal temporal, or parietal function. A group of 30 medicated, schizophrenia patients displayed significantly lower performance IQs (but no significant difference on the verbal scale), than those of the

matched controls; this being suggestive of some deterioration after the onset of illness, as verbal intelligence is a good indicator of premorbid functioning.

According to Ang and Tan, FEP patients show a statistically significant decline in cognitive performance, as measured by academic tests, up to 4 years prior to the onset of significant symptoms, especially in the area of more 'fluid' mathematical skills[121]. In a sample of 70 patients, one study found a significant drop, and difference from control subjects, between the ages of 13 and 16 years (grades 8 through 11) in performance on the Iowa Tests of Basic Skills[122]. Considerable impairments in sports, and handicrafts, were also found in children who develop schizophrenia, and are thought to be indicative of subtle motor deficits[123]. These deficits precede the onset of psychosis, and are believed to be a significant predictor of future illness. After the FEP, two groups emerge: those that have a decline in cognitive ability during the initial 3 to 5 years; and a group demonstrating progressive decline and 'dementia' suggestive of a neurodegenerative process.

This intellectually deteriorated group, accounting for roughly 50% of patients, display impairments of attention, memory, executive function, and oculomotor speed, in addition to intellectual decline, and display an increased frequency of delusions[117]. A recent study by Devinsky implied bifrontal lesions and right hemispheric lesions, with subsequent left hemispheric overactivity, in the development of delusions[124].

Cognitive impairment in First Episode Psychosis

There is ample evidence favoring the association of cognitive impairment with acute illness and the first psychotic episode[21]. These deficits appear to be specific cognitive disruptions which either ameliorate with improvement in primary clinical symptoms, or follow a more progressive course. IQ discrepancies between affected and unaffected twins, favoring the unaffected twin by ten IQ points, have been reported[125]. In a sample of 37 FEP patients, all with prior exposure to medication, a broad range of neuropsychological deficits were reported. Subjects performed 1 to 3 standard deviations below controls on measures of attention, abstraction, memory and learning[77]. These findings were subsequently confirmed in studies by Mohamed et al.[126] and Bilder et al.[21].

Mesholam-Gately et al. published a meta-analysis of 47 publications (1994-2008), on neurocognitive impairment in 2204 FEP patients, representing findings from 14 different countries. FEP patients showed statistically significant impairments in all domains (verbal memory, nonverbal memory, processing speed, working memory, attention and vigilance, language, visuospatial abilities, generalized cognitive abilities, executive functioning, social cognition, and motor skills), with standard Z-scores of 6.48-21.21 ($p<0.001$). The meta-analysis revealed that FEP groups performed significantly worse than controls, the standard mean difference (SMD) being 1.2 (verbal memory) to 0.64 (motor skills). Fifteen of the included studies

incorporated measures of ‘general cognitive ability’ which generated a large SMD of -0.91 (FEP group vs. controls)[127].

Results of a five year study of 42 FEP patients reported some improvement on measures of language and executive functions, but a mild decline in verbal memory[128]. The majority of test scores of 20 FEP patients, evaluated at index hospitalization and at a four year follow up, showed no significant change; yet, test results for concentration, speed and overall global functioning resulted in some improvement[129]. However, in a subgroup of older patients with a lifetime history of early onset of illness and poor functional outcome, prominent cognitive impairments resembling dementia have been reported on[130].

A qualitative review of 11 full reports which focused on assessment of cognition in FEP, and schizophrenia-spectrum disorders at initial presentation, and with follow-up periods of up to 5 years, indicated that FEP patients at presentation for treatment often exhibited compromised cognitive functioning, particularly in the domains of verbal learning and memory, psychomotor speed and attention. Furthermore, FEP patients performed significantly better than patients with a longer duration of illness. Longitudinal studies of FEP reported that cognitive functioning generally remained static, with limited change in performance over the first few years of illness[131].

Cognitive impairment in chronically ill patients

Neurocognitive impairments appear to be an enduring feature of schizophrenia. However, results relating to cognitive changes in chronically ill patients remain contradictory. The studies of Saykin et al.[77], and Stirling et al.[19] substantiated greater cognitive impairment in chronically ill patients vs. FEP patients; while cross-sectional studies by Goldberg et al.[132], and Zorilla et al.[133], found no evidence for increased cognitive impairment in association with duration of illness, or increase in age, respectively. Wilson et al. confirmed that IQ does not deteriorate en masse, but rather that working memory and distractibility seems to be the core neurocognitive disturbance present, and underlies the additional cognitive deficits[134]. In a review of ten longitudinal studies into the trajectory of neurocognitive deficits of 834 patients, it was found that overall measures of IQ and gross cognitive status of community-dwelling outpatients with schizophrenia did not show any deterioration (with some improvement being possible over a five year period). However, there appeared to be a marked decline in cognitive functioning (frequently associated with the emergence of orofacial dyskinesia), in middle-aged and elderly patients who are institutionalized[135].

Limitations of the literature

It is clear that there are numerous incongruities between the various studies. Reasons for this include, inter alia: disparities in patient attributes such as age, gender, severity and duration of illness, language, ethnicity;

comorbidity; and prior substance abuse. While the influence of treatment by type and duration of antipsychotics; and differing methods utilized by the researchers, such as size of the sample, longitudinal/retrospective studies, inclusion vs. exclusion criteria, and measurements employed (for example, dissimilar test batteries); are influential and cannot be ignored .

This situation is convoluted by factors that are peripheral to the sample group, and testing methods used. These complexities may be caused by higher levels of education in members of the control groups, and an overlap in sampling when studies are conducted at the same research centers.

In focusing on the limitations of classical neuropsychological testing in schizophrenia, Frith commented that classical testing cannot compare across samples; and that it is founded in studies of patients with circumscribed lesions, whereas the ‘lesions’ appear to be more widespread in schizophrenia[136].

From the above, it is not only commonsense, but also crucial to standardize assessments of testing procedures in order to eliminate as many of the obstructive variables as possible. A standardized and progressive assessment battery will also enable researchers to compare findings across the continents. It was with this in mind, that the NIMH-MATRICS initiative was launched.

The MATRICS Consensus Cognitive Battery (MCCB)

Cognitive deficits are recognized as core features of schizophrenia and are strongly related to social and vocational outcome[23]. Despite evidence for the importance of cognitive impairment in schizophrenia, identification of new pharmacological treatments to address this problem lags behind treatments aimed at the management of positive symptoms. One of the factors delaying the development of effective interventions for the cognitive deficits has been the lack of agreed domains and tests for evaluating cognition in schizophrenia. In an attempt to address this problem, the National Institute of Mental Health (NIMH), under the direction of Wayne Fenton and Ellen Stover, proposed and funded the development of the "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS) initiative in 2001[55]. The contract was awarded to the University of California, Los Angeles, in September, 2002, with Stephen Marder as principal investigator and Michael Green as co-principal investigator. The goals of the MATRICS initiative are to promote the development of novel compounds to enhance cognition in schizophrenia, to catalyze regulatory acceptance of cognition in schizophrenia as target for drug development, to focus the economic research power of industry on a neglected clinical target, to identify promising compounds and to support proof of concept trials[23].

Although pharmaceutical companies have used various batteries as measures of response to treatment in cognitive impairment, the Federal Drug Administration (FDA) was concerned that acceptance of one of these

measures may unduly benefit a specific manufacturer. In 2002, the NIMH initiated this multi-stakeholder (industry, academia and governmental) research process to stimulate development and evaluation of medications targeting cognitive deficits associated with schizophrenia, including the development of an unbiased, standardized assessment which could assist in FDA approval of pharmacological agents[137,138].

During 2003/2004 six consensus-oriented meetings were held. Prior to the first meeting, a pre-conference telephonic survey was conducted according to the RAND Panel Method[139]. Seventy-four experts were invited to partake in the survey, of which 62 experts, together with six members of the Neurocognition Committee, took part in the survey. This survey aimed to identify cognitive targets and test qualities deemed most important in developing a standardized assessment battery. Cognitive targets identified were executive functions, attention/vigilance, memory processes and problem-solving ability. Essential test qualities identified were test-retest reliability, coverage of key individual cognitive constructs and the availability of comparable alternate forms.

A subgroup of the Neurocognition Committee evaluated empirical evidence for separable cognitive performance factors in schizophrenia. To be considered ‘separable’, cognitive domains had to have distinct causes or neural substrates, or at a minimum be distinguishable at statistical or analytical level. These dimensions had to be independent or only weakly correlated with each other and replicated across several studies. There had

to be evidence for these neurocognitive factors in large normal samples and factor analytic studies. Lastly, the factors had to have likely sensitivity to intervention attempts. Thirteen factor analytic studies of cognitive performance in schizophrenia were identified and examined. Sample sizes varied from 34 to 209 participants and some also included patients with psychosis or severe mental disorders other than schizophrenia. Eight domains were identified, based on review of the literature and input from experts: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, verbal comprehension and general verbal ability[140].

During the initial MATRICS consensus conference, “Identifying Cognitive Targets and Establishing Criteria for Test Selection”[23], the establishment of a reliable, valid and consensus-derived method of assessing cognition, and the development of a battery which can be used as a standardized way to assess the effects of cognitive-enhancing agents across clinical trials, were set as goals. More than 130 scientists, representing academia, government and pharmaceutical industry, discussed the findings of the Neurocognition Committee and agreed on the inclusion of the above domains in a hybrid battery, excluding verbal comprehension (due to resistance to change). Furthermore, due to newly developed interest in social cognition, and the view that it functions as an intermediary translating cognitive capacity into functional outcome (as well as preliminary functional neuroimaging data e.g. for facial affect recognition), it was decided to include social cognition as an eighth domain.

Furthermore, five criteria against which to evaluate tests for inclusion in a standardized battery were identified; namely good test-retest reliability, high utility as a repeated measure, relationship to functional outcome, practicality and tolerability. Good test-retest reliability is critical for detecting changes with treatment and translates into statistical power. To be used as a repeated measure, there should be no substantial practice effects and if practice effects are present, then it should be small enough not to create ceiling effects and reduce variability. The availability of alternate forms alleviates this potential problem. Other factors to take into consideration are potential response to pharmacological agents (thus assessing functional outcome), practicality (from the administrator's perspective, e.g. ease of set-up, training, administration and scoring) and tolerability (from the subject's perspective, e.g. length, difficulty and repetitiveness). Participants in the conference nominated 90 cognitive tests that might be used to measure performance in the above domains.

During the second consensus conference, "Neuropsychopharmacological approaches to modulating cognition in schizophrenia: Approaches to identifying promising compounds"[141], the most promising neural system targets for improving cognition in schizophrenia were identified, as well as promising models for use in drug development and identification of current most promising available compounds. A similar process to the first conference was followed (pre-conference telephonic survey, expert panel, etc.). Putative molecular targets identified include the dopamine receptors in the prefrontal cortex (PFC), the serotonin receptors in the PFC and anterior

cingulate cortex, the glutamatergic excitatory synapse, the acetylcholine nicotinic receptors in the hippocampus, the acetylcholine muscarinic receptors, and the brain GABA system[142,143].

Prior to the third conference, “RAND Panels for Evaluation of Candidate Neurocognitive Tests”, the Neurocognition Committee reviewed all of the tests nominated during the first conference according to the five selection criteria. Individual tests with high test-retest reliability and validity and with duration of less than 15 minutes (to limit total duration to 90 minutes) were sought. Thirty-six candidate tests were selected (approximately six per domain). An interdisciplinary panel of experts systematically evaluated the 36 candidate tests according to the RAND/UCLA appropriateness method[144]. The 20 most promising tests were selected for inclusion in the beta version of the battery.

The MATRICS Psychometric and Standardization Study (PASS) followed[145]. During phase one, psychometric properties, practicality and tolerability of these tests were directly compared in a 5-site trial. One-hundred-seventy-six patients (schizophrenia or schizoaffective disorder, depressed type) were assessed at baseline and 167 were assessed 4 weeks later[146]. These patients were clinically with stable Brief Psychiatric Rating Scale (BPRS) ratings less than 4[147]; 86% were using SGAs and 13% FGAs. The mean age

of the sample was 44.0 years (SD=11.2), mean educational level was 12.4 years (SD=2.4) and 75.7% of the sample was male.

Test-retest reliability for most of the tests was good (0.70 or higher). Practice effects were small. No significant ceiling effects were present. Out of 343 test scores, one ceiling and floor score were reached for CPT-IP and 11 floor and 8 ceiling scores for NAB Mazes. The MCCB is therefore suitable to measure cognitive changes over time. Alternate forms available (HVLT-R, BVMT-R and NAB Mazes) were also comparable and may also help to limit the magnitude of any potential practice effects. Seven-point Likert scales were used to assess practicality and tolerability of each test. From these results, committee members cast votes and a final battery of ten tests was selected (see table 3.1).

Table 3.1 Tests included in the MCCB					
Cognitive Domain	**Test**	**Description**	**Primary score**	**Test-retest reliability over a four week period**	
				Pearson product-moment correlation (r)	**Intraclass correlation coefficient (ICC)**
Speed of Processing	Brief Assessment of Cognition in Schizophrenia (BACS)[148]: Symbol-Coding	Timed paper-and-pencil test in which respondent uses a key to write digits that correspond to nonsense symbols	Total number correct	0.85	0.85
	Category Fluency (Fluency) [149]: Animal Naming	Oral test in which respondent names as many animals as possible in 1 minute	Total number of animals named in 1 minute	0.74	0.74
	Trail Making Test (TMT)[150]: Part A	Timed paper-and-pencil test in which respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper	Time in seconds to completion	0.77	0.75
Attention/ Vigilance	Continuous Performance Test- Identical Pairs (CPT-IP)[151]	Computer-administered measure of sustained attention in which respondent presses a response button to consecutive matching numbers	Mean d-prime value across 2-, 3-, and 4-digit conditions	0.84	0.84
Working Memory (nonverbal)	Wechsler Memory Scale – Third Edition (WMS-III)[152]: Spatial Span	Using a board on which 10 cubes are irregularly spaced, respondent taps cubes in same (or reversed) sequence as test administrator	Sum of raw scores on forward and backward conditions	0.74	0.74

(verbal)	Letter-Number Span (LNS)[153]	Orally administered test in which respondent mentally reorders strings of number and letters and repeats them to administrator	Total number correct	0.81	0.78
Verbal learning	Hopkins Verbal Learning Test-Revised (HVLT-R)[154]	Orally administered test in which a list of 12 words from three taxonomic categories is presented and the respondent is asked to recall as many as possible after each of three learning trials	Total number of words recalled correctly over 3 learning trials	0.69	0.68
Visual Learning	Brief Visuospatial Memory Test-Revised (BVMT-R)[155]	A test that involves reproducing six geometric figures from memory	Total recall score over three learning trials	0.71	0.71
Reasoning and problem solving	Neuropsychological Assessment Battery (NAB)[156]: Mazes	Seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning	Total raw score	0.83	0.83
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT™)[157]: Managing Emotions	Paper-and-pencil multiple-choice test that assesses how people manage their emotions	Branch score using general consensus scoring	0.73	0.73

Adapted from MCCB Manual[158].

This final version of the MCCB was unanimously approved by the NIMH Mental Health Advisory Council in April 2005, and it was subsequently also accepted by the FDA's Division of Neuropharmacological Drug Products. T(TMT)[150]he primary use for the MCCB is in clinical trials of potential cognitive-

enhancing drugs for schizophrenia and related disorders, and to act as reference battery in basic studies of cognition in schizophrenia.

The final step in the development of the MCCB was the standardization and co-norming of the battery (PASS phase 2). Co-norming of a hybrid test (a battery made up from separately developed tests) is essential as normative reference samples for the individual tests may vary considerably in size and composition. For valid interpretation, collecting normative data on the battery as a whole (to determine base rates of test score differences, variance in test scores, and covariance amongst tests) is important. Such norms facilitate communication of information across studies, combination of test scores as composite scores, and construction of cognitive profiles across different cognitive domains.

During this part of the study, normative data was collected at five different sites, representing different geographical areas in the United States, from 300 healthy community subjects, recruited according to a scientific sampling method. Stratification was done by age, gender and education. Age was chosen as the primary stratification measure as age-related effects are fairly large on cognitive tests. The genders were represented on a 1:1 basis. Summing of T-scores of individual tests and subsequent standardization of the sums to T-scores yielded domain scores with a mean of 50 and SD of 10. The T-scores of the different domains scores obtained by the 300 individuals in this study were summed to yield a Cognitive Composite Score,

and the mean and SD of this sum was then computed. Then, the T-scores for this Cognitive Composite Score were computed, with the usual mean of 50 and SD of 10.

Lower cognitive performance was associated with increasing age and lower education. Verbal learning showed no age-related effect. Younger subjects performed better than older subjects only on social cognition scores. Significant differences between men and women were present. Men performed better than women in reasoning and problem solving and working memory, while women out-performed men on verbal learning tasks. No stratification for ethnicity was done. Seventy-six percent of the subjects were white, 18% African American, and 2% Asian. Subsequent to this phase of the PASS study, a computerized scoring program was developed, with age and gender correction as a default scoring option[159].

Further conferences during 2004 included the “Workshop on Clinical Trial Design” (a multi-stakeholder conference held to develop guidelines for the design of clinical trials of cognitive-enhancing drugs), “FDA-NIMH-MATRICS Workshop on Clinical Trial Designs for Neurocognitive Drugs for Schizophrenia”[160] and “New Approaches to Assessing and Improving Cognition in Schizophrenia”[161].

In the years since its development, the MCCB has gained wide acceptance as the ‘gold standard’ for measuring cognitive deficits in patients with

schizophrenia and is now used in many centers and studies across the world.

Conclusion

There is a clear consensus that cognitive impairment is a core feature of schizophrenia. The deficit profile is broad, severe, and is likely to be present in the majority (if not all) patients. Cognitive impairments have been demonstrated in patients before the onset of other clinical features[162,163]; with first degree relatives without any psychotic features demonstrating similar deficits, suggesting that there might be a genetic vulnerability to schizophrenia[89]. Individuals at high risk for the development of psychosis, nevertheless, do not demonstrate the levels of cognitive impairment typically found within and beyond the FEP.

Cross-sectional studies have confirmed the presence of cognitive symptoms throughout the course of schizophrenia irrespective of duration, chronicity and compliance with medication, though chronicity tends to be associated with a greater magnitude of impairment. Cognitive deficits consequently appear to be ‘fixed’, pre-existing risk factors, rather than the result of harmful medication-related effects, or succession of the illness[164]. For that reason, early intervention may reduce cognitive deficits; thereby preventing, lessening the severity, or delaying the onset, of psychosis. Neurocognitive impairment has clear clinical relevance, and impacts adversely on a patient’s

day-to-day life in areas such as social interaction, schooling, employment prospects, and the desire to live.

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CHAPTER 4

TREATMENT OF SCHIZOPHRENIA

Antipsychotic medication has formed the basis for the treatment of schizophrenia for the past 60 years[1]. It is used in acute phase treatment, long-term maintenance[2], as well as for relapse prevention[3].

In the acute phase of a psychotic episode, the specific treatment goals are to prevent harm, control disturbed behavior, suppress symptoms, effect a rapid return to the best level of functioning, develop an alliance with the patient and family, psycho-education, formulation of treatment plans, and the establishment of aftercare services[4].

A therapeutic effect is usually evident within 1-3 weeks of treatment during an acute psychotic episode, with most improvement occurring within 6-8 weeks of starting treatment[5]. However, recent evidence for an earlier onset of action[6] has emerged; with indications that a lack of symptoms reduction by one week of treatment may possibly be a precursor to later non-response[7].

The review by Baldessarini et al. of 44 placebo-controlled studies of antipsychotics, totaling 3 939 subjects, with an average follow-up period of 9.8 months, found prolific evidence that conventional agents minimize the risk of relapse in positive symptoms of schizophrenia; a 14% rate of symptom aggravation on active medication (mean daily dose of 397

chlorpromazine equivalents) compared to 55% on placebo; thereby illustrating a 3.9-fold sparing of relapse accredited to medication[8].

First generation ("typical") antipsychotics

First generation antipsychotics (FGAs) achieve their antipsychotic effect by the highly selective blockade of D_2 receptors in the mesolimbic areas[9,10].

The efficacy of FGA medications in reducing psychotic symptoms in acute schizophrenia was first documented by Guttmacher in 1964. This landmark study found that 60% of patients treated with an FGA for an acute psychotic episode had a near complete resolution of acute positive symptoms, over a six week trial of treatment, compared to 20% of patients treated with placebo[9]. Reviews of randomised control trials (RCTs) have subsequently confirmed the superiority of FGAs compared to placebo[8,11]. In the treatment of psychosis all FGAs are equally effective, with the exception of mepazine and promazine. However, there are differences in therapeutic effect with regard to dose, potency and side effects of these medications[12].

Most of the positive symptoms of schizophrenia are adequately treated with FGAs. In a review of five large comparative studies of an antipsychotic vs. placebo, Klein and Davis found that patients assigned to an antipsychotic experienced a reduction in positive symptoms with a secondary decrease in negative symptoms[13].

Unfortunately, FGAs display side-effects ascribable to dopamine blockade in the tubero-infundibular, nigrostriatal and mesocortical pathways, as well as from effects on other neurotransmitter systems. Adverse neurological effects include extrapyramidal side-effects (EPSEs) such as dystonic reactions (10%)[4], parkinsonism (20%)[14], and akathisia (24%)[15]. Tardive dyskinesia (TD) was found to be present in 5% of patients with schizophrenia prior to initiation of treatment with an antipsychotic, rising to 20% during treatment[16]. Neuroleptic malignant syndrome (NMS), a rare life-threatening disorder, presents in 0.01-0.02% of patients[17], and has a 10% mortality rate[18]. Non-neurological side-effects include hyperprolactinaemia, reduced seizure threshold, postural hypotension (related to α_1-receptors), and anticholinergic side-effects (which may impact negatively on cognitive functioning)[19].

Side-effects depend on drug potency. High potency drugs have a stronger affinity for dopamine receptors than low potency drugs. Drugs with higher potencies (i.e. haloperidol and fluphenazine), have a higher risk of EPSE, moderate risk of sedation, low risk of anticholinergic side-effects, and low risk of anti-adrenergic side effects[20]. Low potency drugs, such as chlorpromazine and thioridazine, have a lower risk of EPSE, but are associated with more anticholinergic and anti-adrenergic side-effects[21].

In recent times, RCTs with FGAs have focused on establishing dosing strategies to determine the most effective dose range, i.e. where optimal

therapeutic response is obtained, while the appearance of side-effects are limited.

When administered judiciously, FGAs have proven to alleviate comorbid depression[22-24], whereas increased risk of dysphoria and EPSE are synonymous with higher doses[14,23]. A number of studies suggest that moderate doses of FGAs are as effective, if not more so, than higher doses[25-27].

The World Federation of Societies of Biological Psychiatry (WFSBP) recommend the following initial target doses in FEP: chlorpromazine 300-500mg/d po, fluphenazine 2.4-10mg/d po, flupenthixol 2-10mg/d po, haloperidol 1-4mg/d po, perphenazine 6-36mg/d po, pimozide 1-4mg/d po and zuclopenthixol 2-10mg/d po[28].

FGAs have proven to be effective in preventing psychotic symptoms in long-term treatment, as well as reducing the risk for relapse[29]. Forty to sixty percent of patients with a FEP, who discontinued treatment, relapsed within one year[20,30-33] compared to a relapse rate of only 30% in patients continuing treatment[34].

Second generation (“atypical”) antipsychotics

Second generation antipsychotics (SGAs) were developed to address the relative inefficacy of FGAs in the treatment of the cognitive and negative symptoms (with ongoing functional impairments) of schizophrenia; and to do

so without causing the severe side-effects (e.g. EPSE, and dysphoria) associated with their first generation predecessors.

The antecedent SGA, clozapine, was introduced in 1990. Kane et al. demonstrated clozapine to be more effective than chlorpromazine in the management of treatment resistant schizophrenia, with 30% of the clozapine treated patients having a response in positive symptoms, vs. only 4% of those treated with chlorpromazine[34]. However, clozapine carries five black box warnings and is associated with risks such as agranulocytosis[35,36], myocarditis[37], seizures[36], gastrointestinal hypomotility[38], hyperglycemia and weight gain[39]. This led to the development of other drugs with pharmacological profiles different from those of the FGAs. These so-called SGAs were supposed to be “clozapine-like” in their effects, without the severe and potentially life-threatening side-effects of clozapine. A number of SGAs were introduced over the last two decades, including risperidone, olanzapine, quetiapine, ziprasidone and others[20,40].

SGAs interact with a wider variety of neurotransmitter receptor types than do FGAs, and differ from one another in receptor interaction, selection, and affinity. It is hypothesized that these variables in receptor activity account for differences in the efficacy, safety, and tolerability of these drugs, and their assumed superiority over typical medications[41].

The concept of 'atypicality'

Pharmacologic tests employed in animals for predicting the antipsychotic effects of drugs in humans investigate the ability of a drug to: 1) block the action of dopamine (DA), thereby causing catalepsy, as a predictor of EPSE in humans, and 2) the blockade of a conditioned avoidance reaction, as predictor of antipsychotic effect in humans[42], and 3) the ability to counteract *d*-amphetamine locomotor stimulation and stereotypy in rats[43,44]. Until recently, it was thought that both cataleptic potential and blocking of a conditioned avoidance reaction in animals was necessary for predicting antipsychotic action in humans. However, data emerged which confirmed the ability of drugs such as clozapine and olanzapine, to block conditioned avoidance in animal experiments, without causing catalepsy[45,46]. This led to the initial view of 'atypicality' as a compound with antipsychotic effect, in the absence the emergence of EPSE.

Atypicality was further expressed as being highly selective for D_2 receptors in mesolimbic areas and, in relative terms, free of adverse effects relating to increased prolactin levels and motor skill side-effects. However, this hypothesis is not entirely accurate as studies have shown that atypicals, such as risperidone, administered in higher doses cause side-effects that include tardive dyskinesia, hypotension, impotence and hyperprolactinaemia[19,47]. Furthermore, the SGAs were also shown to be excitatory at D_1 receptors, and inhibitory at receptors D_3 and D_4[48,49]. Despite their low striatal binding, clozapine and quetiapine occupy a significant

proportion of temporo-limbic D_2/D_3 receptors[65,66]. As illustrated by PET studies, these two compounds never achieve more than the 80% occupation of striatal D_2 receptors needed to cause EPSE[50].

In contrast to the dopaminergic hypothesis of schizophrenia, Carlsson and Carlsson proposed an alternative dopamine deficit hypothesis, whereby a primary defect in dopaminergic synaptic transmission occurs, causing feedback activation, DA receptor upregulation, and therefore increase in dopaminergic tone[51]. Synaptic dopaminergic neurotransmission is responsible for tonic dopaminergic action, while extrasynaptic dopaminergic transmission is phasic, and associated with the appearance of positive symptoms in psychosis[52-54]. Whereas dopamine transmission in the cerebral cortex is predominantly extrasynaptic, the opposite is true for the striatum where the D_2 receptor-mediated transmission is primarily synaptic[55,56].

Typical antipsychotics (FGAs) block synaptic, as well as extrasynaptic dopamine neurotransmission, thereby relieving psychotic symptoms, yet through this action, also induces a hypodopaminergic state in the striatum (that causes EPSE), as well as in the cortex (causing a worsening of negative and cognitive impairments). Conversely, SGAs have their principal effect on extrasynaptic dopaminergic neurotransmission with occupancy of extrasynaptic DA receptors by SGAs nearly equal to that of FGAs, thereby alleviating psychotic symptoms. However, lower occupancy of synaptic receptors by SGAs could possibly explain their low association with EPSE and other adverse effects[50,57].

Yet another theory of atypicality, the dopamine-serotonin hypothesis[58], is that SGAs block serotonin type 2A ($5HT_{2A}$) receptors simultaneous to D_2 blockade (high $5HT_2$:D_2 receptor blocking ratio). In this scenario serotonin and DA levels are balanced, and this assigns “atypicality”. In SGAs, with a high affinity for D_2 receptors, such as risperidone, $5HT_{2A}$ antagonism appears to protect against EPSE at moderate doses. However, this preservation is lost at striatal D_2 receptor occupancies exceeding the 80% limit[59,60]. Antagonism of the $5HT_{2A}$ receptors on the soma of dopaminergic neurons, in the ventral tegmental area (VTA), boosts the output of dopaminergic receptors, and their projections to the PFC. This has been proposed as the model by which SGAs improve cognitive deficits. However, this hypothesis has been refuted in studies including those of Kapur et al.[61], and Trichard et al.[62]. Antipsychotics such as sulpiride and amisulpride have no $5HT_{2A}$ antagonism activity, yet they are known to improve negative and cognitive symptoms of schizophrenia. It therefore seems that serotonergic action does not distinguish between typicals and atypicals[57,63].

According to Kapur et al., the single most powerful predictor of atypicality is the low affinity to, and fast dissociation from the D_2 receptor, and not its high affinity for any other receptor, including $5HT_{2A}$, and D_4[61]. The physiologically functional state of the dopamine receptors is the high-affinity state (D_2 high)[64], with a dissociation constant (K_i) of 1.75 nM (nanomoles of dopamine per liter of water)[57]. FGAs have K_is lower than 1.75nM. This means FGAs have a higher affinity for, and are more tightly bound to D_2 receptors than DA. SGAs have K_is higher than 1.75nM, therefore a lower affinity and bind

more loosely to D_2 than DA[57]. In other words, SGAs 'hit and run'; the so-called 'fast-off-D_2' theory[65]. This 'fast off' action, demonstrated by agents such as quetiapine and clozapine, is a rapid molecular event in which the drugs are continually going on and off the D_2 receptor[65], thereby allowing endogenous dopamine relatively unhindered access to the receptor[57].

Most SGAs, even those with higher K_is, can still 'out-compete' DA[66], thereby causing dose-dependent EPSEs[59]. From the equation $C_{50\%} = K_i \times [1+D/D_2 \text{ high}]$‡ , it can be determined that, to effectively occupy 75% of the D_2 receptors, the concentration of an antipsychotic drug needs to be approximately 3 times greater than is required to occupy 50% of receptors, and is essentially identical to the therapeutic levels of antipsychotic drugs[57]. This would explain the relatively "lower doses" of FGAs producing EPSE and antipsychotic efficacy vs. relatively "high doses" of SGAs. However, clozapine, quetiapine and remoxipride have K_is higher than 20nM and come off the D_2 receptor sufficiently fast to allow DA access to the receptor, therefore virtually never causing adverse neurological side-effects[65].

The International Early Psychosis Association Writing Group[68] estimated appropriate initial target doses for most patients as risperidone 2mg/day or olanzapine 7.5–10mg/day, to which two thirds of patients achieve a good response with regard to reduction in positive symptoms within three weeks of the initial dose. The WFSBP furthermore recommends the following initial target doses in FEP: amisulpride 100-300mg/d po, aripiprazole 15mg/d po,

‡ Where $C_{50\%}$ is the therapeutic concentration needed to block 50% of DA receptors in the presence of DA, D is the DA concentration in the synaptic space, and D_2 high is the dissociation constant of DA at the high affinity state of the D_2 receptor.

quetiapine 300-600mg/d po, ziprasidone 40-80mg/d po and zotepine 50-150mg/d po[28].

Second Generation Antipsychotics in the treatment of psychosis

A meta-analysis of nine placebo-controlled trials evaluating the efficacy of risperidone, quetiapine and olanzapine, calculated the combined effect size across 15 therapeutic dose arms for an *a priori* categorical response rate, as determined by the authors, as 0.46 (SE 0.06) and for the continuous outcome measure, the Brief Psychiatric Rating Scale (BPRS) >0.53 (SE 0.07). These results indicated that SGAs, administered in therapeutic doses, are superior to placebo[69].

Leucht et al. in a systematic review and meta-analysis of 38 RCTs (N=7323) that compared SGAs with placebo, confirmed that SGAs were more efficacious than placebo, but the pooled effect size for overall symptom reduction was moderate (-0.51). The number needed to treat (NNT) was 6, with a 24% placebo response rate, vs. a 41% response rate to SGAs. They further reported that aripiprazole, olanzapine, ziprasidone and zotepine reduced the relapse risk significantly more than placebo during 6-12 months of treatment. The relative risk (RR) for relapse for the SGAs combined was 0.4l (CI: 0.28 to 0.59), while the risk difference (RD) between the SGAs and placebo was 0.20 (CI: -11 to -30), translating to a NNT of 5 ($p<0.0001$)[70]. This is in agreement with an older review on relapse on maintenance

treatment over a period of 9.7 months, documenting substantially lower cumulative relapse rate of 16% in the antipsychotic group compared with 53% in the placebo group[71].

In another meta-analysis evaluating the efficacy of SGAs, 78 head-to-head comparison studies of SGAs, with 178 relevant arms, and 13 558 participants, were examined. Olanzapine proved superior to aripiprazole, quetiapine, risperidone, and ziprasidone. Risperidone was more efficacious than quetiapine and ziprasidone, while clozapine proved superior to zotepine, and in doses >400 mg/day, more efficacious than risperidone[72].

SGAs differ in a number of properties; such as cost, pharmacology, efficacy, and side-effects; and cannot be categorized as a homogeneous class[73]. Therefore, some side-effects are more problematic with the use of some SGAs, but not others. Side-effects include, but are not limited to:

- Metabolic side-effects such as weight gain (especially with clozapine and olanzapine)[74]; dyslipidemia[75], and hyperglycaemia[76].
- Dose-dependent EPSE, such as with risperidone[77].
- Hyperprolactinaemia, which is associated with all antipsychotics especially risperidone[78].
- Prolongation of the QTc time, as with ziprasidone[79]; and
- Sedation, as documented with clozapine and quetiapine[80,81].

Comparing FGAs and SGAs

The American Psychiatric Association (APA) practice guidelines state “The second-generation antipsychotics should be considered as first-line medications for patients in the acute phase of schizophrenia, mainly because of the decreased risk of extrapyramidal side effects and tardive dyskinesia, with the understanding that there continues to be debate over the relative advantages, disadvantages, and cost-effectiveness of first- and second-generation agents” (pg 590)[82].

Meta-analyses have supported the idea that some of the SGAs may have a modest advantage in short term efficacy, decreased EPSE liability and relapse prevention over one year, in comparison with FGAs[83].

In a systematic review and meta-regression analysis of 52 RCTs, including 12 649 participants, substantial heterogeneity was observed when comparing SGAs to FGAs. However, these results were dose-related with evidence that the use of SGAs in doses equivalent to haloperidol 12mg/d, did not display any benefits above FGAs with regard to efficacy or overall tolerability, except for causing less EPSE[84].

In a meta-analysis by Davis et al. of 142 controlled studies (124 RCTs comparing the efficacy of FGAs to SGAs, N=18272 and 18 studies of SGAs, N=2748), the effect sizes for clozapine, amisulpride, risperidone and olanzapine were highly statistically significant with; 0.49 (0.32-0.67), 0.29

(0.16-0.41), 0.25 (0.18-0.33), and 0.21 (0.14-0.28), respectively. However, other SGAs were not significantly more efficacious than FGAs. This finding was different from that of Geddes et al.[84] and concluded that at least some SGAs are more efficacious than FGAs and, therefore, that SGAs are not a homogeneous group[85].

However, another meta analysis of 31 studies, totaling 2 320 patients, comparing SGAs with low-potency FGAs found that; as a group, SGAs were moderately more efficacious than low-potency antipsychotics, irrespective of the comparator doses used. Low-potency FGAs in doses less than 600mg/day chlorpromazine equivalents (CPZE) did not induce more EPSE than SGAs[86].

In their updated treatment recommendations of 2003, the Schizophrenia Patient Outcomes Research Team (PORT), concluded that there was no evidence to support the use of SGAs above FGAs in the treatment of positive and negative symptomatology[87]. Although SGAs have been shown to be superior to FGAs in the treatment of negative symptoms, the magnitude of the effect was deemed not to be clinically significant[88]. SGAs' reduced liability for EPSE was only clear if doses used were less than 12mg haloperidol equivalents, while at these lower doses, efficacy between the SGAs and FGAs was similar. Furthermore, in a year-long, double-blind, RCT in 309 patients with schizophrenia or schizoaffective disorder, who were ill for at least 2 years, olanzapine 5-20mg/d did not demonstrate significant advantages compared with haloperidol 5-20mg/d po with regard to

compliance, symptoms, extrapyramidal symptoms, or overall quality of life. Whereas olanzapine showed benefits in reducing akathisia and improving memory, this came at a trade off, with more weight gain and higher cost[89].

Most of the trials suggesting superiority for SGAs were short term efficacy trials that utilized specifically selected test subjects, and received industry sponsorship. It is possible that some of these trials were therefore biased in favor of SGAs. Subsequently, deliberation on the efficacy and effectiveness of SGAs, as well as costliness and side-effects, led to the inception of two NIMH funded trials, namely CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness)[90] and CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study)[91]. These studies were conducted to test the widespread notion of SGAs as being generally superior to FGAs[92].

CATIE is the most comprehensive RCT ever conducted in chronic schizophrenia, spanning 18 months, and including 1460 patients[90,93]. Patients were randomized to either the FGA perphenazine, or one of four SGAs (risperidone, olanzapine, quetiapine, or ziprasidone)[94].

A 74% all cause discontinuation rate (ACDR) across the spectrum of the antipsychotics used was reported; with suboptimal efficacy and intolerability largely responsible for 1052 patients discontinuing treatment during phase 1 of CATIE. Of this number, 444 took part in a double-blind study comparing the efficacy of ziprasidone olanzapine, quetiapine, and risperidone

('tolerability pathway')[94]; and 99 participated in an open-label study with clozapine, or blinded treatment with clozapine, or quetiapine or risperidone ('efficacy pathway')[92]. Results of these two studies showed quetiapine and ziprasidone to be less effective than olanzapine and risperidone[95]; and that clozapine is more efficacious than either quetiapine, or risperidone[93].

Overall CATIE concluded that all of the drugs were similar in efficacy and SGAs did not prove superior to perphenazine with regard to symptomatic response[96], cognition[97], cost[96], quality of life[98], nor psychosocial functioning. Perphenazine was determined to be the least costly option[96]. However, various criticisms of CATIE were raised. Suboptimal dosing of quetiapine, ziprasidone, and, possibly, risperidone in comparison to olanzapine may have favored the latter[99]. Leucht et al. furthermore suggested that the haloperidol group might have been at a disadvantage[100]. Participants might have received medication on which they had a suboptimal response to in the past. This could have biased results against the efficacy of haloperidol and also increase dropout rates in this group. In patients only moderately ill, and relatively stable on current treatment at baseline, a change in treatment could cause destabilization of patients with exacerbation of their symptoms[101].

Participants who were discontinued from perphenazine in the first phase of CATIE had a relatively poor outcome if they were randomized to risperidone in phase 2, possibly due to similarities in receptor binding profiles of the drugs. The presence of EPSE or TD was previously found to be associated with a more severe and less treatment responsive illness[102]. Therefore,

controlling for TD, where 231 patients with TD were assigned to SGAs and not FGAs, may also account for the lack of difference in effectiveness between FGA and SGAs in the study[103].

CUtLASS, a 12 month open-label trial, compared the effectiveness of SGAs to FGAs. In phase 1, a sample of 227 patients with schizophrenia, displaying poor response, or experiencing side-effects, to current medication were assigned by the treating clinician to receive one of 4 depot or 7 oral FGA preparations (n= 118); or to one of 4 SGAs (risperidone, olanzapine, quetiapine or amisulpride; n= 109). The trial concluded that no significant difference between the FGA and non-clozapine SGA groups was found in either symptom improvement or quality of life[91,92,94,104].

The second phase of CUtLASS included 136 subjects with poor response to 2 or more antipsychotic agents. These subjects were randomized to either clozapine or one other SGA. Results indicated clozapine to be significantly superior in symptom improvement, fewer total adverse side-effects, and a definitive trend toward superiority in quality of life[105]. Criticism of CUtLASS included arguments relevant to the heterogeneity amongst both FGAs and SGAs that may have lessened the statistical power to distinguish between the two groups[106]; and that administration of depot preparations equated to higher patient compliance to treatment and, subsequently, improved outcome[107].

In both CATIE and CUtLASS, the difference of efficacy between FGAs and SGAs was found to be minimal, leading Swartz et al. to conclude that FGAs are as efficacious, and more cost effective, than SGAs[104]. Following on this Leucht et al. conducted a meta-analysis of 150 double-blind studies (N= 21 533), comparing nine SGAs with FGAs for overall efficacy, tolerability and outcome. Amisulpride, clozapine, olanzapine, and risperidone displayed better overall efficacy than did FGAs, with small to medium effect sizes. However, the remaining SGAs did not prove to be more efficacious than FGAs. Individual and class differences among the FGAs and SGAs were noted in relation to side-effects: SGAs caused fewer extrapyramidal side-effects than did haloperidol, even at haloperidol doses of less than 7.5mg/d; whereas no significant differences were recorded in EPSE between low-potency FGAs and SGAs. Criticism of this study pointed out that, while it is known that mid-potency FGAs are less likely to cause EPSE, haloperidol was used as the comparator drug in most of the studies, thereby raising the question of potential bias against FGAs[73].

It is evident that neither FGAs, nor SGAs, are homogenous classes: members of each class differ in mechanism of action, tolerability, efficacy, and cost. As such, antipsychotic treatment should be individualized from patient to patient.

Treatment of First Episode Psychosis

During the past two decades, increasing attention has been given to early intervention in the management of FEP.

The first treatment guidelines specifically differentiating between the treatment of FEP patients vs. multiple episode patients, was the recommendation by PORT which stated that antipsychotic medications, other than clozapine, should be used as first-line treatment for the control of positive symptoms in patients experiencing an acute psychotic episode. They recommend choice of medication to be made on the grounds of patient acceptability, prior individual drug response, individual side-effect profile, and long-term treatment planning[108]. This view is supported by the International Early Psychosis Association Writing Group[68] and the Expert Consensus Guidelines[109].

Patients with FEP generally respond better to antipsychotic agents than those who have had multiple episodes[110]. In a study at Zucker Hillside Hospital, Robinson et al. treated a sample of 118 FEP patients (mean duration of untreated illness 143 weeks, DUP 71 weeks) with a standardized treatment algorithm until they responded. The sequence of medications received was as follows: fluphenazine, haloperidol, haloperidol plus lithium, either molindone or loxapine, and clozapine. By one year 87% of the participants have responded, with a median time to response of nine weeks[111]. However, after five years, only 47.2% of the patients achieved

symptom remission, while 25.5% had adequate social functioning for two years or more[112]. Only 13.7% of subjects in this study met full recovery criteria[113].

The dose of FGA needed to achieve remission in FEP patients is typically lower than in chronically ill patients (with regard to positive symptoms). Lower doses also have fewer side-effects[114,115]. The same holds true for SGAs such as risperidone[35]. In the “Practice Guidelines of the Treatment of Patients With Schizophrenia”, the APA, recommends that FEP patients should receive doses measuring approximately half of that used in chronically ill patients[4].

A placebo-controlled study by Crow et al. of 120 subjects with FEP has shown that when no prophylactic treatment is given, 62% of FEP patients relapsed within one year[31]. Robinson et al. followed 104 FEP patients over a period of five years and concluded that discontinuing antipsychotics increase the risk for relapse five fold[116]. Gitlin et al. found that withdrawing antipsychotic treatment led to a relapse rate of almost 78% after one year without medication, and 96% after two years[30].

In the Comparison of Atypicals in First Episode (CAFE) study, 400 FEP patients were randomly assigned to olanzapine (2.5-20mg/d), quetiapine (100-800mg/d), or risperidone (0.5-4mg/d) as part of a 52-week, randomized, double-blind, flexible-dose, multicenter (United States and Canada) study[117,118], with an ACDR of 70.25%. In this study, the number of

patients who discontinued treatment against medical advice (n= 115) was compared to the number of patients that completed the study (n= 119). Higher cognitive performance at baseline, being of Black ethnic origin, ongoing substance abuse, the presence of ongoing depressive symptoms, and poor treatment response, were associated with lower medication adherence. Furthermore, metabolic side-effects were investigated as a secondary outcome measure. Of the 400 patients recruited, 31% were overweight and 18% were obese at baseline, with 4.3% patients meeting criteria for metabolic syndrome. Treatment-emergent metabolic syndrome was reported in 13.4% of patients after 52 weeks of treatment – this being more common in participants who received olanzapine, while risperidone caused the least metabolic side-effects of the three SGAs examined.

The most recent large multicenter study, the European First Episode Schizophrenia Trial (EUFEST), compared the effectiveness of SGAs with that of a low dose of haloperidol, in 498 FEP patients. FEP patients between the ages of 18 and 40 years, and with minimal exposure to previous antipsychotics, were randomly assigned to one year of open-label treatment with either haloperidol (1-4mg/d), amisulpride (200-800mg/d), olanzapine (5-20mg/d), quetiapine (200-750mg/d), or ziprasidone (40-160mg/d). The primary outcome measure was all cause treatment discontinuation, which was 41.57% within 12 months. Patients treated with haloperidol had the highest discontinuation rate (n= 63; 72%), followed by quetiapine (n= 51; 53%), ziprasidone (n= 31; 45%), amisulpride (n=32; 40%), and olanzapine (n= 30; 33%). Comparisons with haloperidol showed a higher likelihood for

≥50% response with amisulpride (hazard ratio [HR] 2.27; 95% CI 1.51-3.42), olanzapine (HR 2.07; CI 1.38-3.10), and ziprasidone (HR 1.62; CI 1.02-2.56); and a better chance for remission on amisulpride (HR 2.49; CI 1.43-4.35), olanzapine (HR 2.58; CI 1.48-4.48), quetiapine (HR 1.96; CI 1.06-3.64), and ziprasidone (HR 2.03; CI 1.07-3.87). Although proportions of response and remission were higher for most SGAs as compared to haloperidol, symptom reductions were similar (approximately 60%). Furthermore, discontinuation rates were not necessarily consistent with symptomatic improvement[119-121].

Care of patients with FEP has come to be a multimodal, multi-disciplinary approach, with psychosocial, as well as pharmacological interventions[122]. The aim of treatment is to reduce the frequency, duration and severity of episodes, reduce the overall morbidity and mortality of the disorder, and improve psychosocial functioning, and quality of life.

The road forward…

With increased concerns over the safety and efficacy of currently available drugs, there is a considerable need for the research and development of novel agents. The first to claim recognition as a 'third generation antipsychotic' (TGA) is aripiprazole; developed as a DA stabilizer with partial agonist activity at D_2 and D_3 receptors[123], and capable of modulating dopaminergic activity with almost no effect on baseline dopaminergic activation, while reducing phasic excessive dopaminergic activity. In

addition, aripiprazole is a partial agonist at $5HT_{1A}$ receptors, which could possibly explain the lesser EPSE, and contribute to the alleviation of anxiety, negative symptoms, and depression[41].

Other recent developments include: asenapine (which has been observed to have potential to improve both negative and cognitive symptoms)[124]; bifeprunox (a partial D_2 and $5HT_{1A}$ receptor agonist with a reduced risk of metabolic complications)[125,126]; iloperidone (D_2 and $5HT_{2A}$ receptor antagonist)[127]; nemonapride (a typical antipsychotic similar in structure to sulpiride); norclozapine (a D_2 partial agonist with muscarinic agonist activity; the latter believed to be responsible for the observed positive effects it has on cognition)[124]; and paliperidone (the major metabolite of risperidone, having D_2, $5HT_{2A}$, α_1 and α_2 receptor antagonist activity, but no anti-cholinergic activity)[41].

The use of antipsychotics in the treatment of positive symptoms of schizophrenia has enabled millions of patients to live and function outside the confines of institutionalization. However, contemporary research has found that functional outcome - social functioning, independent living and employment[128] - is dictated to more by the presence of negative symptoms[129], and cognitive impairment[130], than by positive symptoms *per se*. Therapeutic strategies for the improvement of cognition will be discussed in the following chapter.

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CHAPTER 5

TREATMENT OF COGNITION IN SCHIZOPHRENIA

Psychopharmacological treatment remains the cornerstone of remedial intervention in the treatment of schizophrenia. Yet, cognitive impairments as primary therapeutic targets have yet to be adequately addressed[1,2].

At a time when institutionalization of patients was the norm, the discovery of the antipsychotic effect of chlorpromazine[3], and its apparent control of the positive symptoms of schizophrenia, led to functional improvement in patients and enabled the movement toward deinstitutionalization. This serendipitous discovery[4] reinforced the thinking of the day, being that improved function and management of the symptoms of schizophrenia were more readily accessible than cure[5].

The ability of first and second generation antipsychotics to rapidly attain their primary effect on the positive symptoms of psychosis has often been noted in the literature[6]. However, claims of the improved efficacy of SGAs on negative symptoms, as well as lower risk of EPSE, has secured their pre-eminence as the medication of choice in the initial treatment of schizophrenia[7,8]; with an apparent lack of consideration for their limited effect on negative symptoms and cognitive deficits, and the frequent incidence of metabolic side-effects[9,10].

When first describing *"dementia praecox"* in the 19th century in his 1896 *"Textbook of Psychiatry"*, Emil Kraepelin inferred the central importance of cognitive functioning[11]. A decade later, Eugen Blueler renamed the illness "schizophrenia", and shifted the emphasis from cognitive deficits to the positive and negative symptoms of the disease[12]. In the closing years of the 20th century the realization that functional deficits significantly contribute to the disability of the illness, and that cognitive impairments are a major influence on these disabilities, led to a resurgence of interest in the role of cognition in schizophrenia[13].

With the re-emergence of cognitive deficits as a central feature of, and prime contributor to, functional disability in schizophrenia, efforts have been increased in the field of research to produce actual treatments for these impairments[14]. An unfortunate reality underlying drug development *per se*, is that it is a protracted and costly exercise; often leading to extended delays in the developmental program. For this reason few advances have been realized in the treatment of cognition in schizophrenia during the past decade[15].

Cognitive dysfunction in schizophrenia is linked to neuronal dysfunction[16]. As a result of the MATRICS initiative, and the identification of 3 drug mechanisms of specific interest (cholinergic, dopaminergic, and glutamatergic), the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) project was initiated to select potential cognitive-

enhancing agents, and evaluate their potential efficacy in the context of proof of concept or clinical efficacy trials[2].

At present, three primary strategies for the treatment of cognitive symptoms have emerged: treatment with SGAs, augmentation strategies, and behavioral interventions, all with variable outcomes[17]. However, the treatment options available for the management of the cognitive deficits of schizophrenia have thus far been disappointing, with at best modest results. For this reason the pursuit for effective interventions continues[18].

DOPAMINERGIC STRATEGIES

Dopamine (DA) was first recorded as a neurotransmitter in 1958 by Carlsson and Hillarp[19]. It is a catecholamine commonly found in numerous animal species and it plays an important role in cognition, behaviour, and the suppression of prolactin production[20,21]. DA has been found to interact with at least 5 types of DA receptors and their derivatives[22,23]. These receptors are divided into 2 primary groups: the DA type 1 (D_1)-like group, consisting of types 1 (D_1) and 5 (D_5) that are similar in drug sensitivity and structure[24,25]; and, the DA type 2 (D_2)-like group, consisting of types 2 (D_2), 3 (D_3) and 4 (D_4) being similar in structure but with significantly varied drug sensitivities[26]. It appears that D_1 and D_4 receptors are responsible for the cognitive-enhancing effects of dopamine [27,28], while D_2 is the target for antipsychotic effect[29].

The ‘classical’ DA hypothesis of schizophrenia states that schizophrenia is associated with an exaggerated dopaminergic activity in the brain[30]. This followed the work of Connell who described amphetamine-induced psychosis, closely resembling schizophrenia that was associated with increased levels of dopaminergic activity in the brain[31].

Although PCP induced psychosis was stated as evidence for the glutamatergic hypothesis of schizophrenia[32] it was found that it also induces a decrease in basal and stress-related DA levels in the PFC[33].

This led to the formulation of the revised dopaminergic hypothesis of schizophrenia which posits the “co-existence of a hyperdopaminergic state in the mesolimbic pathway along with hypodopaminergia in the mesocortical tract”[34,35] with positive symptoms due to the former, and cognitive and negative symptoms due to the latter. However, recent animal research by Kellendonk et al. has rejected the position of frontal hypoactivity, which is said to cause striatal dysfunction, being the primary deficit in schizophrenia. Instead, an over-expression of striatal D_2 receptors, resulting in working memory (WM) and behavioral deficits, with an increased DA turnover, and activation of D_1 receptors in the frontal cortex, is suggested[36].

The revised dopaminergic hypothesis was subsequently defined as the 'alternative' DA hypothesis of schizophrenia. This hypothesis proposes that the primary disturbance in schizophrenia is failure of synaptic dopaminergic transmission, which may result in the cognitive and negative symptoms of schizophrenia. This hypodopaminergic state leads to a feedback process which stimulates both synaptic (more common in the striatum) and extrasynaptic (more common in the temporal cortex) DA transmission. However, an increase in extrasynaptic neurotransmission can cause general hyperarousal, which may develop into psychosis (positive symptoms)[37].

Results of studies of the D_1-like receptors have indicated that this group is not clinically significant in the remedial action of antipsychotic drugs[38,39]. However, the presence of high concentrations of D_1 receptors in the PFC suggest that this family of neurotransmitters is more likely to be involved in cognitive processes, such as attention, problem solving and memory[40]. Animal studies involving non-human primates have demonstrated increased DA levels in the PFC during the execution of WM tasks[41]. The converse was demonstrated when neurons issuing from the VTA (en route to the PFC) of rodents were negated; thereby effecting a considerable decline in aggregation of DA levels in the PFC to sub-baseline levels, resulting in performances of WM tasks being severely impaired[42].

Within the D_2-like receptor group, it is only the D_2 receptor itself that is effectively blocked by antipsychotic agents in relation to their antipsychotic potencies[43-45]. Therefore, every pharmaceutical with antipsychotic activity is a D_2-like receptor antagonist; hence this action is imperative to moderating

psychotic symptoms[29]. Antipsychotic action (antipsychotic threshold) measurement results of radioligand binding, using either single photon emission computerized tomography (SPECT), or PET, in the striatum of patients administered clinically therapeutic antipsychotic doses, show that clinically effective dosages of antipsychotic drugs occupy between 60% and 80% of D_2 receptors; whether FGAs or SGAs[26].

Superiority of atypical antipsychotics over typical compounds has been suggested in the literature. However, inconsistencies in findings, and relatively minor effect sizes, have hampered attempts to analogise between studies. This stems from several issues in methodology, such as small and heterogeneous sample groups; diagnostic changes (e.g. use of symptoms checklist from older studies, or DSM-III-R[45]); non-randomization to treatment; construct validity; disparity in drug doses; effects of established adjunctive medication; non-standardization of, and failure to compensate for practice and retest effects on, neurological tasks[40].

1. First generation antipsychotics

Blyler and Gold summarized results from narrative reviews published during the initial 30 years of antipsychotic availability, starting in the 1950s, as follows: “Chronic treatment with conventional agents appears to have limited cognitive benefit. More specifically, positive effects have been noted on aspects of selective/sustained attention, and mild negative effects have been observed on aspects of motor function”[40].

Following on from these early studies, subsequent clinical observations found that FGAs either have no effect on[47,48], or cause a dose-related worsening of, psychomotor speed[49]. Although various studies have declared some positive effects for FGAs on continued performance tasks[50-52], these may have been mediated through symptomatic improvement. However, studies are also lacking in evidence regarding FGAs lack of influence[53], possible detrimental effects[54], and performance on mazes[48].

Clear, cognitive benefits for FGAs continued to elude researchers throughout the 1990s. Despite this, contradictory conclusions continued to emerge. In a review of 28 published studies between 1990 and 1997, FGAs such a haloperidol were found not to be very effective in improving cognitive deficits of schizophrenia[40]. In contrast, Davis et al.[55] and Mishara and Goldberg[56] stated that FGAs may benefit cognitive function and negative symptoms.

Results of trials up until the present may have been biased against FGAs and therefore fail to reflect any cognitive benefits FGAs might have. Claims that FGAs would have no effect on cognition appear to be unnecessarily severe, since studies confirmed the ability of FGAs to alter regional brain metabolism[57]. The lack of benefit and possible detrimental effects of FGAs on cognition could be a result of methodological problems inherent to studies sponsored by the pharmaceutical industry. Some of these problems may include factors such as not taking into consideration inter-drug differences,

and the use of non-equivalent, and relatively high doses of, FGAs when compared to SGAs[58-61]. Results, particularly from older trials done in the 1990s and the early part of this century should therefore be interpreted with caution.

A related issue is the fact that high potency agents, such as haloperidol, pose a greater risk of causing EPSE than low-potency agents, such as chlorpromazine and thioridazine. Therefore, the use of haloperidol frequently requires the adjunctive administration of anticholinergic medications that are known to have detrimental effects on cognition[62,63]. Theoretically, utilization of drugs such as flupenthixol, which resemble SGAs in various ways, should result in fewer cognitive "problems"[64] (to be discussed in chapter 6).

Furthermore, the approach to neuropsychological assessment has remained virtually unchanged over decades. Multiple lines of evidence indicate that most of these cognitive measures appraise stable traits in patients and control groups, and are therefore likely to reflect individual differences that are unrelated to the illness. It is plausible that these instruments, although they may possess high test-retest reliability, are not sensitive to the subtle state changes that are the object of the investigation, and therefore may have failed to detect any beneficial effect of FGAs on cognition[40].

2. Dopamine Agonists

A number of non-human studies have indicated the importance of these receptors in WM. D_1 agonists such as D-amphetamine improve WM performance[27]. In contrast, D_1 antagonists worsen this function and thereby indentify D_1 as a target for the rehabilitation of cognitive deficits in schizophrenia[65,66]. It appears that there is also a therapeutic window of D_1 agonism, with low doses of agonists improving WM, though causing impairment at higher levels[67]. Relatively few efficacy studies in schizophrenia have been undertaken with agonists such as tolcapone (a selective COMT inhibitor and indirect DA agonist in the PFC) used in treating Parkinson's disease[68], atomoxetine (a noradrenaline reuptake inhibitor and indirect acting DA agonist in the PFC) currently registered for use in Attention Deficit Hyperactivity disorder[69], and dihydrexidine[70]. These studies produced variable results.

3. Dopamine stabilizers

With the discovery of DA autoreceptors, DA stabilization was adopted as the new approach to treating schizophrenia. Present day antipsychotics are antagonists at the D_2 receptor, however their efficacy is somewhat limited due to hypodopaminergic-induced side-effects. Though evidence points toward increased dopaminergic activity in schizophrenia, it has been suggested that the problem may not be one of a continuously elevated baseline, but one of instability of release. It was proposed that this could be

rectified by stabilizing DA with a drug capable of dynamically occupying antagonistic pre- and post-synaptic receptors, whilst concurrently modulating their activation to a degree whereby tonic baseline dopaminergic activation remains largely unchanged, and phasic excessive dopaminergic activity is retarded[71].

One such DA stabilizer that was developed, with partial agonism at D_2 and D_3 receptors, is aripiprazole. The first published report on the neurocognitive effects of this drug was on the findings of an open-label comparative study of aripiprazole and olanzapine by Kern et al. A sample of 255 patients with schizophrenia or schizoaffective disorder were randomly treated with aripiprazole (30mg/d) or olanzapine (15mg/d), with neurocognitive and clinical assessments conducted at baseline, week 8, and week 26. Of the initial sample, 169 subjects completed the study. Within this group 38% were treated with aripiprazole, and 47% with olanzapine. Neurocognitive data were reduced to a 3-factor solution: verbal learning, executive function, and general cognitive function. From baseline, the aripiprazole group improved significantly in verbal learning; neither group improved significantly in executive functioning; and both groups improved in general cognitive functioning, with effects remaining relatively stable for the duration. This study concluded the neurocognitive effects of aripiprazole to be on a par with those of olanzapine[72].

CHOLINERGIC STRATEGIES

Acetylcholine receptors are dispersed throughout the brain, in areas including the basal ganglia, neocortex, thalamus, and hippocampus[73]; these being components of different neural circuits involved in the facilitation of simple and complex cognitive processes. The nucleus basalis of Meynert (nbM), part of the cholinergic group (Ch) 4 neuronal cell bodies, located in the substantia innominata of the basal forebrain, has a broad projection to the neocortex[74], while the septal area has projections to the hippocampal region[75]. The cholinergic supply to the striatum is interneuronal, with additional input from Ch1-Ch4[76].

Contemporary studies suggest that disruptions of the cholinergic system, specifically in the mesopontine cholinergic projections to the thalamic, cortical, and striatal structures, may be underlying to the cognitive deficits seen in patients with schizophrenia[2]. Disruptions in this connection is specifically implicated in deficiencies in a number of neuropsychological processes evident in patients with schizophrenia, such as motor dysfunction, eye tracking abnormalities, sensory gating impairments, processing speed impairments, memory problems, and disruptions in the sleep-wake cycle[77].

Although most studies confirm the presence of ample receptors in the limbic cortex, neocortex, and subcortical regions, cognitive deficits appear to result from disruptions of the cholinergic pathway; similar to those observed in the mechanism of Alzheimer's disease[78,79]. Lesion studies have established that

scopolamine and atropine-induced memory dysfunction in rats, primates and humans, is reversible with the administration of acetylcholinesterase inhibitors (AchEI)[80-82] such as physostigmine. It follows that cholinergic enhancing agents may therefore counteract the cognitive impairments present in schizophrenia[83].

Detrimental effects of FGAs on cognition have been noted. However, studies of schizophrenia patients and healthy individuals[84] have shown that anticholinergic agents may also have a detrimental effect on learning and memory. Research has established that co-administration of anticholinergic agents for the treatment of EPSE, produces deficits in the performance of memory tasks of schizophrenia patients[62,85]. It follows that in cases requiring this concomitant treatment, a reasonable washout period should be observed prior to the start of the patient's cognitive assessment.

1. Nicotinic receptors

Nicotinic acetylcholine receptors (nAChR) appear to act as modulators of cognitive function, with presynaptic nAChR controlling neurotransmitter release, and post-synaptic nAChR in the hippocampus and cortex participating in the modulation of cognitive functions by controlling ganglionic and fast cholinergic neurotransmission[83,86].

- $\alpha_4/ß_2$-nAChR

The pharmacological attributes of the nAChR implicates it as a possible role-player in schizophrenia[78]. Studies show almost 80% of patients with schizophrenia to be smokers. Patients have significantly higher urinary cotinine levels, reflecting deeper inhalation, and take in 50% more nicotine per cigarette than non-affected smokers; a possible attempt at self-medication[87,88]. Furthermore, auditory sensory gating, a function moderated by nAChR, is impaired in patients with schizophrenia[83]. Positive neurocognitive effects in schizophrenia, attributable to nicotine, are in keeping with the connection between deficiencies in attention and impaired sensory gating[89]. The effect of nicotine on attention is mediated via $\alpha_4/ß_2$-nAChR receptors[90]. A single dose of nicotine improves some aspects of cognition (response inhibition, working and declarative memory)[91], however, multiple administrations are of no benefit due to the brisk onset of receptor desensitization (tachyphylaxis), and are, therefore, not a treatment option[92,93]. However, in a study by Levin et al., nicotine was administered to schizophrenia patients treated with haloperidol, subsequent improvements were documented in a number of cognitive domains, such as reaction time, memory and attention[94].

- α_7-nAChR agonists

As the α_7-nAChR has been implicated in the pathophysiology of schizophrenia through numerous genetic and neurobiological data[95], it has

subsequently been identified as a target for therapeutic intervention and treatment of cognitive deficits in schizophrenia[96].

Feuerbach et al. administered JN403, a selective partial α_7-nAChR agonist, to DBA/2 (Dilute Brown Non-Agouti) mice. The authors found rapid onset of efficacy, lasting for 6 hours, with respect to: the restoration of sensory gating; amelioration of learning and memory performance deficits, alleviation of pain; anxiety, and epileptic seizures[97].

In a three-arm, double-blind, crossover trial, Freedman et al.[86] examined 31 non-smoking patients with schizophrenia. In addition to their current medication, the subjects received one of two doses of 3-(2, 4-dimethoxybenzylidene) anabaseine (DMXB-A), or placebo, for periods of four weeks. Although no significant differences were documented in cognitive performance between DMXB-A and placebo over the three treatment arms, there was a significant improvement of negative symptoms at the higher DMXB-A dose, and some improvement in attention/vigilance and working memory on the Scale for the Assessment of Negative Symptoms (SANS) total score[88].

2. Muscarinic receptors

Aggregations of muscarinic (M) receptors in the nbM and the basal cholinergic system are noted to be reduced in the PFC of patients with schizophrenia[83].

- M_1 and M_4 agonists

The dense distribution, and post-synaptic location, of M_1 receptors in the hippocampus and cerebral cortex[98] identified M_1 as a possible site for cognitive-enhancing agents. M_4 has a similar distribution as M_1, as well as aggregations in the substantia nigra and striatum. M_1/M_4 agonists, such as xanomeline[99], demonstrated utility in improving constructional praxis, orientation, spoken language ability, and word-finding difficulties in spontaneous speech in dementia patients[100]. However, due to the non-selectivity of the drug, the presence of antimuscarinic side-effects is problematic[101]. Allosteric modulators, such as N-desmethylclozapine, which has selective activity as a M_1/M_4 agonist[102], may enhance cognitive functioning.

3. Acetylcholinesterase inhibitors

Evidence for the use of AchEI in the treatment of dementia associated with neurodegenerative diseases, is well documented. It may affect improvements and delay deterioration of cognition. These effects are well documented for guanfacine, donepezil, tacrine, rivastigmine, and galantamine[103-108]. To date, however, data on AchEI as concomitant therapy for cognitive impairments in schizophrenia are lacking; being limited to small sample sizes and predominantly open label, uncontrolled studies.

In a 12-week, double-blind, placebo-controlled RCT, galantamine, an AchEI and allosteric modulator of $\alpha_4/ß_2$-nAChR and α_7-nAChR, was administered to a sample of 42 schizophrenia patients, with a control group of 44 assigned to placebo. Results suggested that galantamine may possess selective advantages for certain characteristics of psychomotor speed and verbal memory, but during the execution of an attention task it disrupts practice effect[109].

In a 2009, 12 week open-label trial by Chung et al., donepezil was administered in a daily dosage of up to 10mg concurrent to an established atypical antipsychotic regimen in 28 stable schizophrenia patients. Results were: significant improvements in attention, memory, psychomotor speed, and mental set-shifting ability, as measured by Schizophrenia Cognition Rating Scale (SCoRS), and Computerized Neurocognitive Function Test (CNT)[110].

In their quantitative systematic review of controlled, crossover, and open trials of the effects of AChEI agents on the cognitive domains of attention, language, motor and executive functions in subjects with schizophrenia, Chouinard et al. included 12 studies (N= 444) of add-on donepezil, rivastigmine, or galantamine. The results of this review indicated subtle improvements in attention, and a trend toward motor task improvement[111]. There is, however, insufficient data at present to conclude whether AChEI are suitable, effective agents in the treatment of cognitive impairments in schizophrenia[105,112].

GLUTAMATERGIC STRATEGIES

Dopaminergic dysfunction has taken pre-eminence in the more traditional models of schizophrenia. Nonetheless, the last 15 years has seen glutamatergic models emerging, as aspects of the disorder relating to positive, negative and cognitive symptoms are inadequately accounted for by dopaminergic dysfunction alone. This theory originated from study results documenting how PCP and ketamine, both NMDA receptor antagonists, induced neurobehavioral disruptions and psychoses similar to those seen in schizophrenia[113].

Glutamate, the most prolific excitatory neurotransmitter in the vertebrate nervous system[114], is involved in fast synaptic transmission, plasticity and higher cognitive functions. Glutamate receptors are divided into 2 groups, ionotropic, and metabotropic. The ionotropic receptors are characterized pharmacologically by binding of particular agonists: NMDA, kainic acid (KA), and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors[115].

Believed to be involved in the amplification of the glutamate signal, NMDA receptors are a primary molecular apparatus engaged in the control of memory function and synaptic plasticity. The NMDA receptor is both voltage-dependent and ligand gated. When at rest, NMDA channels are blocked by extracellular magnesium ions (Mg^{2+})[116]. When glutamate binds to AMPA receptors, the ion channel opens, thus facilitating the process of sodium

(Na^+) influx. The ensuing excitatory post-synaptic agitation initiates the release of Mg^{2+} from the NMDA receptors, opening the NMDA ion channels that allow for the Na^+ and calcium influx which 1) facilitates the NMDA channel's contribution to the electrical response of the cell, and 2) activates the cyclic adenosine monophosphate (cAMP) response element-binding (CREB), which effects changes in protein synthesis and therefore permanent structural changes[117].

Regulatory sites on the NMDA receptor channel complex include a glycine-binding site that facilitates the increase in frequency of agonist induced channel opening, as well as binding sites for MK-801 and PCP, both with inhibitory actions. These properties create a potential for a number of mechanisms for positive and negative control of NMDA receptor channel function[40].

Glutamate is involved in long term potentiation (LTP): the sustained increase in synaptic strength subsequent to high-frequency stimulation of a chemical synapse. It is one of the intrinsic phenomena that enable chemical synapses to change their strength (synaptic plasticity)[118,119], which is believed to be a component involved in the encoding of memory[114] in the *cornus amonis* area 3 (CA3) region of the hippocampus.

Examination of glutamate in the cerebrospinal fluid (CSF) of patients with Huntington's chorea, schizophrenia, and sciatic nerve compression (control

group), showed that glutamate levels in Huntington's and schizophrenia patients were lower by nearly half when compared to the control group, despite similar serum glutamate levels. This was not related to neuroleptic treatment[120]. Lesion studies in rodents, with selective abrogation of cortical and hippocampal NMDA receptors in mice, during the early postnatal period, caused distinct schizophrenia like cognitive and behavioral symptoms with onset after adolescence[121].

Pharmacological challenge studies with NMDA antagonists such as ketamine[122], PCP and MK801[123], induce symptoms resembling the positive, negative and cognitive symptoms of schizophrenia. From these observations followed the NMDA receptor hypofunction hypothesis of schizophrenia, which proposes that NMDA receptor blockade reduces activation of GABAergic inhibitory neurons, causing a failure of mesolimbic and mesocortical regulatory projections, which can cause an excessive downstream release of glutamate and acetylcholine[124,125].

From the interaction between glutamate and dopamine followed a variant of the NMDA hypothesis of schizophrenia in which deficits in the NMDA system result in abnormal functioning of the dopaminergic system. In the healthy brain, descending glutamatergic projections from the cortical pyramidal neurons, via GABA interneurons, results in tonic inhibition of DA release from the mesolimbic pathway. However, NMDA receptor hypofunction will cause mesolimbic dopaminergic hyperactivity and positive symptoms of schizophrenia. Furthermore, glutamatergic hypoactivity in the cortico-

brainstem neurons, which under normal circumstances projects directly onto, and stimulates, mesocortical dopaminergic neurons, causes dopaminergic hypoactivity in the mesocortical areas, resulting in cognitive, negative and affective symptoms of schizophrenia[126].

1. N-methyl-D-aspartate receptor agonists

N-methyl-D-aspartate antagonists impair cognitive functioning in laboratory animals as described above. These impairments are reversible with administration of NMDA agonists, such as glycine[127]. Milacemide, a glycine prodrug[128], as well as d-cycloserine (a partial agonist at the NMDA glycine-binding site) proved to enhance learning[129] in rodents. In a six week study of 22 treatment resistant in-patients with schizophrenia, Heresco-Levy et al. demonstrated significant reduction of 16% (±11%; 95% CI: 10%-21%) cognitive deficits with administration of glycine (target dose 0.8g/kg) compared to an appearance- and taste-matched placebo on the PANSS cognitive factor score[130]. Unfortunately no specific cognitive measures were included in this study.

The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST), investigated the use of adjunctive glycine, d-cycloserine (DCS), or placebo, for relief of negative and cognitive symptoms of schizophrenia. This 16-week double-blind, double-dummy, parallel group, RCT involved 157 in-patients and outpatients, who met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder, and were deemed to have moderate to severe

negative symptoms. The primary outcome measures were the average 'rate of change' on the SANS[131] scores, and change in the average cognitive domain Z-scores. There were no significant differences in change in the SANS total score, cognitive symptoms, or negative symptoms change between the groups, with the conclusion that neither glycine, nor DCS are an effective therapeutic option for treating negative symptoms, or cognitive impairments in schizophrenia[132].

Although small increases in NMDA-dependent glutamate transmission enhances cognition, too large an increase can lead to neurotoxicity and degeneration. Studies with the use of agonists, such as d-serine, glycine and DCS, have suggested that these agents are effective in treating some of the cognitive and negative symptoms of schizophrenia[133], whereas others have not[134]. Study results for the therapeutic benefit of NMDA agonists in the treatment of schizophrenia therefore remain inconclusive.

2. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor

Development of compounds that stimulate AMPA and KA receptors is another glutamatergic approach for cognitive enhancement in schizophrenia. The AMPA receptors are considered to modulate fast glutamatergic excitatory neurotransmission in the central nervous system (CNS), and the expression and maintenance of LTP[135,136]; therefore vitally important for cognitive functions such as learning and memory[137,138].

Rodent studies have reported ampakines to offer a degree of protection against excitotoxic brain damage[139], to improve neurological signs in Parkinson's disease[140], and to increase cell proliferation in the dentate gyrus[141].

However, AMPA agonists rapidly desensitize after stimulation, and are not likely to be useful therapeutically[137]. In an effort to counteract this desensitization, a class of compounds known as kainates (allosteric potentiators of AMPA receptor function) is being researched as possible treatments in enhancing cognition in schizophrenia[142]. AMPA receptor-positive modulators (ampakines) facilitate learning and memory in animal models[143,144], and in preliminary trials in human subjects[145]. Unfortunately, initial clinical trials for the use of CX516, the first ampakine to be studied for cognitive enhancement in stable patients with schizophrenia, failed to demonstrate efficacy as add on treatment to clozapine, olanzapine, or risperidone. It therefore remains inconclusive whether the modulation of AMPA receptors has any therapeutic benefit in the treatment of cognitive impairments in schizophrenia[145]. Research in this area is however ongoing.

3. Metabotropic glutamate receptor agonists

Compounds that act as agonists at metabotropic glutamate receptors (mGIuRs) to modulate pre- and post-synaptic gluatamatergic neurotransmission for the treatment of cognitive dysfunction in schizophrenia are currently in preclinical development. Of the eight subtypes of mGIuRs

($mGIuR_{1-8}$), assembled into three groups, the main focus of investigation for cognitive enhancement in schizophrenia has been on group 1 ($mGIuR_1$ and $mGIuR_5$)[146].

$mGIuR_5$ receptor agonism potentiate presynaptic glutamate release and post-synaptic NMDA transmission[147], thereby enhancing cognition, and has been observed to inhibit PCP induced DA release in the PFC of male Sprague-Dawley rats[148]. However, $mGIuR_5$ agonism is likely to induce tachyphylaxis, therefore restricting their therapeutic usefulness[149]. Recently developed selective allosteric modulators of mGIuR show promise as therapeutic compounds[150], and preliminary positive results with an $mGIuR_{2/3}$ agonist have been documented in phase II trials[151].

4. Glycine reuptake inhibitors

Glycine transporters, GlyT1 and GlyT2, are located on neuronal and glial cells in the central nervous system[152], and are thought to be responsible for the regulation of extracellular glycine concentration. Inhibition of glycine transporters increases extracellular glycine concentration, which enhances NMDA receptor neurotransmission[135], thus exhibiting therapeutic potential for treatment in schizophrenia[153].

Rodent studies investigated effects of GlyT1 inhibitors on amphetamine-induced disrupted latent inhibition (LI) and MK-801-induced abnormally persistent LI, as pharmacological, and neurodevelopmental models of schizophrenia respectively. Both SSR103800 and SSR504734 reversed

amphetamine-induced disrupted LI, and reversed MK-801-induced abnormally persistent LI. Furthermore, selective high-affinity glycine transporter inhibitors, such as Org-24598, SSR-504734, and N-[3-(4'-fluoropheny)-3-(4'-phenylphenox-y)propyl] sarcosine, have been demonstrated to reverse PCP-induced hyperactivity in rats[154,155]. These preclinical data allude to the possibility that GlyT1 inhibition may display activity in the positive, negative and cognitive symptoms of schizophrenia[153].

Tsai et al. documented that sarcosine (N-methyl glycine), a low-potency glycine inhibitor, administered concomitant to current antipsychotic treatment of schizophrenia patients, effected a highly significant reduction in negative symptoms and a modest but significant reduction in cognitive and positive symptoms[156].

5. Gamma-amino-butyric acid (GABA)

Post mortem studies of schizophrenia patients have revealed decreased ribonucleic acid (RNA) levels for glutamic decarboxylase (GAD), the enzyme responsible for the conversion of glutamate to GABA[157]. Other studies report $GABA_A$ α_2 subunit increases in patients with schizophrenia[158]. Chandelier cells in the PFC synchronize the activation of pyramidal neurons via $GABA_A$ receptor subtypes. Some evidence suggests that diminished GABA transmission in chandelier cells may be secondary to NMDA receptor dysfunction, and may prove to be a 'final common pathway' of prefrontal dysfunction in schizophrenia. It follows that compounds modulating

GABAnergic neurotransmission, such as the $GABA_A$ α_2 selective benzodiazepines, may prove to be effective in ameliorating cognitive deficits in schizophrenia[159]. Unfortunately, benzodiazepines impair cognitive function, working memory, cause sedation and are habit-forming[151].

Functional magnetic resonance imaging (fMRI) in patients with schizophrenia compared to healthy controls, confirmed the association between GABAnergic functioning and cognition. Working memory performance on an N-back task was assessed as a target discrimination index at several levels of difficulty. Activation of the frontoparietal cortex increased with task difficulty, and was positively correlated with deactivation of the temporocingulate cortex. After placebo administration, schizophrenic patients had abnormally attenuated activation of the frontoparietal cortex and deactivation of the temporocingulate cortex. A similar pattern, associated with impaired WM, was found when lorasepam was administered to controls, while exacerbating it in schizophrenic patients. In contrast, flumazenil (a negative allosteric modulator of the $GABA_A$ receptor complex) enhanced deactivation of the temporocingulate and activation of the anterior cingulate cortices, and improved WM performance[160]. It therefore stands to reason that disrupted inhibitory GABAnergic function may be related to cognitive impairment, and is therefore treatable by compounds targeting GABA neurotransmission.

$Alpha5_{1A}$, a $GABA_A$ receptor selective inverse agonist, enhances LTP and cognitive performance in rodents. Unfortunately, preclinical toxicity and

safety studies determined that alpha5 is unsuitable for prolonged administration to humans. However, doses of up to 6mg were well tolerated by young and elderly subjects, and it reversed ethanol-induced impairment in the cognitive performance of young normal volunteers[161].

Baclofen, a $GABA_B$ receptor agonists, improved cognitive impairment in mice administered subchronic methamphetamine treatment (1mg/kg for 7 days), whereas gaboxadol, a $GABA_A$ receptor agonist exhibited no significant effect, suggesting that $GABA_B$ receptors may prove to be a novel target in the treatment of patients with schizophrenia[162].

SEROTONERGIC STRATEGIES

Serotonin (5HT) is a monoamine neurotransmitter synthesized from L-tryptophan[163], and has a number of functions, such as regulation of mood, sleep, appetite, and cognitive functions including learning and memory[164]. serotonergic nuclei are located in the dorsal raphe nuclei in the brainstem, from where axons fan out to encompass nearly every part of the CNS. In so doing, they innervate the limbic- and neocortex, as well as parts of the basal ganglia[165,166].

Bosia et al. genotyped and evaluated the attention and cognitive flexibility, of 233 patients with schizophrenia. Results indicated that the presence of the high-activity long allele (L) of the 5HT transporter was a predictor of better executive performance, but impaired attention. Therefore, it would appear

that disruptions in 5HT availability may, through complex modulation of the various performance components, play a particular role in cognitive processes, particularly declarative memory[167].

Fourteen 5HT receptors have been identified, of which $5HT_{1A}$[168], $5HT_{2A}$[169], and $5HT_6$[170] seem to be playing an important in the role in cognition and schizophrenia. The highest density of $5HT_{1A}$ receptors are found on the cortical and hippocampal pyramidal cells[171], thus suggesting that these receptors play a role in modulating cognitive functions[172]. Studies into the $5HT_{1A}$ partial agonist tandospirone in schizophrenia patients receiving FGAs or SGAs, reported modest ability of this drug to improve some cognitive domains, such as verbal memory, semantic memory, working memory and attention[173].

A high concentration of $5HT_{2A}$ receptors is found in pyramidal neurons originating from cortical layer V, where they aggregate with NMDA glutamate receptors[151], as well as on DA neurons in the VTA, therefore playing a role in regulating DA and glutamatergic activity. Studies in animals show that antagonism of $5HT_{2A}$ receptors inhibits DA release in the basal ganglia, and improves cognitive deficits[172]. A double blind, randomized, placebo controlled study of primavanserin (ACP-103), a selective $5HT_{2A}$ receptor inverse agonist, in 60 patients with L-3,4-dihydroxyphenylalanine (L-DOPA) or PCP-induced psychosis, demonstrated significant improvement in psychosis in patients receiving pimavanserin compared to placebo. In this study pimavanserin did not separate from placebo with regard to motor

impairment, hypotension, sedation, or other side effects. This supports the hypothesis that attenuation of PCP-induced psychosis may be achieved through selective $5HT_{2A}$ receptor antagonism[174].

High concentrations of $5HT_6$ receptors are located in the olfactory cortex, neocortex, limbic striatum, and hippocampus. In addition to their D_2 antagonism and inverse agonistic effects, antipsychotic such as olanzapine and clozapine were found to have a high affinity for $5HT_6$ receptors[172], leading to concerted efforts to establish and understand this receptor's potential as a future therapeutic target[175].

NORADRENERGIC STRATEGIES

The central noradrenergic (NA) system originates from the locus ceruleus (LC) from where it projects to the PFC, playing an important role in cognitive function[176,177]. In addition, this action is thought to be reciprocated by the PFC supplying cortical afferents to the LC[178,179]. Stein and Wise were the first to propose a progressive deterioration of central NA pathways in schizophrenia, leading to anhedonia and loss of drive[180]. However, this has not been confirmed, as neuronal activity measurement and post mortem studies in schizophrenia patients have produced conflicting results[181,182], and even increased NA levels in the CSF[183-185]. It is possible that NA disruptions in schizophrenia are not homogenous throughout the CNS, and may explain the coexistence of low and high NA states mediating different system clusters in schizophrenia. Furthermore, activation of pre-synaptic

α_2 autoreceptors inhibits the release of NA, while stimulation of post-synaptic α_2 receptors has an agonist effect[186].

Lesion studies in the NA system in rats demonstrated deficits in sustained attention[187], shifting attention[188], and learning[189]. Rats administered diethyldithiocarbamate (DDC), a DA-β-hydroxylase (DBH) inhibitor that depletes NA stores in the brain, exhibit complete retention failure of passive avoidance learning[190]. Similarly, puromycin-induced reduction of NA induces amnesia of maze learning in rats[191]. Deficits in the DDC treated rats were reversed with a single intraventricular dose of NA[192]; as was the puromycin-induced amnesia when treated with agents that increase NA activity, such as tranylcypromime, imipramine, d-amphetamine, and specific NA reuptake inhibitors[191].

The LC is believed to be activated by the presentation of novel stimuli that attenuate the influence of distracting stimuli, therefore focusing attention on task-relevant behaviours[177], such as new learning, vigilance and distractibility[193]. Lesion studies in the PFC of rodents resulted in disinhibited firing of the LC, suggesting that PFC dysfunction may disrupt regulation of the LC[179]. This means that, theoretically, cognitive dysfunction related to LC dysregulation may be experienced by schizophrenia patients, in addition to the cognitive deficits associated with PFC dysfunction[194].

Animal studies have provided ample evidence that memory deficits can be ameliorated by β-adrenergic agonists[195]. In human studies endogenous

levels of β-adrenergic receptor activation selectively enhanced memory associated with emotional arousal[196]. Unfortunately, β-adrenergic agonists have a significant side-effect profile, thus limiting their clinical utility as cognitive enhancing agents in humans. NA activity enhancement with compounds such as tricyclic antidepressants (imipramine), monoamine oxidase inhibitors (tranylcypromine), d-amphetamines, and specific NA reuptake inhibitors (reboxetine), is problematic, since these agents can cause angina, tachycardia, and other arrhythmias[197].

Alpha$_2$-adrenergic receptors are thought to be integral to cognitive functioning in humans[176,177]. Treatment with clonidine[198] and guanfacine[199], both α_2-adrenergic agonists, improves cognitive performance in patients with schizophrenia, while concomitant administration of risperidone and guanfacine significantly improves tasks of attention and WM[199]. Atypical antipsychotics such as clozapine are potent agonists at α_2-adrenergic receptors[200]. Concomitant treatment of a FGA with idazoxan, a highly selective α_2-adrenergic receptor agonist, exhibited a profile of antipsychotic activity similar to that of clozapine[201].

Alpha$_2$-adrenergic receptor activity may well be important in the development of new drugs to improve cognition, balancing α_2-adrenergic receptor activity to effect antipsychotic and precognitive efficacy, in schizophrenia[151].

OTHER PHARMACOLOGICAL STRATEGIES

Other potential strategies for pharmacotherapeutic advances in the management of cognition in schizophrenia include phosphodiesterase 4D allosteric modulators[202], recombinant human erythropoietin[203,204], histamine receptor type 3 antagonists[205], and modafanil[206], but evidence for therapeutic application is still lacking.

NON-PHARMACOLOGICAL STRATEGIES

Although antipsychotics have proven to be effective in reducing positive, and to some extent negative symptoms, these medications have only proved to be of limited benefit with regard to cognitive symptoms and functional outcome. Psychosocial strategies therefore aim to address residual symptoms, to improve functional (work and social) outcome, and to reduce risk of relapse[207].

Remediation and rehabilitation of cognitive deficits involve assisting the patient in achieving, and maintaining, a durable level of functionality and independence, and providing continued support for indigent areas[208]. Although individual psychodynamic therapy[209,210] has not been of benefit, family intervention[211] and personal therapy[212] may have modest benefits. It seems that the biggest disadvantage of personal therapy, and family intervention, is the patient's lack of ability to generalize the skills acquired to

real-world settings[213]. Other psychosocial intervention strategies however do have evidence for improving functional outcome[214].

Social skills training (SST) is aimed at basic skills training, where complex social repertoires are dissected into smaller units, such as eye contact, speech modulation, and body language, and taught through repetition and modeling[215,216]. Another strategy is social problem solving skills training, which attempts to correct deficits in receptive learning, information processing and cognitive processes[217]. These remedial processes were found to improve social functioning, and positive symptoms such as hallucinations[218]. However, limitations regarding the ability to generalize these skills, and the durability thereof, have remained.

Researchers realize that cognitive deficits in patients must first be addressed in order to meet the need for the improved effectiveness of SST. Cognitive remediation (CR) programs, such as neurocognitive enhancement therapy (NET), were therefore developed with the aim to address deficits in the patient's thinking and memory abilities. Cognitive remediation can be individual or grouped based interventions, which usually involves task practice via repeated drill and/or strategy coaching. Techniques employed include instruction, didactic training, monetary reinforcement, verbalization of action criteria (the patient 'talks' him/herself through the task at hand), and task simplification. Previous studies have found benefits for CR with regard to improvements in attention[219], working memory[220], verbal memory[221], social functioning, and symptomatic improvement[222] in schizophrenia, with

some benefits retained at six months post-treatment[223]. Wykes et al.[224] estimated that an improvement of at least 50% in different cognitive domains is needed for the benefits to generalize to improvement on social functioning. It is unclear whether these improvements are ascribable to restorative or compensatory mechanisms.

Computer based NET showed some success in improving cognition. Dickinson et al.[25] randomly assigned 69 schizophrenia patients to 36 sessions of computer-assisted cognitive remediation or an active control condition. Sixty-one patients completed the study. Although significant improvements were seen in performance on computer exercises, it did not generalize to significant benefits on any neuropsychological or functional outcome measure, either immediately after treatment, or at the three month follow-up. In another study, 72 patients received vocational training, or vocational training and NET, for a period of 12 months. The patients receiving combined treatment had a significant better occupational outcome with more hours worked, and higher rates of competitive employment[226].

Evidence for the efficacy of cognitive behavioral therapy (CBT) in addressing positive and negative symptoms of schizophrenia is still contradictory. Although effectiveness was established for addressing positive symptoms[227,228], CBT appears to be less effective in addressing negative symptoms[229,230], while some studies reported no benefit at all[231]. Although CBT has not been shown to improve functional outcome[232], or reduce relapse rates[233], it did improve medication compliance[234]. Subsequently, a

CBT therapy intervention program for relapse prevention in FEP, has been developed by the Early Psychosis Prevention and Intervention Centre (EPPIC)[235]. Other psychosocial strategies employed are psychoeducational programmes[236], and supported employment programmes[237].

A logical next step

Decades of research have established the need for psychopharmacological and psychotherapeutic interventions in addressing cognitive deficits in schizophrenia. Antipsychotics remain the cornerstone in treatment of this disease. However, further research and development of agents more efficacious in addressing cognitive symptoms are clearly needed. Unfortunately, research and development of novel drugs is a slow and expensive process. In the meantime, it would behove researchers and clinicians to consider and reconsider agents which are already available, but have not been adequately researched.

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CHAPTER 6

FLUPENTHIXOL

Flupenthixol, a thioxanthene derivate developed by H. Lundbeck A/S as an antipsychotic agent, was first tested in 1965[1,2]. Zapletalek et al.[3] can be credited for the first therapeutic administration to patients with schizophrenia, while Rimestad et al.[4] described a three year trial with use of flupenthixol in various disorders. Since 1965, various studies, especially in the Scandinavian countries, have reported, in addition to the antipsychotic efficacy of flupenthixol, evidence for efficacy in the treatment of neuroses, reactive depression, psychosomatic disorders and functional organic disturbances. Flupenthixol has been commercially available in the UK since 1962 and in the rest of the world (except the United States) since 1972.

Chemical structure

2-trifluoromethyl-9-(3[4-(2-hydroxyethyl)-1-piperazinyl]propylidene)-thioxanthene's, better known as flupenthixol, chemical structure is $C_{23}H_{25}F_3N_2OS$, with an average molecular mass of 434.52 g/mol (see figure 6.1). It is available as a dihydrochloride (for oral use), as well as a decanoate (for intramuscular use)[5].

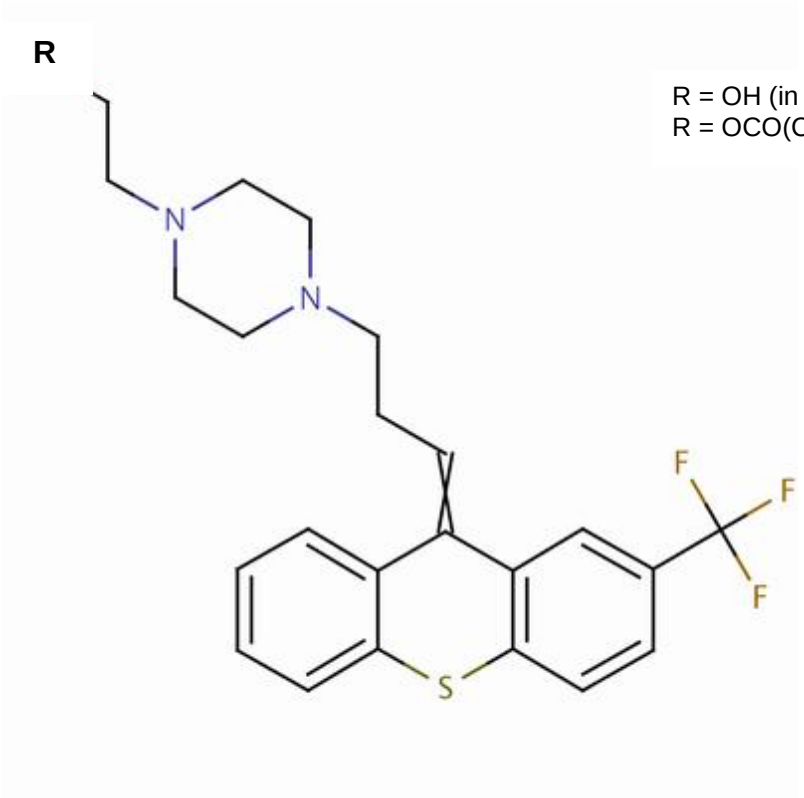

Figure 6.1: Chemical structure of flupenthixol

Flupenthixol exists as two geometric isomers, the cis(Z) and trans(E) forms. Only cis(Z)-flupenthixol is pharmacologically active. Flupenthixol hydrochloride is soluble in water and ethanol. Esterification of cis(Z)-flupenthixol forms a highly lipophilic substance, which, when dissolved in oil, can be injected intramuscularly. The ester diffuses slowly from the oil to the body-water phase where it is rapidly hydrolyzed to release the active cis(Z)-flupenthixol[5].

Pharmacokinetics

Absorption[6-9]

Absorption of flupenthixol is fairly slow and incomplete. First pass metabolism reduces oral bioavailability with 40%. There exists a linear relationship between administered dose and serum level, and maximum serum levels (T_{max}) are reached within 4-5 hours after oral, and 3-7 days after intramuscular, administration.

In these early pharmacokinetic studies, relatively high doses of flupenthixol were used (5mg/d po or 40mg 2 weekly IMI)

Distribution[8-11]

Plasma protein binding is more than 99% and the volume of distribution (V_d) 14.1 ℓ/kg. The highest levels of flupenthixol are found in parenchymatous organs such the lungs and liver, with much lower concentrations in the CNS. Flupenthixol hydrochloride has a half-life of ($t_{½}$) of 19-39 hours, reaching steady state (c_{ss}) after 7 days, while flupenthixol decanoate has a $t_{½}$ of 8-17 days, with c_{ss} of 3 months.

Metabolism[8,12,13]

Flupenthixol has no active metabolites. Biotransformation occurs following 3 routes: sulphoxidation, side chain N-dealkylation and glucoronic acid conjugation.

Elimination and excretion[6,12,14]

Elimination $t_{½}$ was found to be between 5 and 113 days, with a mean of 35 days. Systemic clearance (Cl_s) was calculated as 0.46 ℓ/min in healthy volunteers to 0.31 ℓ/min in psychiatric patients, with a mean Cl_s= 0.29 ℓ/min. Metabolites are excreted mainly in feces (63%), with a minor amount excreted in urine (17.4%), and in trace amounts present in bile and breast milk. Reduced kidney function does not appear to significantly impact excretion.

Pharmacodynamics

Flupenthixol acts as an antagonist at various DA (especially D_1 and D_2), $5HT_2$, adrenaline (α_1), and histaminergic (H_1) receptors. The following *in vitro* receptor binding affinities (K_i nmol/ℓ) have been calculated: D_1 binding = 0.91; D_2 binding = 0.35 and $5HT_{2A}$ binding = 4.2; while *in vivo* potency (ED_{50}) has been established as D_1 binding = 0.15, D_2 binding = 0.03 and $5HT_{2A}$ binding = 0.04. Due to very low H_1 affinity, flupenthixol does not cause sedation, and it is devoid of any cholinergic muscarinic and α_2 blockade effects[15].

Flupenthixol can be considered an ‘atypical typical’, or ‘partial atypical’ and resembles SGAs in various ways[16]. The antipsychotic effect of flupenthixol is mediated through D_2 antagonism, with D_1 and D_2 affinity more similar to clozapine than to fluphenazine (while it has almost only D_2 affinity). Flupenthixol displays 40-50% $5HT_{2A}$ receptor occupancy at 10mg/d with improved efficacy against negative symptoms and depressed mood[17], and reduced risk of EPSE, in comparison to phenotiazines. Unlike the phenotiazines, flupenthixol also resembles tricyclic antidepressants in some aspects; with antidepressant and anxiolytic effects thought to be mediated via preferential D_2/D_3 autoreceptor blockade, resulting in increased post-synaptic dopaminergic activity when used at lower doses of 1-1.5mg/d[18-21].

Limited data is available with regard to toxicity, although it is thought that toxicity is cause by the same mechanisms as those producing clinical effects. The median lethal oral dose (LD_{50}) is 300 mg/kg (in mice) and 791 mg/kg (in rats).

Indications

Flupenthixol is used to treat both positive and negative symptoms of schizophrenia, and has been documented to ameliorate associated depressive symptoms[18,22-25].

The application of flupenthixol in low dose as an antidepressant was first described by Holst[26], Sonne[27] and Reiter[28], and is licensed in the treatment

of mild to moderate depression. Flupenthixol was shown to reduce anxiety, while depression scores demonstrated it to be[29], more efficacious than placebo[30] and diazepam[31]; yet as effective as amitriptyline[32-35], nortriptyline[36], fluvoxamine[37] and mianserin[38]. In all of these studies, flupenthixol was found to have a quick onset of action with symptomatic improvement evident during the first week. Flupenthixol was superior to the comparator drugs in reducing general somatic, gastrointestinal and autonomic symptoms[14,20,24] causing fewer side-effects[24], and a lower patient drop-out rate. Although efficacy for both oral and intramuscular use have been demonstrated, it is advised that the use of flupenthixol decanoate be restricted to: short courses of treatment; patients refractory to other treatments; and to patients suspected of poor compliance; as depressed patients are known to be more susceptible to EPSE, and should rather use oral preparations[35].

In a number of controlled studies low dose administration of flupenthixol has been seen to be effective in treating psychosomatic disorders[24,33,39-41], especially in the presence of pain, lowered mood, anxiety or asthenia[42]. It demonstrated efficacy in reducing suicidal acts in borderline personality disorder[43,44]; the treatment of mania in bipolar mood disorder[45]; and reducing craving and enhancing abstinence in cocaine dependence[46,47]. Although evidence for enhancing abstinence in alcohol dependence is lacking, a potential indication for treating “dual diagnosis” patients (schizophrenia and alcohol abuse) exists[48]. Hashash et al. has demonstrated clinical efficacy in the treatment of functional dyspepsia[49].

Side-effects and contraindications

Flupenthixol is generally well tolerated, with a low incidence of mild adverse effects, which tend to disappear after the first few months of treatment. The most common side-effects reported are insomnia (5%), drowsiness (3.5%) and EPSE (0.8% at doses of 3mg/d or less). According to the product monograph[5], EPSE are usually minor, and temporary, with onset typically occurring within the first few days after depot injection[5,50]. However, this author could find no substantiating evidence in the literature. Other studies report the incidence of EPSE to be much more common, and similar to that occurring with fluphenazine decanoate[51-53].

Flupenthixol is contraindicated in patients with a known hypersensitivity to any of the following components, patients with circulatory collapse, central nervous system depression, comatose states, blood dyscrasias or pheochromocytoma[5].

Flupenthixol is relatively contra-indicated in excitable or hyperactive patients, especially in low doses (below 6mg/day) as it may exacerbate these features. It is also contraindicated in parkinsonism, severe arteriosclerosis, senile confusional states and severe renal, hepatic or cardiovascular disease. Caution is advised with use in organic brain syndrome, convulsive disorders, and advanced hepatic disease. Concomitant use with lithium increases the risk of neurotoxicity, while concomitant use with metoclopramide and piperazine increases the risk of EPSE[54]. Although there

is no evidence of teratogenicity, it should nevertheless be avoided in early pregnancy[55].

Administration

The following doses for the use of flupenthixol are advised:

1. For the treatment of depression, and for anxiolytic and activating benefits, 1-2mg/d, to a maximum of 3 mg/d *per os*[54].

2. For the treatment of psychosis, especially in apathetic, withdrawn, depressed and poorly motivated patients, 3-15mg/d, with a maximum of 40mg/d *per os*; or 20-60mg 2-4weekly, to a maximum of 18mg/d (100mg/2weeks) per deep intramuscular injection (IMI)[50].

Flupenthixol 3mg/d is generally accepted to be equal to 100mg/d CPZE[56]. Though consensus has been reached for the equivalent doses between different depot antipsychotics, discrepancies exist concerning the oral equivalent of depot antipsychotics. Atkins et al.[57] concluded that flupenthixol decanoate 40mg 2 weekly IMI is equal to 100mg/d CPZE.

Flupenthixol in the treatment of schizophrenia

Various studies since the 1960s confirmed the efficacy, and tolerability of flupenthixol. Although only one placebo-controlled trial[58] could be traced,

phase II and phase III clinical trials have proven the efficacy and tolerability of flupenthixol.

Johnstone et al.[58,59] evaluated 45 patients with acute schizophrenia in a double-blind trial in which they received either α-flupenthixol (activity as a DA receptor blocker), ß-flupenthixol (inactive), or placebo. Alpha-flupenthixol was found to be significantly more effective in treating positive symptoms than either of the other two treatments. The authors concluded that DA blockade is necessary for antipsychotic effect, and demonstrated that α-flupenthixol is active as such. Thirty-eight patients were reassessed at one year[58] with regard to clinical, social and cognitive functioning. However, assessment procedures are vague and no conclusions with regards to efficacy or tolerability were made.

In one the most extensive studies, Carney and Sheffield [60] reported on their clinical experience with flupenthixol decanoate (FD) during 1970-1974. After initial stabilization, patients with schizophrenia received 15mg FD, 20mg one week later, 30mg another week later, and then 30-120mg 3 weekly. One-hundred-and-thirty-four patients were initially included, but the study was then extended to include 199 patients, with a mean duration of follow-up of 21 months. The mean dose of FD required was 31.97-33.46mg every three weeks. Twenty-eight percent of patients developed mild parkinsonistic features which did not require any intervention, while 10% of patients required re-admission due to relapse. There was an annual default rate of 7%. The authors concluded that FD is efficacious and suitable for outpatient

and maintenance therapy. Although they did not compare FD to fluphenazine, they did report an observation that patients appeared more sociable, active and communicative on FD[51,60].

Gottfries and Green[52] and Curson et al.[61] confirmed the efficacy of FD preventing relapse. In a 12 year observational study[52] 22 of 58 completers (of 101 included participants), did not experience relapse. Although relapse and admission histories may reflect severity of illness, FD discontinuation increased relapse rates to 45% within 13 months[61].

In a more recent trial of one year duration, 62 patients with chronic schizophrenia were assigned to one of three different maintenance doses of FD. Forty-seven patients did not relapse, and completed the study. A consistent clinical improvement of 14-18% occurred after 3 to 6 months of treatment as measured by the BPRS. Negative symptoms, as measured by the SANS, also diminished with 22%. During the course of the trial, 26.4% of patients developed mild involuntary movements as measured by the Abnormal Involuntary Movement Scale (AIMS) for which 23.5% needed anticholinergic treatment[62].

Two studies investigated the use of large doses (50-400mg FD 2-3 weekly)[63,64]. These high doses utilize the sedative effect of FD, and the authors suggest that high doses should be considered for patients with poor response in previous or present psychosis, and whose syndrome is characterized by extreme psychomotor agitation, anxiety or aggression, or

treatment resistance. However, patients experienced four times more tremors, and this practice cannot be recommended.

In standard-of-care studies, non-inferiority of FD compared to fluphenazine in the treatment of schizophrenia was repeatedly established, with FD 40mg 2-3 weekly at least as effective as fluphenazine decanoate 25mg 2-3 weekly in reducing symptoms, as measured by the BPRS, and Clinical Global Impression scale (CGI)[29,53,65-68].

In 1975, Johnson and Malik did a double-blind comparison of FD and fluphenazine decanoate in 40 consecutively admitted patients with Schneiderian first rank symptoms of schizophrenia. All patients had a 7 day run-in period during which they received either oral chlorpromazine or other short-acting intramuscular preparations, followed by half a dose of FD or fluphenazine decanoate, with a full dose one week, and a further two weeks later. In addition, patients also received chlorpromazine 50-300mg/d *per os* (blinded). No difference was observed in antipsychotic effect, or the presence of EPSE, during the 56 days of the study[69].

In a double-blind cross-over design study, 30 patients received one month of placebo, followed by 12 weeks of either FD or fluphenazine decanoate, then again one month of placebo, and then the alternate depot antipsychotic. Twenty-two patients completed the trial, and the two depots proved to be equipotent[70].

Wistedt and Ranta entered 32 relapsed chronic schizophrenic patients into a double-blind randomized study. Participants received either FD (mean dose 31mg) or fluphenazine decanoate (mean dose 27mg) for a period of two years. No differences were reported with regard to global effect or effect on schizophreniac symptomatology during the first six months. However, after one year of treatment, FD showed a trend for better effect on control of schizophrenic symptoms[53].

Studies also suggested that FD demonstrated added benefit in the treatment of depressive symptoms, withdrawal, anxiety and psychomotor retardation and recommended that FD should be the treatment of choice in patients with a depressed mood, or a history of depression[18,29,53,69-71]. This held only true when FD was used in relatively low doses[72], and was disputed by Knights et al.[73].

Furthermore, FD may have a role in reducing the risk of relapse. In a double-blind six month withdrawal study of 41 chronic schizophrenic outpatients[74], FD (20-40mg every 3rd week) or fluphenazine decanoate (12.5-25mg 3 weekly) were used in comparison to placebo. Drugs were significantly more effective than placebo in preventing relapse and readmission to hospital, with a relapse rate of 62% in the placebo group, compared to 27% in the drug group.

In further double-blind active-comparator trials, FD was also demonstrated to be as efficacious as pipotiazine undecylenate[75], penfluridol[76], pimozide[77] and trifluoperazine[78].

In a Cochrane review of studies conducted between 1966 and 1998, FD demonstrated no differences with regard to outcomes such as death, global impression, relapse, or discontinuation when compared to other depot preparations[79]. However, the review suggested that that flupenthixol causes less movement disorder than other depot preparations (OR 0.23; CI: 0.08-0.7; NNT 5). This did not hold true for tremor (OR 1.2; CI: 0.3-4) and tardive dyskinesia (OR 1.60; CI: 0.4-6). It has to be kept in mind that, a meta-analysis/ reviews of results can only be as good as the data it is based on.

A few recent studies compared flupenthixol with the SGAs risperidone[80,81], amisulpride[82,83], and olanzapine[84,85]. Hertling et al. compared the effects of oral flupenthixol (mean dose 6.6 [±2.9] mg/day), and risperidone (mean dose 3.6 [±1.2] mg/day) in a multicenter, double-blind trial of chronic schizophrenic patients with mainly negative symptoms. Both groups showed a significant improvement regarding subjective quality of life (as measured by the EuroQol-Visual Analogue Scale), and positive attitude towards medication (assessed by means of the Drug Attitude Inventory-30). The flupenthixol group improved significantly more with regard to the ‘ability to cope with stress’, ‘feel more relaxed’, and the ‘ability to achieve something’[80].

In a six month randomized double-blind study in 144 chronic schizophrenic patients, comparing oral flupenthixol 6.23 (±2.86)mg/d with risperidone 3.56 (±1.20) mg/d, flupenthixol demonstrated non-inferiority with regard to effectiveness on negative symptoms (as measured by the PANSS negative subscale). The authors reported a trend in favor of flupenthixol concerning

the improvement of depressive symptoms, and a trend in favor of risperidone concerning the improvement of preexisting parkinsonian symptoms[25].

Flupenthixol (mean daily dose 22.6mg) was used as an active comparator in a randomized double-blind six week study of 132 patients with acute schizophrenia, investigating efficacy and tolerability of amisulpride (mean daily dose 956mg)[83]. Intention-to-treat evaluation demonstrated significant improvement under both medications, with 62% of patients in each group being responders. However, the mean difference in decrease of symptoms (BPRS) was 5.6 points (95% CI: 0.55-10.65) in favor of amisulpride. Withdrawal, due to intolerability, favored amisulpride (6%) over flupenthixol (18%), with less EPSE in the amisulpride group. Further analysis showed that amisulpride was significantly superior to flupenthixol regarding depressive features, but not negative symptoms, nor anhedonia-apathy[82].

Gattaz et al. compared the efficacy and the safety of olanzapine and flupenthixol in a four week double-blind RCT, in twenty-eight in-patients with schizophrenia. Sixty-nine percent of the olanzapine and 74% of the flupenthixol group were considered responders (a 40% decrease in BPRS). No significant group differences were reported with regard to overall efficacy (BPRS, Negative Symptoms Rating Scale [NSRS], and CGI scales)[84]. Statistically significant ($p<0.01$) more EPSE were reported in the flupenthixol group, and weight gain in the olanzapine group. A case report by Haberfellner also reported remission of TD when switching from flupenthixol 20mg, to olanzapine 10mg every three weeks. Both agents were

administered concurrent with an established lithium dosage. At two months the olanzapine was increased to 15mg, with complete remission of TD four months thereafter[85].

Two phase IV, post marketing surveillance trials on the use of flupenthixol in schizophrenia were recently published[86,87]. In the first study, 658 patients were treated for approximately ten weeks. Seven-point-eight percent of the sample was FEP, while 90.6% had been suffering from schizophrenia for a mean duration of 7.7 years. Sixty-six-point-three percent of the participants were treated with FD (mean dose equivalent of 9.2 mg/d) while the remainder received oral flupenthixol (mean daily dose 6.3 mg/d). Concomitant medication was allowed. Clinical efficacy was demonstrated in 77.8% of patients, with the CGI improving from 5.83 to 3.43 during the course of treatment. Tolerability was good with only 4.6% of patients experiencing treatment related side-effects. Quality of life (QOL) also improved with SWN (Subjective Well-being under Neuroleptic treatment; short version) scores improving from 61.2 to 78.5[86]. In a continuation study, 128 of the initial 658 patients were followed up for a subsequent 18 months. At the end of follow-up period, 68% of patients received FD, while 31.3% received oral flupenthixol, both at a mean daily dose of 6.7 (± 5.9)mg. The efficacy of flupenthixol treatment increased over time, with 89% of participants improving significantly over the 18 months. QOL further improved to SWN scores of 80.0. Physicians rated efficacy of flupenthixol as good, or very good, in 73.3% patients. Tolerability was assessed as good, or very good, in 86%. Although the rate of side-effects reported was only 5.5%,

22.7% of patients were reported to have needed anti-parkinsonism medication at some point during therapy[87]. The results of this study suggest that flupenthixol is a potent and safe antipsychotic for the long-term treatment of schizophrenia in routine clinical practice.

Flupenthixol and cognition

Despite flupenthixol being extensively administered for more than 40 years, only six studies mentioning the effect thereof on cognition could be traced[58,88-93].

A 1979 study by Johnstone et al. documented assessment of patients in clinical, cognitive and social terms. However the methods are vague, and the singular mention of cognitive assessments is the use of “memory for faces test”. No results are given, and no conclusions stated[58].

In 1985, Rösler et al. described the use of endogenous event-related brain potentials (ERP) as a measure of pharmacopsychological effects on cognitive functioning. The investigators documented a detrimental effect on perceptual and psychomotor functions, as well as memory retrieval after four days of treatment with flupenthixol 2mg/d *per os*[91]. It has to be noted that the aim of this study was to demonstrate the use of ERP as a measurement instrument, and not to document cognitive effects of flupenthixol.

The Scottish Schizophrenia Research Group[88] studied 46 patients with a FEP over a period of 12 months in a double-dummy double-blind trial of pimozide versus FD. Patients were assessed at baseline, at 3, 6, 9 and 12 months. Only 57% of patients were retested at one year, with only 44% realizing a good outcome in terms of absence of schizophrenic symptoms and relapse. Pimozide and FD were equally effective. Repeat psychometric assessment at 12 months found modest improvements from baseline on the Progressive Matrices[94], the Block design sub-test of the Weschler Adult Intelligence Scale (WAIS)[95] and the Digit Copying test[96]. No changes were documented for performance on the Mill Hill Vocabulary Scale[97] and the Similarities sub-tests of the WAIS.

Classen and Laux examined sensorimotor and cognitive performance of schizophrenic in-patients treated with antipsychotics. They assigned 50 patients to treatment with either haloperidol (10-30mg/day), flupenthixol (5-20mg/day) or clozapine (150-200mg/day) for seven days. Patients were assessed with the “Motorische Leistungsserie”[§], the “Bettendorff Reaktiometer”[**], a color-word-interference-test (FWIT, Stroop-test), and verbal and spatial ability tasks from the “Leistungsprüfsystem”[††]. There were no differences between treatment groups with regard to verbal or spatial abilities. Patients treated with clozapine performed better on the cognitive parameter “naming colored stripes” compared to patients treated with flupenthixol and haloperidol. Interhemispheric processing was reported to be less affected by clozapine and flupenthixol than by haloperidol. The authors

[§] Schoppe, KJ; 1974
[**] Bettendorff, SA; 1974
[††] Horn, W; 1983

concluded that risks in driving a car, or working at highly technical machinery, are due to impaired attention, rather than impaired motor function[93].

In 2007, Dunn and Killcross investigated the reversal potential of different substances on acute PCP induced disruption of a conditional discrimination task. Rats were taught a conditional discrimination task, wherein reinforcement was contingent on an appropriate lever press during a specific auditory stimulus. In the first experiment, PCP disrupted task performance at 1.5mg/kg, attenuated correct lever pressing at 2.5mg/kg, and abolished overall responding at 5 mg/kg. In the second experiment, PCP disrupted instrumental conditional discrimination performance in a dose dependent fashion, with 1.5 and 2.5mg/kg PCP having no disruptive effects on basic sensory, motor or motivational processes; while 5mg/kg PCP did disrupt these processes. They demonstrated that acute pretreatment with clozapine, SCH 23390 and α-flupenthixol (all known to have D_1 antagonistic effects) could attenuate PCP (1.5mg/kg) disruption of conditional discrimination; however, pretreatment with haloperidol (a D_2 antagonist) did not attenuate task disruption. The authors ascribe this effect to the relative abundance of D_1 receptors in the prefrontal cortex, whereas D_2 receptors are present in most cortical areas. They concluded that cognitive deficits in schizophrenia can be accounted for by D_1 receptor overstimulation[89].

One other RCT compared the efficacy of flupenthixol and risperidone in a sample of 144 patients with stable schizophrenia. Patients were randomized to flexible doses of flupenthixol 2-6mg/d po or risperidone 2-6mg/d po. The

primary outcome measure was the change in PANSS negative subscale score. The authors concluded that flupenthixol was non-inferior to risperidone in the treatment of negative symptoms. Furthermore, they also report improvement in cognition, as measured by the PANSS cognitive factor (consisting of P2, N5, G10, G11 and G13), in both treatment arms. No neuropsychological assessments were done. Although the incidence of EPSE was reported to be low in both groups, the total number of patients receiving biperiden was significantly higher in the flupenthixol group (53.7%) vs. the risperidone group (32.6%) ($p<0.01$)[25].

By its very absence, the literature on the efficacy of flupenthixol, in relation to aspects of cognitive functioning and functional outcome in schizophrenia, attests to an urgent need for more studies into these therapeutically important aspects of the illness.

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CHAPTER 7

THE USE OF DEPOT ANTIPSYCHOTICS

Schizophrenia is a life-long, chronic disorder, often marked by frequent relapses, incomplete inter-episode remission, chronic deterioration, and disability. According to Andreasen et al. remission is “a state in which patients have experienced an improvement in core signs and symptoms to the extent that any remaining symptoms are of such low intensity that they no longer interfere significantly with behavior and are below the threshold typically utilized in justifying an initial diagnosis of schizophrenia”[1]. Criteria for remission state that patients should be assessed on three dimensions of psychopathology: psychoticism (or reality distortion), disorganization, and negative symptoms. Simultaneous severity scores of mild, or less, should be maintained for a period of six months on all relevant items.

Although prospective and retrospective studies report that a minority (10%) of patients has a persistent, unremitting course[2,3] only one third of patients have a relatively good outcome, with no more than mild symptoms and impairment of functioning, while the remainder of patients will experience moderate to severe symptoms and functional impairment[4].

According to Robinson et al. recovery requires concurrent remission of positive and negative symptoms, therefore being relatively free of psychopathology, as well as adequate social and vocational functioning in the community. In a five year study of 118 patients with FEP, Robinson et al.

found that although sustained symptomatic and functional recovery is possible, the overall rate of recovery during the early years of the illness is low. After five years, 47.2% of their sample achieved symptom remission, and 25.5% had adequate social functioning for two years or more. Only 13.7% of subjects met full recovery criteria for two years or longer[5].

Considering the high relapse rates, and the possibility that with each relapse, patients are less likely to return to previous levels of functioning[6], a major focus of attention in FEP should be early, effective intervention and, subsequently, the prevention of relapse in order to improve long-term outcomes[7].

Medication adherence prevent relapse

The ability of antipsychotics to prevent relapse is well documented. As early as 1975[8], a review of 33 studies, summarizing double blind studies in outpatients observed for at least six months, documented frequency of relapse as 4-35% on treatment, compared to 29-80% on placebo, while May et al. also proved antipsychotics to be superior to psychotherapy[9]. Although there are many potential causes for relapse, the strongest predictors appear to be poor compliance and medication discontinuation[10,11], with a direct relation between degree of adherence and level of symptomatology[12].

Weiden and Glazer[13], studied 131 consecutively admitted patients with schizophrenia. Of these, 63 were considered “revolving door” patients, and

had an average of 1.3 hospitalizations per year over the three years prior to the index admission, and were only out of the hospital for a median period of five months before the index admission. Of the 50 patients with complete histories about precipitants for the index episode, the most common reason for rehospitalization was considered to be non-adherence to medication (n= 25; 50%), followed by medication non-response (n= 13; 26%). Monthly relapse rates for patients on antipsychotic medication were estimated as 3.5%, and 11.0% per month, for patients who had defaulted treatment. Over a period of two years, noncompliance contributed to 40% of rehospitalization costs, while loss of medication efficacy accounted for 60% of the costs[14].

In an open treatment withdrawal study of 32 schizophrenic outpatients on depot neuroleptics, 81% relapsed within one year, and 93% within two years of treatment discontinuation[15]. In a Cochrane review of 10 RCTs (N= 1042) examining the impact of medication withdrawal in patients with schizophrenia, stable on chlorpromazine, the relative risk for relapse (RRR) was 6.76 (CI: 3.37-13.54) within two months, and a RRR of 1.70 (CI: 1.44-2.01) after six months, of discontinuation[16].

Non-adherence to treatment in schizophrenia is high: by ten days after discharge, 25% of patients are non- or partially adherent[17]. Within the first 12 months of treatment after a FEP, 26% to 39% of subjects were found to be non-adherent, and 20% partially adherent with treatment[18-20]; this despite literature suggesting a one year post-hospital relapse rate in FEP of 41% on placebo vs. 0% on antipsychotic medication[21]. A 1986 review by Young et al.

reported a median default rate of 41% (range 10-76%) on oral antipsychotics and 25% (range 14-36%) with depot antipsychotics over periods of up to one year[22]. Non-compliance with oral antipsychotics was calculated at 40-60% over 4-6weeks, compared to 10-15% over two years with depot preparations[23]. Fenton et al. summarized findings from subsequent medication adherence studies in schizophrenia as a median one month to two year noncompliance rate of 55% (range 24-88%)[24]. Sustained delivery of a treatment that improves compliance is therefore particularly relevant to patients with FEP[25].

The development of long-acting depot antipsychotics during the 1960s was specifically aimed at addressing the issue of poor compliance and, although all findings were not consistent, they have been shown to be superior to conventional oral agents in preventing relapse[26]. In a review of studies that compared conventional oral and depot antipsychotic medications, mirror-image studies, in which patients served as their own controls, provided evidence of substantial benefit for depot antipsychotics. Across the studies reviewed, the one-year relapse rate for long-acting depot medication was 27% compared with 42% for patients who received oral medication[19].

In a South African study, premature discharge (i.e. early discharge due to bed pressure, against clinician's opinion), and depot use were the two significant predictors of high-frequency vs. low-frequency users of mental health in-patient services[27]. Under-utilization of depot antipsychotics

therefore seems to contribute to high-frequency use of mental health services.

Perceptions about depot antipsychotics

Despite evidence that depot antipsychotics enhance treatment compliance and decrease relapse rates, depot preparations remain less frequently prescribed than their oral counterparts[28]. In many countries fewer than 20% of individuals with schizophrenia receive depot antipsychotic medication, with rates ranging from 5% in the USA to 20% in the Scandinavian countries. Frequently stated reasons are psychiatrists', patients' and relatives' objections to depot treatment[29].

Psychiatrists remain reluctant to prescribe depot antipsychotics, with less than 10% offering depot treatment as an option after a FEP. Some clinicians regard the use of depot antipsychotics as stigmatizing, coercive, and frequently unacceptable to patients. Although a survey in a sample of 225 participants, of whom 83 were patients, confirmed that patients do harbor a fear with regard to constricted autonomy and painful injections; it was found that 67% of the patients did not receive adequate information to be able to make an informed decision[29]. A cross-sectional study by Patel et al. of 202 out-patients with schizophrenia confirmed that depots were perceived as more coercive than oral antipsychotics. However, patients' preference was associated with current medication formulation: depots were preferred by 43% (33/76) on depot vs. 6% (8/146) on orals ($p<0.001$). Patients who had

been treated with both tend to favor their current formulation[30]. A systematic review of the literature found that most patients have a positive attitude towards the use of depot antipsychotics[31].

Depot antipsychotics bypass pharmacokinetic issues with regard to absorption and first-pass metabolism[32] cause less fluctuation in drug levels[33] and therefore potentially cause fewer dose-related side-effects. Although clinicians frequently raise concerns with regard to EPSE, data on the incidence of EPSE with depot formulations are controversial, with some studies reporting an increased incidence with depot use, while others show no difference between oral and depot antipsychotics[34]. Recent studies reported the opposite, with lower rates of EPSE with the use of long-acting risperidone when compared to oral risperidone[35].

Recommendations

According to Kane et al., any patient for whom long-term antipsychotic treatment is indicated should be considered for depot antipsychotics[36]. These drugs have been described as a milestone in the development of psychopharmacology and a breakthrough in the treatment of psychosis[37]. Furthermore, depot antipsychotics improve adherence[32,38], and promote increased clinician contact and ease the detection of non-compliance[39]; a combination that may reduce relapses and hospitalization.

However, functional recovery depends on more than merely symptomatic stabilization and treatment[19]. Therefore, antipsychotics should never be used in isolation, but should form part of a treatment plan which includes psychosocial interventions, such as family psychoeducation, social skills training, and cognitive-behavioral therapy. In choosing which drug to prescribe, the clinician should consider previous experience, personal patient preference, patients' history of response (both therapeutic and adverse effects), and pharmacokinetic properties.

Depot antipsychotic maintenance therapy should be strongly considered, and may be used as the first-option maintenance strategy for persons who have difficulty to adhere to oral medication, who experience frequent relapses despite being compliant with oral medication; and those who prefer the depot regimen[40].

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CHAPTER 8

PURPOSE OF THIS STUDY

Despite the enormous impact of the illness, schizophrenia remains largely under-researched in South Africa. The overall outcome in schizophrenia remains poor[1], and is typically characterized by prominent impairment in social and occupational functioning, frequent relapses, and hospitalization[2].

Initial research and treatment of schizophrenia was primarily focused on the positive symptoms of the illness. The introduction of antipsychotics enabled millions of patients to live and function outside the confines of mental institutions. However, contemporary research into this illness has recognized other symptom domains of this disorder to be extremely important in determining outcome. Among these, cognitive impairment is considered to be a major contributing feature[3,4] to the overall burden of schizophrenia.

During the past decade there has been an increased interest in the early intervention and management of FEP. The primary aim has been to reduce overall morbidity and mortality; and the frequency, duration and severity of these episodes. Cognition has also become the main focus of detailed research to develop specific, targeted treatments[5-7]. Unfortunately, the search for new drugs is a protracted and costly exercise; often hampered by extended delays in the developmental process that limit advances in treatment.

Cognitive functioning can be improved by psychopharmacological intervention[8]. SGAs are thought to be more beneficial in the treatment of cognitive impairments, as outlined in various guidelines[9,10]. At the same time, contradictory study results continue to emerge regarding the efficacy and tolerability of FGAs.

A review of 28 studies that were published between 1990 and 1997 found that FGAs such as haloperidol have not proven to be very effective in improving cognitive deficits of schizophrenia[11]. However, Davis et al.[12], and Mishara and Goldberg[13], stated that FGAs may benefit cognitive function and negative symptoms. A number of possible scenarios exist that may explain the reasons for these discrepancies. It remains an issue of debate whether SGAs are truly pro-cognitive, or have reduced cognitive liability[14], compared to FGAs.

To illustrate this conundrum, one may consider the suggestion that the lack of efficacy and possible detrimental effects of FGAs on cognition fails to take into consideration the considerable inter-drug differences between FGAs. For example, haloperidol, a high potency agent, poses a greater risk of causing EPSE than low-potency agents such as chlorpromazine, and thioridazine. Therefore, the use of haloperidol frequently requires the adjunctive administration of anticholinergic medication that is known to have detrimental effects on memory[15,16]. Also of relevance is the fact that drugs with less specificity (i.e. prominent D_2 and D_1 blockage) will have the dual action of being an antipsychotic, and demonstrate adverse cognitive effects.

In both the CATIE[17] and CUtLASS[18] studies, the difference in efficacy between FGAs and SGAs was found to be minimal, leading Swartz et al. to conclude that FGAs are as efficacious, and more cost effective, than SGAs[19].

Flupenthixol has been therapeutically administered since 1962, yet only six documented studies could be traced that make mention of its effect on cognition[20-26]. It is clear that flupenthixol is not 'just another FGA', if such a thing exists at all. In many ways, it can be considered an 'atypical typical', or 'partial atypical' as it resembles SGAs in various ways[27]. The receptor binding profile (D_1 and D_2) of flupenthixol is more similar to clozapine than to fluphenazine, and it also has additional $5HT_{2A}$ receptor occupancy[28], with D_2/D_3 autoreceptor blockade, resulting in increased post-synaptic dopaminergic activity[29-32].

With the increased awareness of the importance of sustained drug delivery as a cornerstone in the effective long-term management of schizophrenia, there is a strong drive for the wider use of depot antipsychotic medications. By its very absence, the literature on the efficacy of flupenthixol, in relation to aspects of cognitive functioning and functional outcome in schizophrenia, as well as an absence of studies comparing flupenthixol with SGAs, attests to an urgent need for more studies. Clearly, none of the industry leaders are likely to pursue research into the efficacy of drugs that are 'off-patent'; therefore it will be up to academic departments to do so.

This study formed part of a larger project: a prospective longitudinal study of patients with FEP treated according to a standard protocol. The aim of the project is to investigate clinical, socio-demographic, biological (including structural and functional brain-imaging, genetic and biochemical markers) and treatment aspects related to outcome.

The aim of this study was to investigate cognitive deficits in patients with FEP, and its response to treatment with a depot formulation of the FGA flupenthixol (FD).

The specific objectives of this study were:

1. To document the specific cognitive deficits associated with FEP in a sample of South African patients.
2. To assess the changes in these cognitive deficits over time.
3. To investigate the relationships between cognitive deficits and:
    a. Psychopathology (in the following domains: psychosis, disorganization, negative, excitement and depression)
    b. Treatment outcome, in response to FD, in terms of:
        i. Symptom reduction
        ii. Achieving remission
        iii. Social and occupational functioning
        iv. Quality of life
4. To assess the value of cognitive assessments at baseline in predicting the outcome of FEP.

5. To examine the relationship between subjective and objective assessments of cognitive impairment.

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CHAPTER 9

METHODOLOGY

This was a prospective, non-randomized, single arm, open-label, longitudinal study of participants with FEP; treated with a long-acting antipsychotic, according to a fixed protocol, over a period of 12 months.

Subjects

We recruited 60 participants within 18 months. Participants were recruited from first admissions to Tygerberg and Stikland hospitals, as well as outpatients presenting at community clinics within our catchment area. The catchment area covers the metro and rural areas of the North Eastern part of Cape Town, the Winelands, and the Cape West Coast. The population of this area is approximately 1.5 million people.

Approval to conduct the study was obtained from the Institutional Review Board of the University of Stellenbosch (N06/08/148) and registered with the Medical Research Council of South Africa (MRC). The study was conducted in accordance with Guidelines on Ethics for Medical Research issued by the Medical Research Council of South Africa[1], the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP) [2] and the World Medical Association Declaration of Helsinki[3].

Patients who presented with FEP were approached by the researcher, dr R Schoeman or the co-investigator, dr B Chiliza. Each potential participant was adequately informed of the aims and methods of the study, the institutional affiliation of the researchers, the anticipated benefits and potential risks of the study, and sources of funding. The participants were assured that refusal to participate, or the withdrawal of consent, would not affect their current, or future, care in any way, shape or form. The subjects' integrity, privacy and confidentiality were ensured at all times. After the researchers explained the study, ensured that the potential participants had ample time to ask questions, and that questions were adequately answered; voluntary, written, informed consent was obtained before any study-related procedures were undertaken.

In the case of minors, or where a participant was unable to give consent due the severity of illness, the investigators obtained assent from the potential participant, and written informed consent from the legally authorized representative of the participant, according to the Mental Health Care Act[4]. As soon as the participant was able to give consent, written, informed consent was obtained. For the purposes of this study the mental condition which could potentially render a participant unable to give consent (i.e. psychosis), was a necessary characteristic of the research population.

Participants received ongoing treatment after completion of the study. The clinical treatment of the participant remained priority, and participants could be withdrawn from the study if deemed necessary by the investigator; for

example, another treatment was indicated due to the development of adverse effects, or non-response.

Inclusion criteria:

1. Male or female in- or outpatients
2. Aged between 16 and 45 years (extremes included).
3. DSM-IV-TR[5] diagnosis of schizophreniform disorder, schizophrenia or schizo-affective disorder.
4. Participants who had, during their lifetime, been exposed to a maximum of four weeks of antipsychotic medication.
5. An educational level of at least Grade 8.

Exclusion criteria:

1. DSM-IV-TR[5] diagnosis of delusional disorder, brief psychotic disorder, bipolar mood disorder with psychotic features, major depressive disorder with psychotic features, substance induced psychotic disorder, psychotic disorder secondary to a general medical condition, and psychotic disorder not otherwise specified.
2. Subjects who had been treated with a long-acting depot antipsychotic.
3. Significant physical illness.
4. Mental retardation.
5. Subjects unable or unwilling to give informed consent.

Withdrawal criteria:

1. If the investigator deemed it in the best interest of the participant to be withdrawn for any reason, this included the development of side-effects, or lack of efficacy.
2. Withdrawal of consent.

Procedures

All potential participants were assessed by one of the two investigators, dr R Schoeman or dr B Chiliza; both being qualified psychiatrists. Extensive interrater reliability (IRR) training was done on all rating scales used in the study, and an IRR coefficient of >80% was achieved on all scales. IRR was re-tested every six months.

Cognitive assessments were conducted by Dr Schoeman who completed her Masters level in psychology, and is a certified psychometrist. She attended a course, and received training in the use, and scoring of the MCCB in Boston, USA. IRR training sessions formed part of this course. Dr Schoeman acquired substantial experience in the assessments, qualifying her to train two suitably qualified research assistants to assist in the administration thereof. Regular IRR training sessions were completed, and a high level of IRR was maintained.

The following information was gathered at baseline by means of a clinical psychiatric interview and evaluation.

1. Demographic data and personal history, such as age, gender, ethnicity, first language, language of education, educational level, occupational history, marital status, and current living conditions. Collateral history was obtained, where possible, from participants' mothers (or other family members, if applicable), particularly regarding obstetric and developmental history.
2. Psychiatric history, including the chief complaint, the history of the current illness, specifically also attending to duration of untreated illness (DUI), and DUP, and changes in social, interpersonal and occupational functioning. We also explored any past psychiatric history, previous and current substance use/abuse/dependence, and previous psychiatric illness and treatment.
3. Medical history, including any presence of head injuries, epilepsy, or other significant illnesses, past and current treatment.
4. Previous and concomitant treatment was recorded as completely as possible.
5. Specific attention was also paid to collecting history with regard to a family history of psychiatric illness, and treatment received, as well as a family history of medical diseases, such as hypertension or diabetes.
6. Mental status examination, specifically evaluating the participant's appearance, orientation, attention and concentration, mood and affect, speech, thought processes and behaviour.

Each subject underwent a full physical examination at baseline, including a neurological evaluation. Safety and side-effect measures included weight, height, waist circumference, glycated haemoglobin (HbA1c), fasting blood-glucose, fasting lipogram, serum prolactin and an electrocardiogram. These assessments were repeated every three months.

At baseline and on each of the visits, participants were asked about substance use since the previous visit, and urine metamphetamine and cannabis drug screens were performed at baseline and every three months thereafter.

The following rating scales and instruments were used to assess all of the participants:

1. The Positive and Negative Syndrome Scale for Schizophrenia (PANSS)[6].
The PANSS was used as a primary meaure of psychopathology and treatment response. It consists of 30 clinician-rated items with ratings based on all information relevant to the week prior to ratings. The information derives from both the 30 to 40 minutes semi-structured clinical interview, as well as collateral information obtained from, for example, the primary caregiver. During the interview attention was being paid interpersonal behaviour, cognitive-verbal processes, thought content, physical behaviour, and response to structured questioning; thereby permitting direct observation of affective, motor, cognitive, perceptual, attentional, integrative and interactive functioning of the patient (see table 9.1)

Table 9.1: The Positive and Negative Syndrome Scale for Schizophrenia				
	Description	**Primary score**	**Test-retest reliability: Pearson product-moment correlation (r)**	**Internal consistency: α coefficients**
Positive Scale	7 items: P1 delusions, P2 conceptual disorganization, P3 hallucinatory behaviour, P4 excitement, P5 grandiosity, P6 suspiciousness/persecution and P7 hostility.	Each item has a 7-point rating (where 1 indicates the absence of a symptom or sign, while 7 is the most extreme presentation). The PANSS is scored by summation of item scores, with total scores ranging from 30 to 210	0.8 ($p<0.001$)	0.73 ($p<0.001$)
Negative Scale	7 items: N1 blunted affect, N2 emotional withdrawal, N3 poor rapport, N4 passive/apathetic N5 emotional withdrawal, N6 lack of spontaneity and flow of conversation and N7 stereotyped thinking.		0.68 ($p<0.1$)	0.83 ($p<0.001$)
General Psychopathology Scale	16 items: G1 somatic concern, G2 anxiety, G3 guilt feelings, G4 tension, G5 mannersims and posturing, G6 depression, G7 motor retardation, G8 uncooperativeness, G9 unusual thought content, G10 disorientation, G11 poor attentionm, G12 lack of judgment and insight, G13 disturbance of volition, G14 poor impulse control, G15 preoccupation, G16 active social avoidance.		0.68 ($p<0.2$)	0.79 ($p<0.001$)

2. Clinical Global Impression rating scales (CGI)[7]

The CGI was used as a secondary measure to provide a global rating of illness severity, improvement and response to treatment. This is a clinician rated scale, requiring the clinician to compare the subject to the clinician's past experience with patients who have the same diagnosis. The CGI is rated on a 7-point scale, with the severity of illness scale (CGI-s) using a range of responses from 1 (not ill)
through 7 (extremely severe), while the change in illness scale (CGI-c) scores range from 1 (very much improved) through 7 (very much worse). Each component of the CGI is rated separately and the instrument does not yield a total score.

3. Calgary Depression Scale for Schizophrenia (CDSS)[8]

The CDSS is a nine item structured interview used for assessing the presence of depressive symptoms during a two week period. Items assessed are: depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early awakening, suicide, and observed depression. Each item has a four point distribution, anchored by descriptors, with 0 indicating an absence of symptoms, while 3 indicate severe symptoms. The possible total score range from 0 to 36, with a score of 7 being the cut-off for depression. The intraclass correlation coefficient (ICC) was estimated at 0.895, while the Cronbach's alpha was 0.79[9]

4. Extrapyramidal Symptom Rating Scale (ESRS)[10]

The ESRS was used as a side-effect measure and rates the presence of parkinsonistic, dystonic, and dyskinetic side-effects. The scale includes a subjective questionnaire used by the clinician to ask the patient about the presence of symptoms which may not be observable or present during the interview. Scores can range from 0 (absent) to 3 (severe) for each of the 12 items.The individual items are analyzed separately and a subtotal of scores is calculated for parkinsonism (items 1 to 7), dystonia (items 8 and 9) and dyskinesia (items 10 and 11). Item 12 (dizziness when standing up) is rated separately. A total score is derived by totaling the sub-scores of these items. Hereafter symptoms are assessed following a standard procedure as described in the manual[11], which forms part of a routine neurological assessment. The presence and severity of parkinsonism is rated by 18 items evaluating expressive automatic movements, bradykinesia, rigidity, gait and posture, tremor, akthisia, sialorrhea, and postural stability. Eighteen items evaluate the presence of acute and non-acute/chronic dystonia in the limbs, head, jaw/chin, tongue, lips and trunk; and 7 items evaluate the presence and severity of dyskinetic movement in the tongue, jaw, bucco-labial area, trunk, limbs, and face. Four items assess the clinical global impression of severity of parkinsonism, dystonia, dyskinesia and akathisia. Each item has a seven point distribution, anchored by descriptors, with 0 indicating an absence of symptoms, while 6 indicate extremely severe symptoms. IRR coefficients were determined for each item of the scale and ranged from 0.80 to 0.97[10]. While for the different divisions, IRR ranged from 0.88 to 0.97[12].

5. Premorbid Adjustment Scale (PAS)[13]

The PAS was used to evaluate the degree of achievement of developmental goals at each of several periods of a subject's life, prior to the onset of schizophrenia. The aspects evaluated include social accessibility-isolation, peer relationships, ability to function outside the nuclear family, and capacity to form intimate socio-sexual ties. The four life periods assessed are Childhood (up to 11 years), Early Adolescence (12-15years), Late Adolescence (16-18 years), and Adulthood (19 years and beyond). A general section also evaluates the highest level of functioning obtained prior to illness onset, as well as the duration and characteristics of onset of illness, and information pertaining to level of education. Each item has a seven point distribution, anchored by descriptors, with 0 indicating the healthiest adjustment, while 6 indicate the least-healthy end of the spectrum of functioning. Subscale scores for the specific life periods are calculated by summing the item scores and dividing this total by the maximum possible score for the items. An overall score is calculated by averaging the subscale scores. The ICC for IRR for the subscales were calculated as 0.62 (Childhood), 0.83 (Adolescence) and 0.91 (Adulthood), while for the overall score, the intraclass coefficient was 0.74 ($p<0.001$).

6. Social and Occupational Functioning Assessment Scale (SOFAS)[14]

The SOFAS is rated by a clinician as an indication of an individual's level of social and occupational functioning on a scale from 0 to 100, where 1-10 represent the individual with a persistent inability to maintain minimal personal hygiene, being a risk for harm to the self or others, and who needs

considerable external support such as nursing care and supervision; while 91-100 is indicative of excellent functioning. Impaired functioning can be due to both mental and/or physical limitations.

7. WHO Quality of Life (WHOQOL-BREF)[15]

The WHOQOL-BREF is a self-administered scale, but if the subject does not have the ability to complete it independently, he/she may be assisted by the interviewer. Twenty-six items are scored from 0 (not at all satisfied) to 5 (completely satisfied) and items are summed in order to obtain 4 domain scores, denoting an individual's perception of quality of life with regard to the specific domain. Physical health (consisting of activities of daily living, dependence on medicinal substances and medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest, work capacity), Psychological health (bodily image and appearance, negative feelings, positive feelings, self-esteem, spirituality/religion/personal beliefs, thinking, learning, memory and concentration), Social relationships (personal relationships, social support, and sexual activity) and Environment (financial resources, freedom, physical safety and security, health and social care: accessibility and quality, home environment, opportunities for acquiring new information and skills, participation in and opportunities for recreation/leisure activites, physical environment [pollution/noise/traffic/climate], and transport) are evaluated.

Domain scores are scaled in a positive direction (i.e. higher scores denote higher perceived quality of life), with 100 being complete satisfaction.

8. The Wechsler Adult Intelligence Scale (WAIS): Vocabulary Subscale[16]

The Vocabulary Subscale score of the WAIS (3rd ed) was used as estimation of premorbid intelligence. It is a measure of expressive word knowledge, and is the subscale with the highest mean proportion of predictable variance for validity ($r=0.95$; $p<0.05$). For this subtest, the subject has to give oral definitions for words presented by the clinician. Thirty-three words are presented to the subject. Reponses are scored according to sample responses, where a two-point response indicates that the subject has a good understanding of the word; a one-point response is not incorrect, but shows poverty of content; while a zero-point reponse is an entirely incorrect response. The test is discontinued after six consecutive zero-responses. The maximum score obtainable is 66. Hereafter, the Z-score is calculated according to suitable norms provided in the manual. The test was translated and back-translated into Xhosa, enabling us to administer the test in the participant's first language (Afrikaans, English, or Xhosa).

9. The MATRICS Consensus Cognitive Battery (MCCB)[17]

The MCCB was used as primary outcome measure of cognition. Domains assessed were Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and problem solving, and Social cognition (see table 3.1, p70-71 for details). Testing can usually be completed in one session of 60 to 90 minutes. Breaks can be provided as needed, and testing can be extended over multiple sessions if the situation warrants it. Detailed instructions for administration are provided in the manual. All of the ten tests are clinican administered. Nine of the tests are pencil-and-paper tests, while the CPT-IP is a computerized test. Participants

were randomized to alternative versions of the tests included in the battery, where available, in order to limit the practice-effect of repetitive testing over time.The MSCEIT™ and CPT-IP results are computer generated. The MCCB Computer Scoring Program was used to convert the primary raw scores obtained on the tests into T-scores and percentile scores. The program also provides T-scores and percentiles for the seven cognitive domains, as well as a Cognitive Composite T-score and percentile score.

10. Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS)[18]

The SSTICS, a 21-item self-report measure, which allows a quantitative approach to the subjective experience of cognitive deficits in schizophrenia. Subjects are asked to rate the frequency of their cognitive difficulties according to a four-point Likert-type scale ranging from 0 ("never") to 4 ("very often"). The questions formulated focused on participants' perceived impairments in four cognitive areas: memory, attention, executive functions, and praxia. Eleven questions assess working memory and explicit (episodic and semantic) memory. Attention is explored by five questions with regard to distractibility, alertness, selective attention, divided attention and sustained attention. The executive functions are assessed by three questions on planning, organization, and flexibility. The last two questions assess language and praxia. The scale has a good internal consistency with a Cronbach's alpha coefficient of 0.858. The Spearman's correlation coefficient for test-retest reliability at a mean interval of 11 days was 0.82 ($p<0.01$). Factor analysis revealed subjective cognitive domains of

complaints such as Sustained executive function, Memory of information, Consciousness of effort, Daily life, Distractibility, and Alertness. This questionnaire was only used after the initial six months of the study, due to difficulty translating and applying the instrument in our cultural context.

11. Birchwood Insight Scale (BIS)[19]

The BIS is an eight-item self-report measure with possible responses to the items being "agree," "unsure," or "disagree" that are scored on a three-point Likert-type scale ranging from 0 to 2. Two items evaluate the ability to re-label experiences as part of one's illness, two items assess the individual's awareness of illness, and 4 items evaluate the individual's awareness of the need for treatment. Subscale items are summed, and the Need for Treatment subscale is divided by 2, yielding a total score for each subscale. Total scores may be summed for a BIS total score ranging from 0 to 12, with higher scores indicating greater insight. The BIS is widely used in research on psychosis and has very good test-retest reliability (0.90; $p<0.001$), validity (Cronbach's alpha of 0.75; $p<0.001$), and sensitivity to change.

The duration of the clinical evaluation and completion of the first 7 rating scales was 2.5-3 hours. Participants' cognitive assessments were completed the following day during a 2-2.5 hour period (instruments 8 to 11).
Where participants were judged to be too ill to undergo neuropsychological testing, these tests were postponed until such participant was considered to be adequately stabilized by the investigator and treating team.

After baseline evaluation, each subject was seen daily for the first week, for monitoring of adverse events, and completion of the PANSS and CGI. Hereafter, participants underwent 8 scheduled visits over a 12 month period, with order of evaluation and administration of instruments as indicated (see table 9.2). Subjects were monitored for side-effects and adverse events throughout the study. Some participants were seen more regularly due to unforeseen events. Cognitive assessments were done at baseline, four weeks, and then at 3, 6, and 12 months.

Table 9.2: Study plan

Visit	Baseline	Week 0	Week 2	Week 4	Week 6	Month 3	Month 6	Month 9	**Month 12**
Consent	x								
History	x								
Physical Examination	x								x
Vital signs	x					x	x	x	x
Heigth and weight	x								x
ECG	x								x
Lab tests	x					x	x	x	x
Drug screen	x			x	x	x	x	x	x
Adverse events and concomitant medication	x	x	x	x	x	x	x	x	x
PANSS	x	x	x	x	x	x	x	x	x
CGI	x	x	x	x	x	x	x	x	x
CDSS	x	x	x	x	x	x	x	x	x
ESRS	x	x	x	x	x	x	x	x	x
PAS	x								

SOFAS	x						x		x
WHOQOL	x						x		x
WAIS	x								x
MCCB	x			x		x	x		x
SSTICS	x			x		x	x		x
BIS	x						x		x

Treatment

There was a wash-out phase of up to seven days, during which all psychotropic medications were discontinued. Treatment with oral flupenthixol 1-2mg/d was started for one week, prior to the first FD dose (so as to rule out hypersensitivity to flupenthixol), and then for a further week if needed, to allow FD to take effect. However, due to the development of EPSE in two of the first five participants, the protocol was amended so that all participants received oral flupenthixol 1mg/d *per os* for seven days only. Hereafter, FD was introduced. The starting dose of FD was 10mg every 2nd week, with dose increases allowed, at 6-weekly intervals, in increments of 10mg, to 30mg per fortnight. These dose increases were determined according to clinical response of the participants, as well as tolerability.

<u>Criteria for dose increments</u>**:**

- At week 6: failure to have an adequate response, as defined by a decrease in PANSS total score of 20%, as well as at least minimal improvement on the CGI.

- At week 12 (3 months): failure to attain remission, as defined by PANSS score of 3 or less on items P1, P2, P3, N1, N4, N6, G5 and G6, as well as CGI much/ very much improved[20].

- At week 18: at least a 20% reduction in PANSS total score, but CGI was not much/very much improved, AND CGI severity mild or less

- At week 24 (6 months): at least a 20% reduction in PANSS total score

If by 6 months participants did not have at least a 20% reduction in PANSS total score, they were discontinued due to non-response and offered clozapine.

In cases where additional antipsychotic medication was required due to acute exacerbation of symptoms between visits, oral flupenthixol tablets 1mg/d were given at the discretion of the clinician.

Concomitant medication:

1. Any medication for physical conditions, in use prior to the commencement of the trial, was allowed to be continued. Medication for other conditions that arose during the course of the trial was permitted at the investigator's discretion.
2. Lorazepam was prescribed for additional sedation in doses of up to 12mg/day during the acute phase of the study; thereafter doses could not exceed 4mg/day.

3. Orphenadrine and/or biperidine were permitted for the treatment of EPSE.
4. Propranolol could be prescribed for akathisia.

Participants were not allowed to receive lorazepam, propranolol or anticholinergics for a 12 hour period prior to an assessment. The following medications were not permitted: other antipsychotics, mood stabilizers, and psychostimulants.

Data analysis

All data was recorded in case record forms. Statistical analyses were conducted with the assistance of a biostatistician. Statistical analyses were conducted using STATISTICA version 9[21]. A 5% significance level ($p<0.05$) was used as the guideline for significant differences. Mixed model repeated measures of variance analysis (ANOVAs) were conducted to examine mean T- and Z- score changes over time. The mixed models included all patients at a specific time point, whether they have completed the study or not. Therefore patients are not excluded from the analyses if they did not complete the study. Non-parametric Mann-Whitney U and Kruskal-Wallis tests were used to compare different groups of patients. To investigate the relationships between cognitive domains (obtained from the MCCB, WAIS, SSTICS, and BIS) and psychopathological symptoms (obtained from the PANSS), Spearman's rank correlation coefficients were computed. No formal sample size had been calculated for. Within analyses of specific variables (for ANOVA and mixed models) Fisher LSD was used for multiple testing

corrections. No corrections were applied between analyses of different variables.

Funding

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CHAPTER 10

RESULTS: DEMOGRAPHIC DATA

A total of 60 participants were included in the study. However, two were excluded from analyses due to protocol violations.

Age, gender and marital status

The final sample (N=58) consisted of 19 (33%) females and 39 (67%) males, with a mean age of 23.26 years (± 5.81) (see figure 10.1).

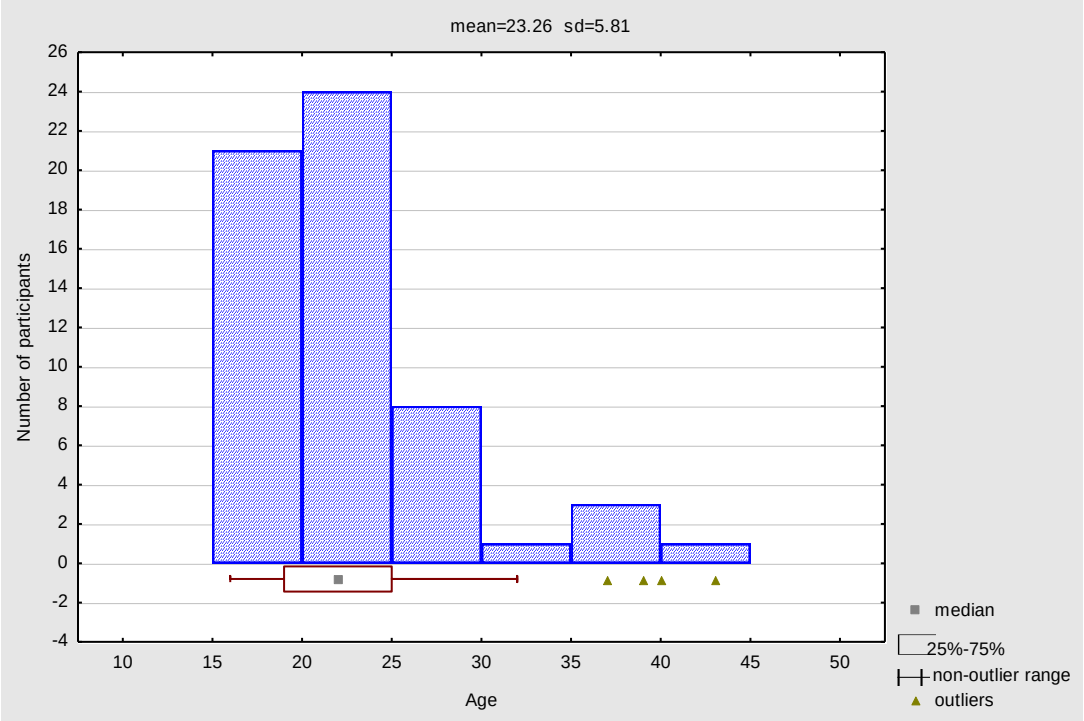

Figure 10.1: Age distribution of participants

Five of the participants (4 females and 1 male) were married, one male was divorced, one female widowed and one female was in a *de-facto* relationship. The remainder of the sample was single.

There was a significant correlation ($p<0.01$) between age at baseline and severity of illness at baseline (mean PANSS[1] Total score = 100.5, ± 15.89; r=-0.40), age at baseline and premorbid IQ estimation at both baseline (mean WAIS[2] Vocabulary Z-score = -2.20, ± 0.91; r=0.46) and at one year (mean WAIS Vocabulary Z-score = -1.93, ± 0.96; r=0.50), and baseline age and overall cognition (mean MCCB[3] Cognitive Composite Score = 20.51, ± 13.45; r=0.50) at one year.

Male participants were younger than their female counterparts at baseline (see figure 10.2).

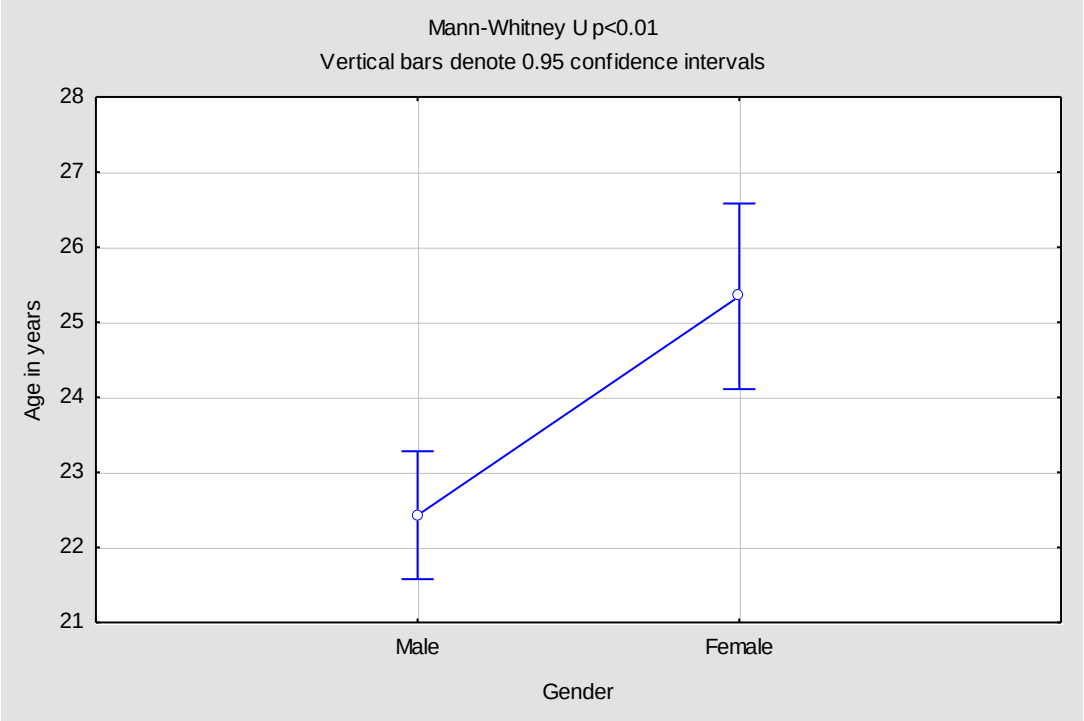

Figure 10.2: Gender and age of inclusion

There were no significant differences between genders with regard to severity of illness at baseline and one year, premorbid IQ estimation at baseline and one year, or overall cognition (MCCB Cognitive Composite Score) at baseline and one year.

Language and ethnicity

The majority of the sample was of Mixed (African-Caucasian) ethnic origin, while 22% were of either White (Caucasian) or Black African ethnic origin (see figure 10.3). All of the participants were South African, except for one female who held Ugandan citizenship.

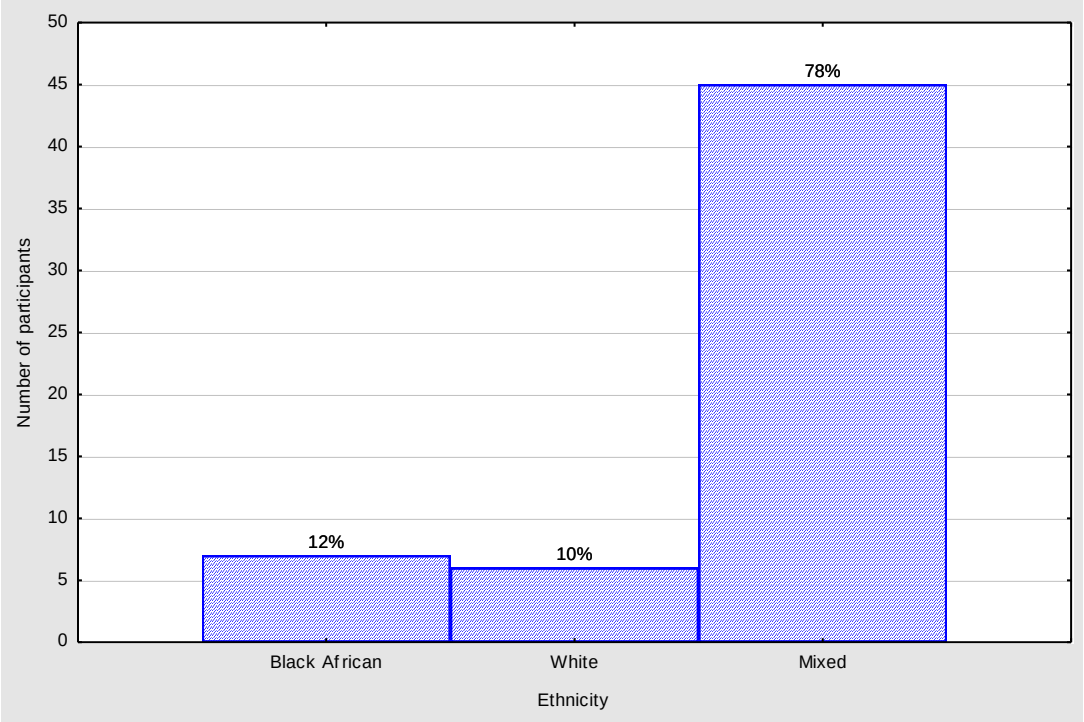

Figure 10.3: Ethnic origin of participants

Seventy-nine percent (46/58) of the participants' home language was Afrikaans, 8.6% (5/58) English, 10.3% (6/58) Xhosa and 1.7% (1/58) French. Assessments were completed in patients' preferred language with 60.34% (35/58) Afrikaans and 39.96% (23/58) English.

There was a significant difference between participants assessed in Afrikaans or English at baseline with regard to illness severity (p=0.03) (see figure 10.4), which disappeared by one year.

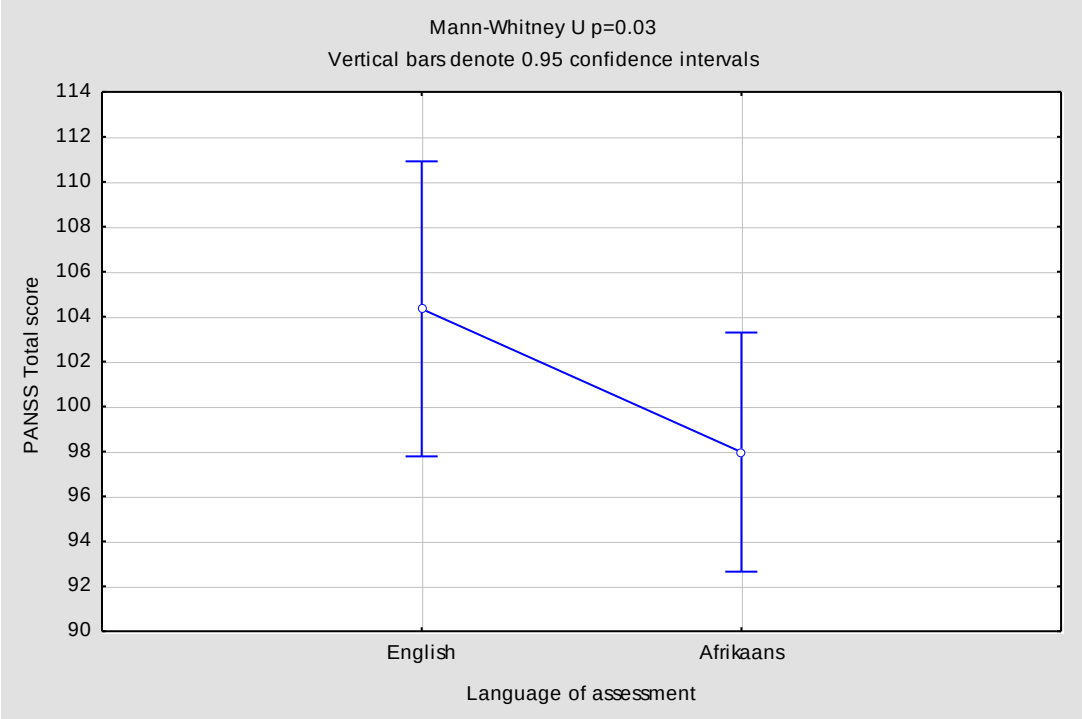

Figure 10.4: Language of assessment and difference in mean PANSS Total score at baseline

There was a significant difference between participants assessed in Afrikaans or English with regard to premorbid IQ estimation at baseline (p=0.03) and one year (p=0.03), favoring Afrikaans speaking participants. Although there was no difference between Afrikaans and English groups with regard to mean MCCB Cognitive Composite Score at baseline, at one year, Afrikaans speaking participants performed significantly better than English speaking participants (p=0.04), with mean MCCB Cognitive Composite Scores of 25.17 (± 14.67) and 14.94 (± 8.91) respectively (see figure 10.5).

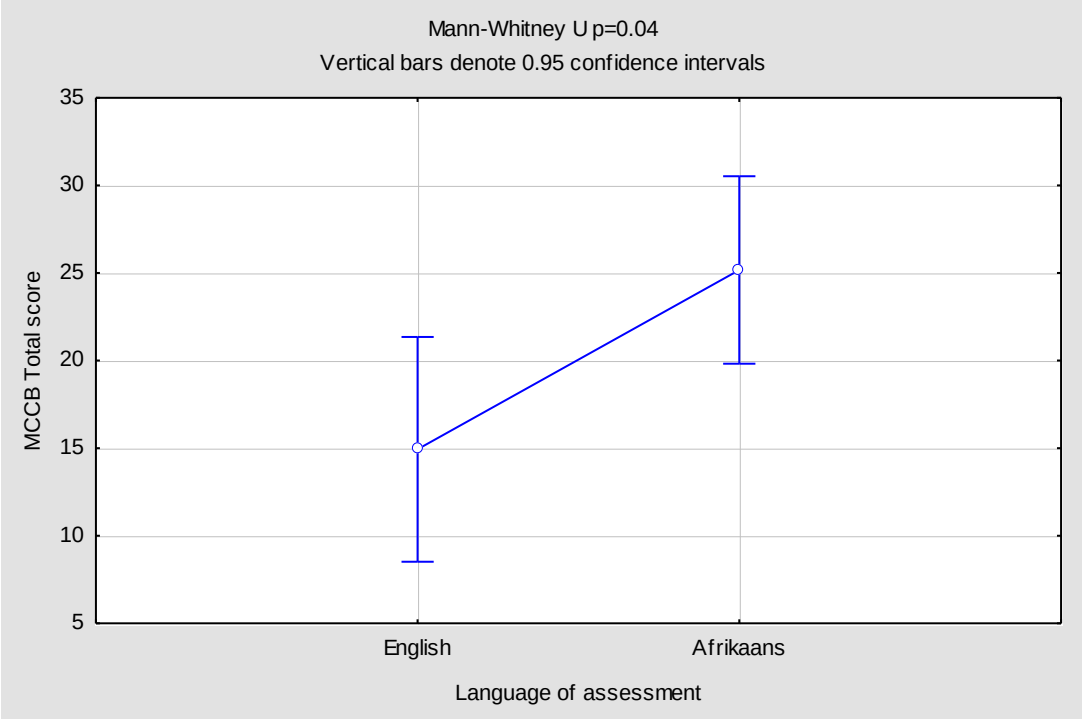

Figure 10.5: Language of assessment and difference in mean MCCB Cognitive Composite Score at 1 year

There was a significant difference between Black Africans and those of Mixed ethnic origin with regard to premorbid IQ estimation at both baseline (p=0.03) and one year (p=0.02) (see table 10.1 and figure 10.6). However, these results should be interpreted with caution due to the small number of participants in the White and Black African groups.

Table 10.1: WAIS vocabulary Z-score

	Baseline (SD)		One year (SD) *	
	N	**Mean**	**N**	**Mean**
White	6	-1.08 (± 0.71)	4	-0.77, ± 0.93
Mixed	45	-2.33 (± 0.89)	34	-2.11, ± 0.86
Black African	7	-2.13 (± 0.67)	6	-1.86, ± 1.06

* LOCF

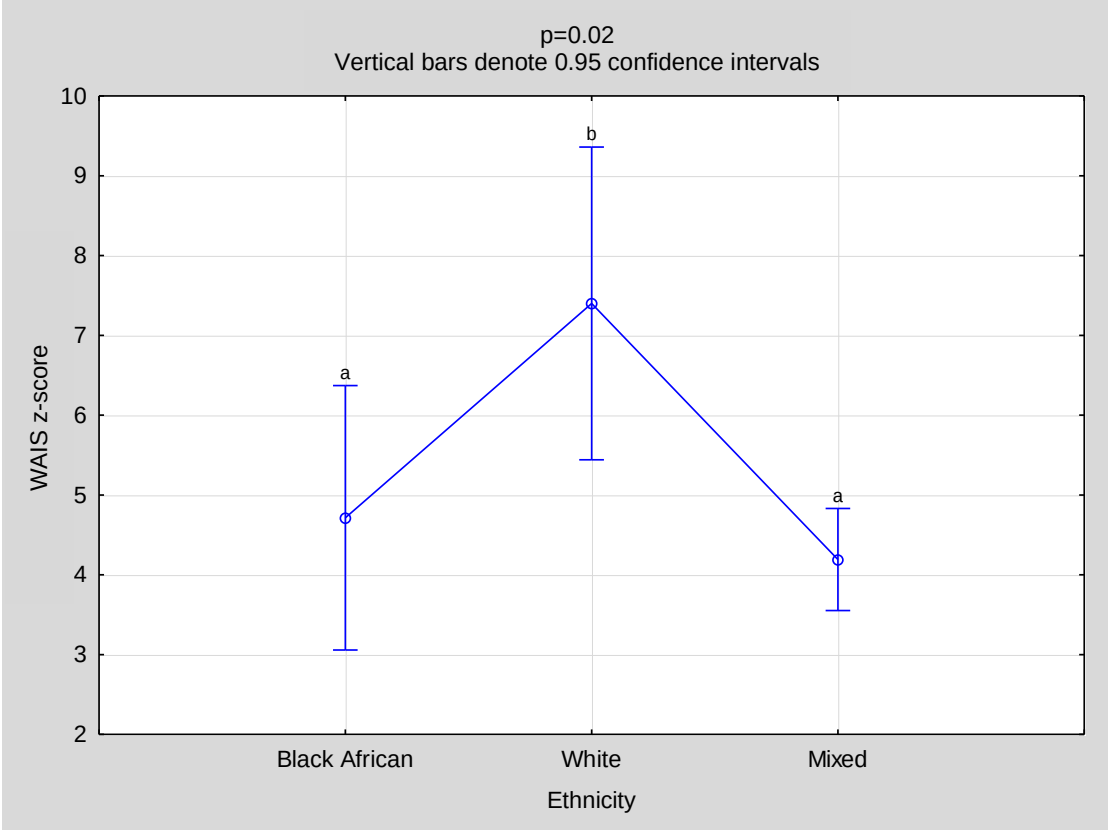

Figure 10.6: Ethnicity and WAIS vocabulary mean score at baseline

There were no significant differences among ethnic groups and illness severity at baseline and one year, or among ethnic groups with regard to cognition (MCCB Cognitive Composite Score) at baseline and one year.

Developmental, family and medical history

Although most of the participants were born from normal pregnancies, complications were reported in 22% (13/58) of pregnancies (see figure 10.7). One participant's mother was informed during several antenatal care visits that the baby had died *in utero*, but later gave birth to a healthy baby. One mother was on fluphenazine decanoate for the duration of the pregnancy, and another mother suffered from multiple sexually transmitted diseases (STDs) during pregnancy.

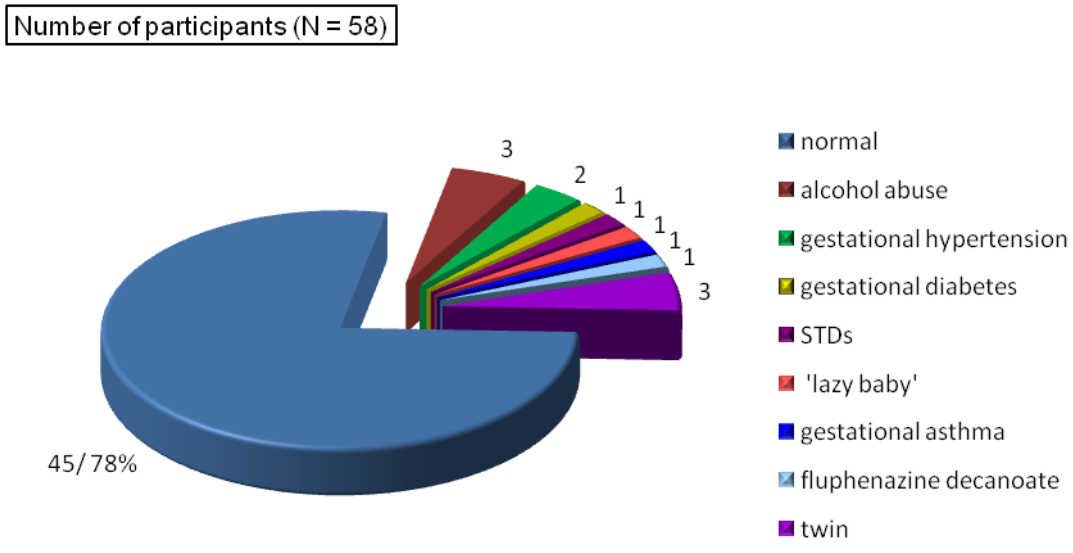

Figure 10.7: Pregnancy history

The majority of participants were born by way of normal vaginal deliveries. However, 12% (7/58) births were complicated. There were two emergency caesarian sections (1 due to uterine rupture, and 1 due to pre-eclampsia), two elective caesarian sections (previous caesarian sections), two forceps deliveries, and two babies born with low Apgar scores after prolonged labour and induction.

All participants attained normal developmental milestones.

The family history of mental disorders was known in 55 of the participants, though specific detail was not always accessible (see figure 10.8). One patient's family history included both depression and post traumatic stress disorder. Other affected family members included a younger sibling with fetal alcohol syndrome, and a cousin who committed suicide.

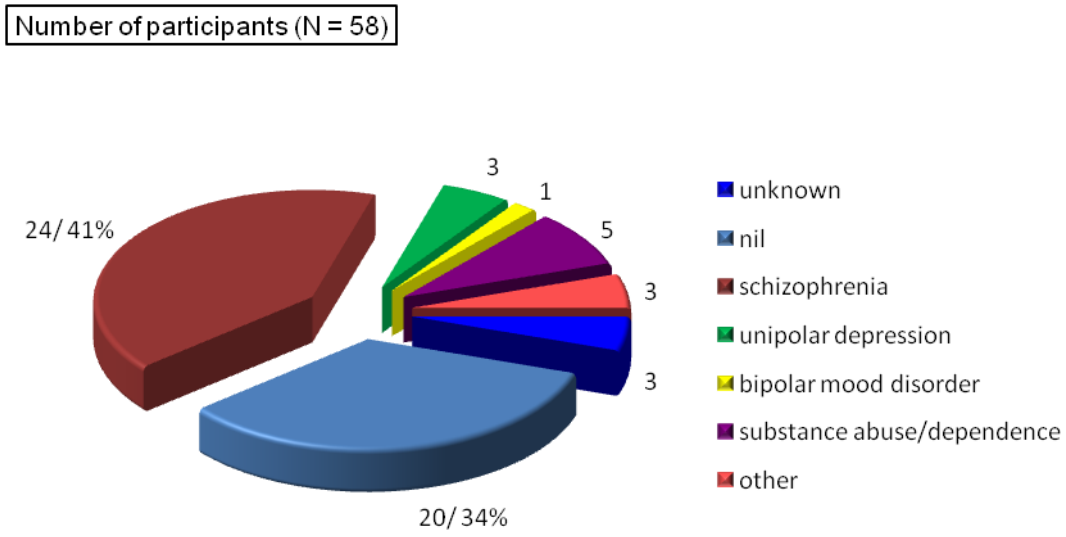

Figure 10.8: Family history of mental illness

Most participants were physically healthy at time of inclusion (other than the index disorder), and remained so throughout the study. The mean weight of the participants was 59.02 (± 11.62) kg, with a mean height of 166.01 (± 9.49) cm, and a mean BMI of 21.42 (± 4.01). Two participants suffered from diabetes mellitus; the one using insulin, and the other oral anti-hyperglycaemic medication. Both were well controlled on treatment. One participant, known with well-controlled asthma, used an inhaler as needed, and another participant had well-controlled epilepsy (after meningitis) for which he used clonazepam. One female was diagnosed with subclinical hypothyroidism and iron deficiency. She withdrew her consent after the 6 month follow-up visit. One female, age 16, had a BMI of 14 at inclusion. She developed akathisia on the FD and was withdrawn from the study after one month. One female had positive serum syphilis tests (RPR and TPHA) at 2 weeks. Neurosyphilis was excluded (CSF tested VDRL negative). She was treated with benzatine penicillin 2.4 million units/week IMI for three weeks. A 21 year old male developed catatonia three days after baseline. He received oral flupenthixol 1mg per day for three days, but left the study prior to receiving any flupenthixol decanoate.

Substance abuse

Five participants tested positive at baseline (urine drug screening) for substances of abuse: four used cannabis, while one participant used both cannabis and methaqualone. There was no difference in severity of psychosis (mean PANSS Total score), or the presence of positive (mean

PANSS P score), negative (mean PANSS N score) and depressive symptoms (mean PANSS D[4] score) between the group of participants testing positive for substances at baseline (users) and those without (non-users). There was no difference in overall cognitive functioning (MCCB Cognitive Composite Score) between the two groups. The mean PANSS Cognitive factor[5] (PANSS C) score did not differ between the groups, although insight (PANSS G12) differed significantly between the two groups (see table 10.2).

Table 10.2: Baseline substance abuse

	Users (n=5)	**Non-users (n=53)**	
Item	**Mean (SD)**	**Mean (SD)**	**Mann-Whitney p**
PANSS Cognitive factor	19.20 (± 3.03)	16.15 (± 3.47)	0.07
PANSS G12	6.00 (± 0.00)	4.94 (± 1.03)	0.05

At 3 months, 16/56 (28.6%) tested positive for substance use (13 for cannabis, 7 for methaqualone and 7 for methamphetamines). Seven of these participants were polysubstance users. Although there were no significant differences between the two groups with regard to symptoms severity (mean PANSS Total score) or cognitive symptoms (mean PANSS C score and mean MCCB Cognitive Composite Score), the non-users had better insight (p=0.05) (see figure 10.9)

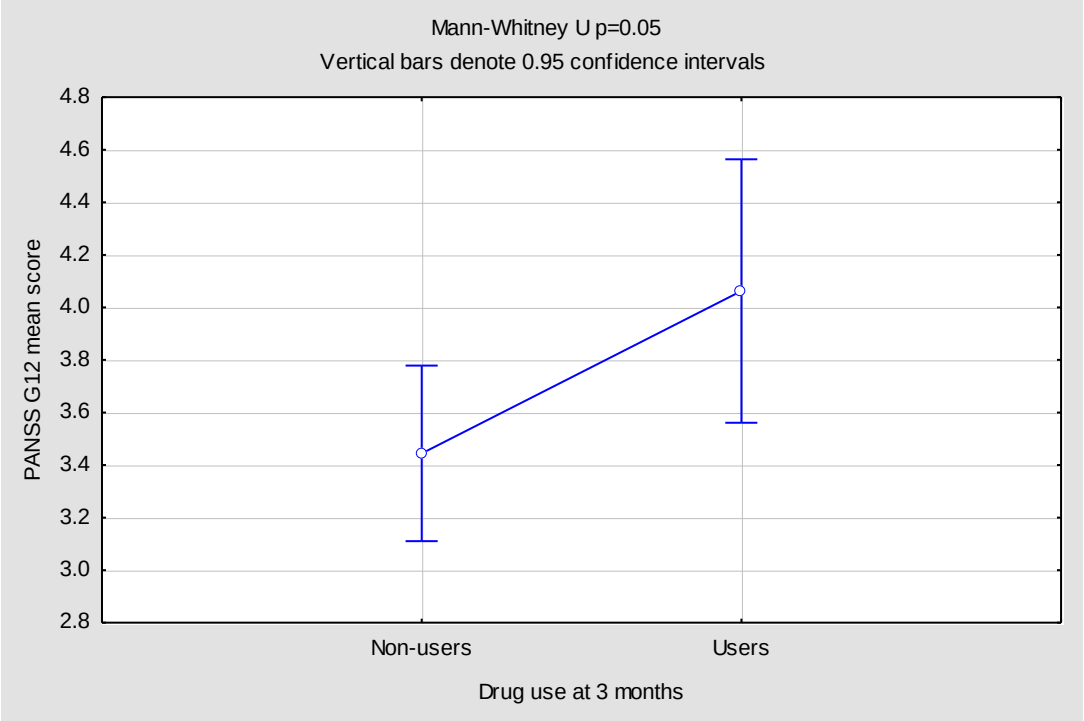

Figure 10.9: Group differences in insight at 3 months

At 6 months 26/48 (54.2%) tested positive for substance use (19 for cannabis, 12 for methaqualone and 11 for methamphetamines). At 12 months 21/41 (51.2%) tested positive for substance use (17 for cannabis, 9 for methaqualone and 13 for methamphetamines). Ten of these participants were polysubstance users. There were no significant differences between the users and non-users with regard to illness severity, or cognitive functioning at both 6 months, and 12 months.

Premorbid adjustment and functioning

Premorbid Adjustment Scale[6] (PAS) ratings were completed on 37 participants (63.79% of the sample) at baseline. Mean scores on the PAS scale indicate that during early childhood, participants attained 83% (±

11.73) of expected levels of adjustment, during early adolescence 72% (± 16.46), while by late adolescence only 62% (± 19.93) of what was expected. By adulthood, participants reached 55% (± 24.15) of expected levels of adjustment. General adjustment, referring to the participants' highest level of functioning achieved prior to onset of illness, was 42.8% of expected achievement (mean 5.72, ± 0.03). This refers to participants' adjustment with regard to education, employment, independence, social-personal adjustment, degree of interest in life, and energy level. There was a significant failure to attain optimal levels of functioning, which propagated throughout the participant's lifetime (see figure 10.10).

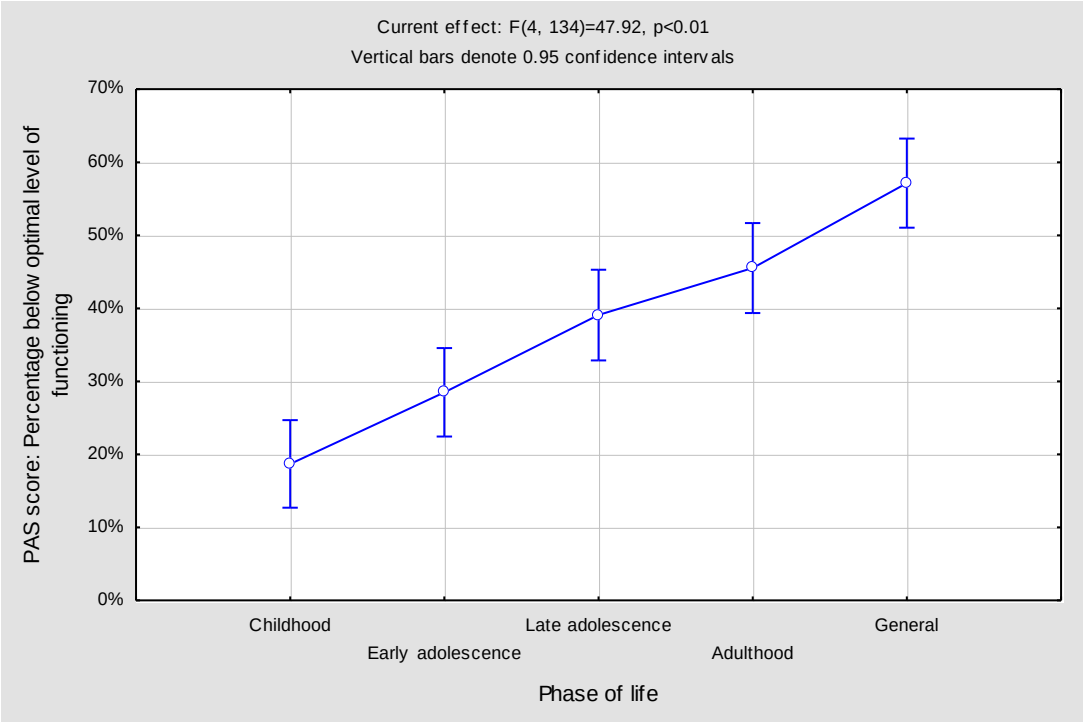

Figure 10.10: Deficits in premorbid adjustment over lifetime

There was a positive correlation between mean childhood PAS scores and positive symptoms (PANSS P; r=0.39; p=0.02), as well as insight (PANSS

G12; r=0.40; p=0.02) at baseline, indicating that worse premorbid adjustment during childhood was associated with more severe positive symptoms and worse insight at baseline. Childhood PAS scores had an inverse correlation with Attention and Vigilance (r=-0.12; p=0.05) at baseline. Adult PAS scores also had a positive correlation with positive symptoms at baseline (r=0.49; p<0.01) and DUI (r=0.37; p=0.03). General premorbid adjustment had a negative correlation with the mean SOFAS[5] score at baseline (r=-0.42; p=0.01).

Education and employment

The participants had a mean educational level of 9.71 (± 2.13) completed years of schooling (see figure 10.11). There was a significant difference in educational level attained between female and male participants with mean years of schooling in females being 10.63 (± 1.98) vs. 9.26 (± 2.07) in males (p=0.03).

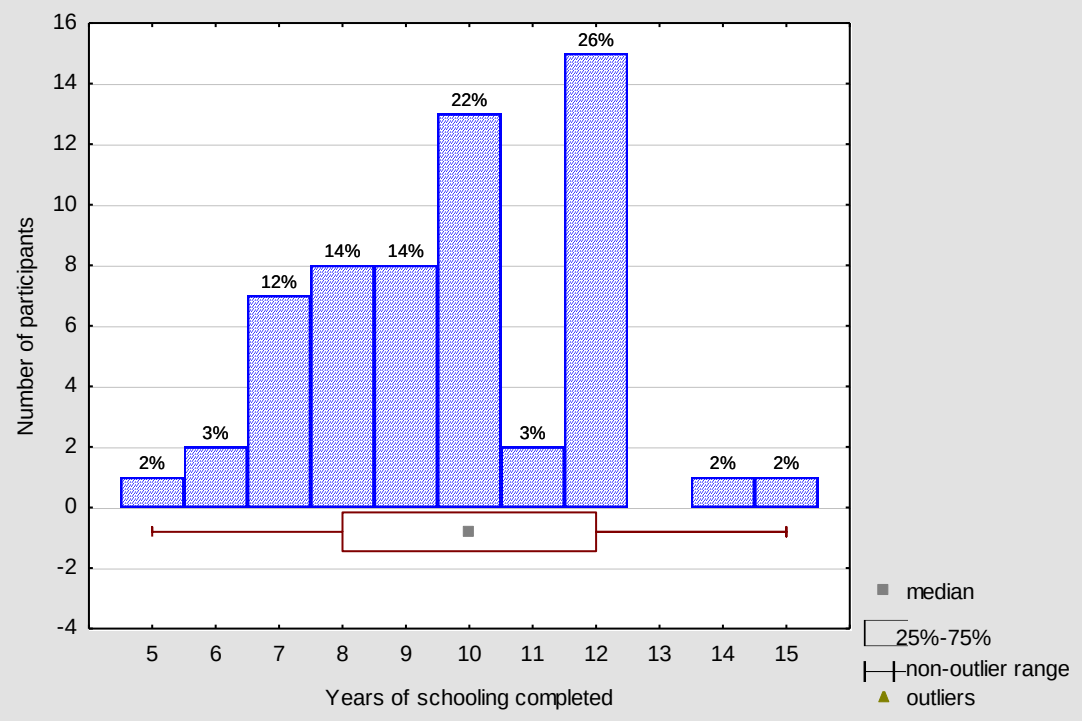

Figure 10.11: Educational level attained

Furthermore, participants who chose to be assessed in Afrikaans completed more years of schooling ($p<0.01$), even when corrected for age (see figure 10.12).

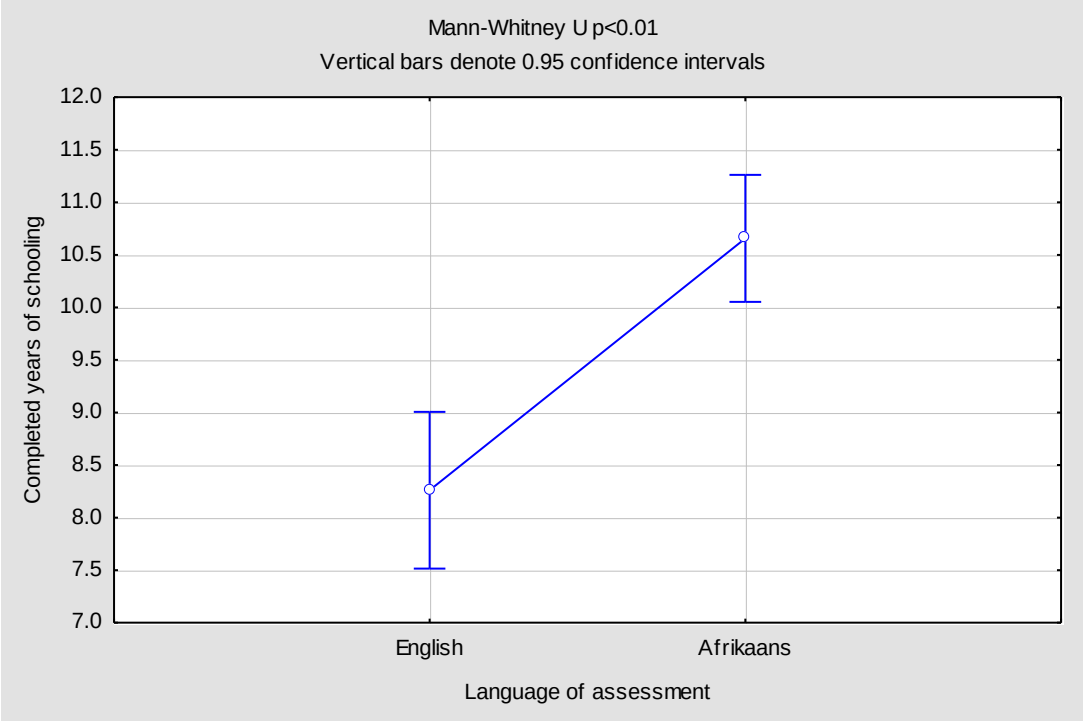

Figure 10.12: Relationship between language of assessment and educational level

There were no significant differences among ethnic groups in the level of educational attainment. There were positive correlations between years of completed schooling and premorbid IQ estimation at both baseline (r=0.36; p<0.01) and at one year (r=0.38; p=0.01), between years of education and social cognition at one year (r=0.39; p=0.01), and between years of education and mean MCCB Cognitive Composite Score at one year (r=0.37; p=0.02).

The majority of the participants (45/58) were unemployed at baseline (see figure 10.13)

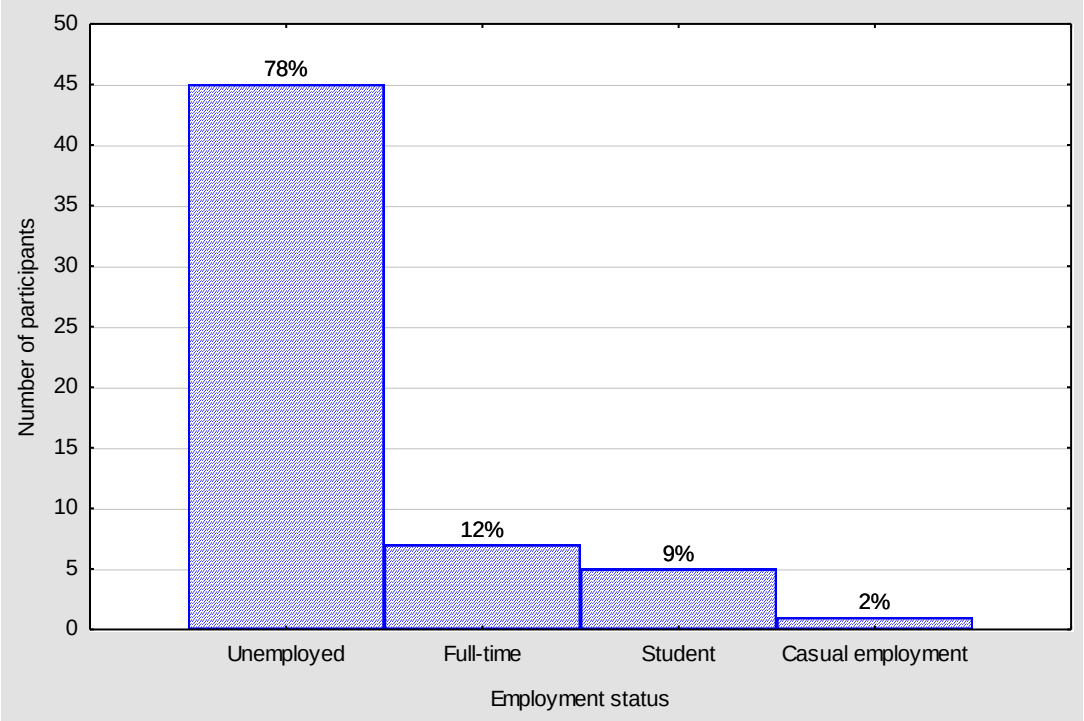

Figure 10.13: Employment status at baseline

At baseline, the participants had serious impairment in social, occupational and school functioning, as indicated by a mean SOFAS[7] score of 42.07 (± 9.81) (see figure 10.14)

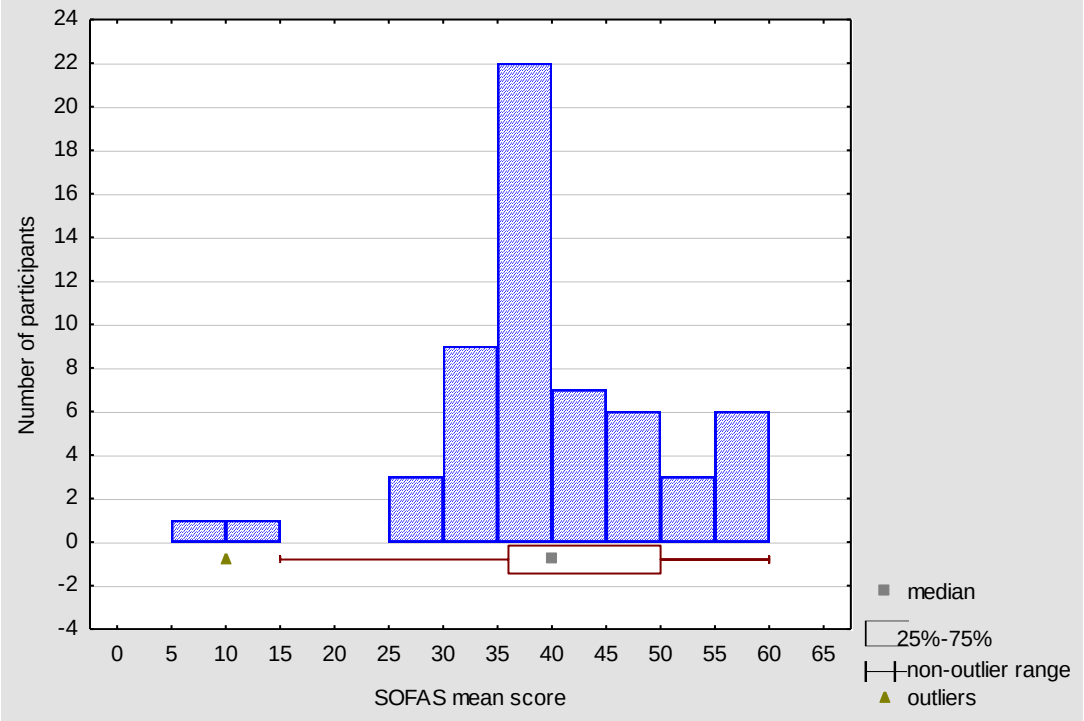

Figure 10.14: Social and Occupational Functioning at baseline

Baseline SOFAS had an inverse correlation (r=0.51; p<0.01) with illness severity (PANSS Total). Outpatients' level of functioning was significantly higher than those of in-patients (p=0.05) at baseline (see figure 10.15). However, the correlation between level of functioning and length of hospital stay was not significant.

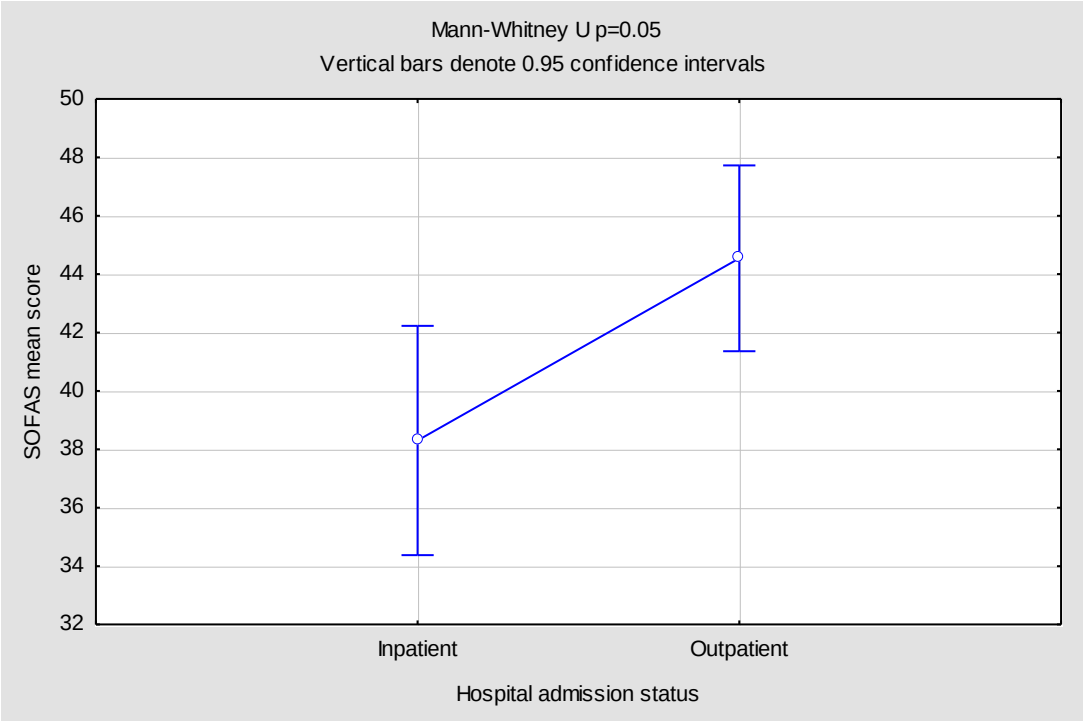

Figure 10.15: Level of functioning at baseline and admission status at baseline

Although there were no significant correlations between MCCB Cognitive Composite Score and educational level, and between MCCB Cognitive Composite Score and premorbid IQ estimation, a significant positive correlation between MCCB Cognitive Composite Score and SOFAS at baseline was found (r=0.29; p=0.04).

Fifty-seven participants completed the WHOQOL-BREF[8] at baseline, with the assistance of the interviewer. The raw scores were transformed to percentages, where higher percentages represent more satisfaction (with 100% being the ideal). Participants' perceptions on the quality of their lives are depicted in figure 10.16.

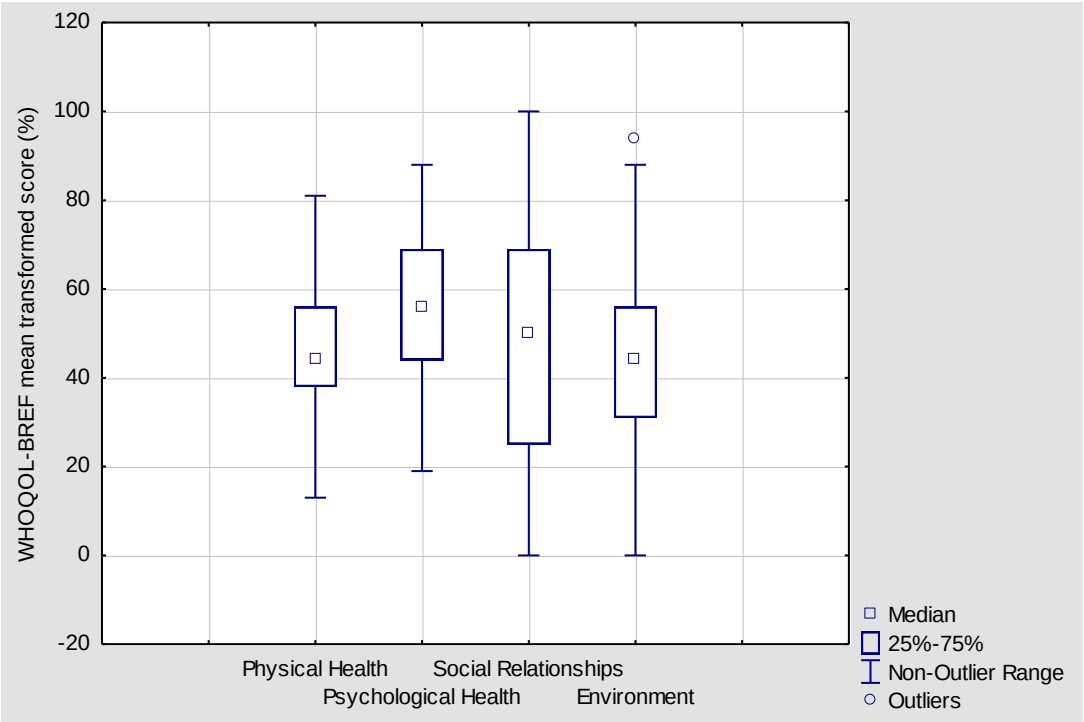

Figure 10.16: Participants' baseline perceptions on Quality of Life

WHOQOL Physical Health and Psychological Health at baseline did not correlate significantly with any of the following (p set at 0.05): age, gender, language, educational level attained, illness severity (PANSS Total and CGI[9]), DUI and DUP, social and occupational functioning (SOFAS), premorbid IQ estimation, neurocognition (MCCB Cognitive Composite Score), premorbid level of adjustment (PAS) or depressive symptoms[10] (CDSS). However, there was positive correlation between Reasoning and

Problem solving abilities and perceptions of physical health (r=0.31; p=0.02), and an inverse relationship between Working Memory and perceptions of psychological health (r=-0.29; p=0.03). There was a significant difference between Afrikaans and English participants with regard to WHOQOL Social Relationships (p=0.02), with Afrikaans participants reporting more satisfaction (50.74, ± 24.68) than English participants (35.55, ± 26.11). WHOQOL Environment scores correlated inversely with the severity of positive symptoms (PANSS P; r=-0.28; p=0.04) and insight (PANSS G12; r=-0.29; p=0.03), and demonstrated a positive correlation with social and occupational functioning (SOFAS; r=0.29; p=0.03).

Duration of untreated illness, Duration of untreated psychosis and Hospitalization

The mean DUI and DUP for the participants are depicted in figures 10.17 and 10.18 respectively. Twenty-seven of the participants received oral antipsychotics prior to enrollment in the study, with a mean treatment duration of 11 days
(± 6.36) at 152 CPZE/day (± 81.23).

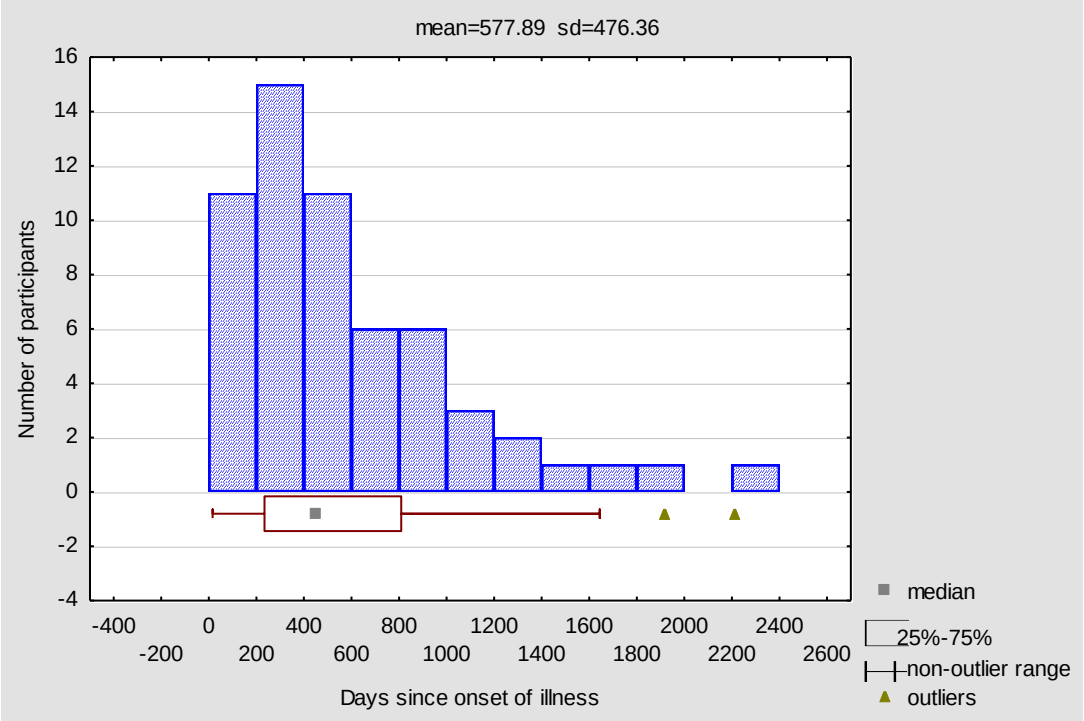

Figure 10.17: Duration of untreated illness

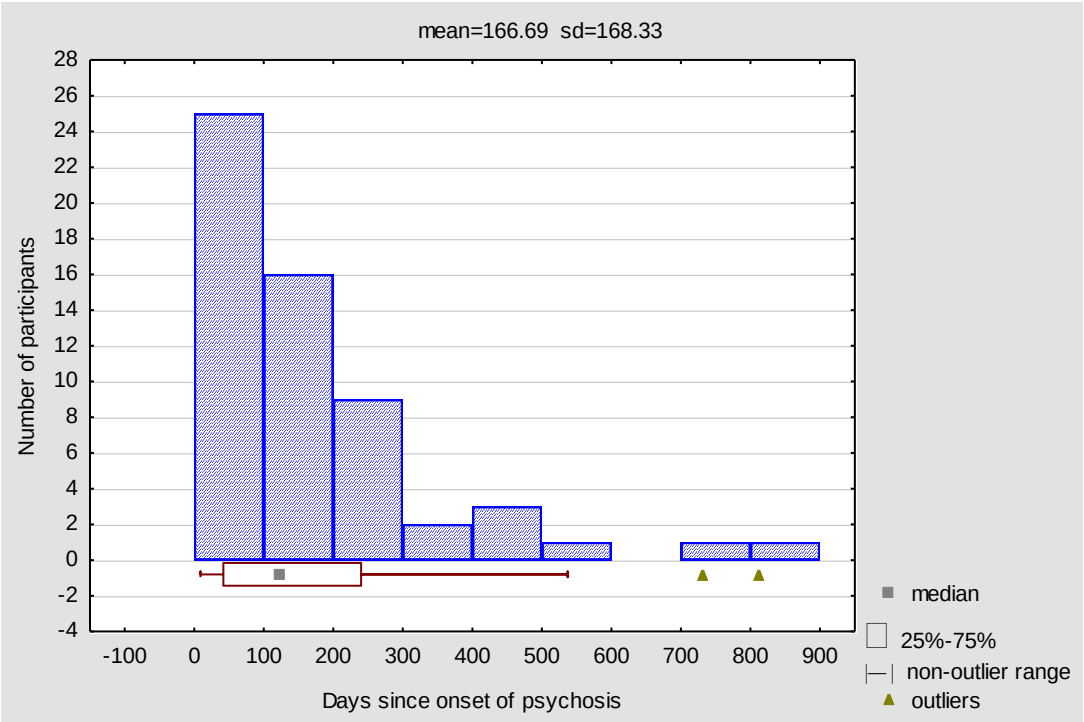

Figure 10.18: Duration of untreated psychosis

DUI and DUP did not correlate significantly (p set at 0.05) with age, gender, language, level of education, baseline symptoms (PANSS), or cognition (MCCB). Of the participants, 23 (39.66%) were in-patients and 35 (60.34%) were outpatients at the time of enrollment. Although DUI did not relate to admission status, an inverse correlation between DUP and admission status was found, with shorter DUP related to in-patient status (r=0.31; p=0.02) (see figure 10.19).

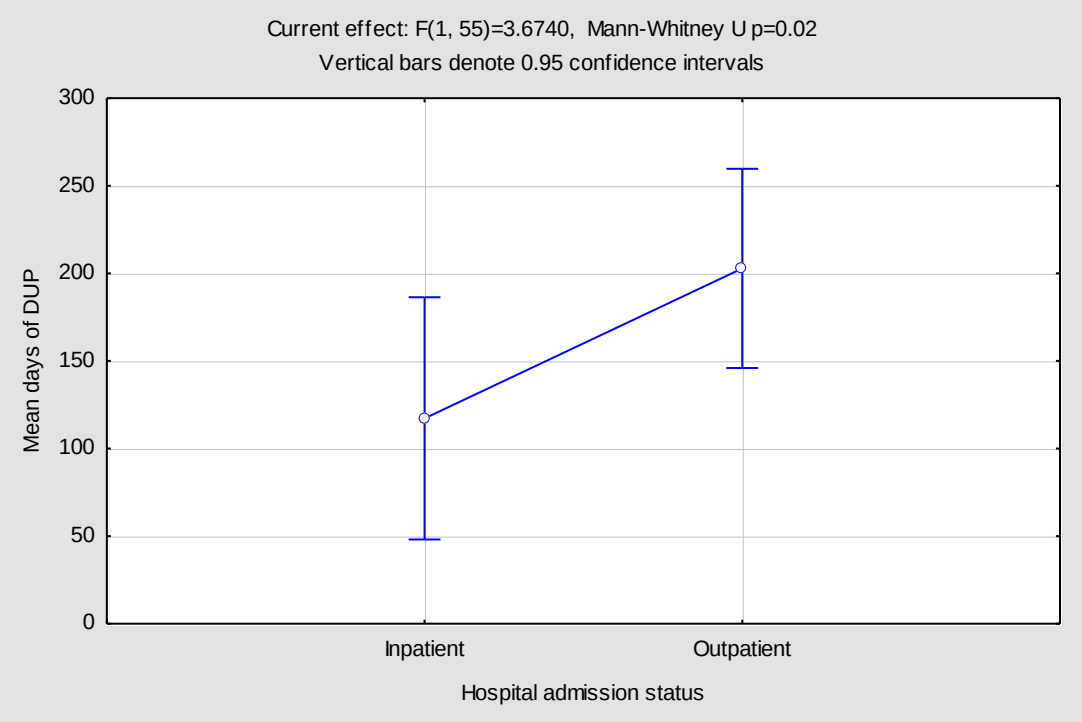

Figure 10.19: Duration of untreated psychosis and insight

There was no difference with regard to baseline illness severity (PANSS Total) and admission status. However, outpatients had better insight than inpatients (PANSS G12 scores 4.74, ± 1.02 and 5.43, ± 0.89 respectively; p=0.02). The mean duration of hospitalization from baseline was 67.74 (±

33.13) days. Duration of hospitalization did not correlate with DUI, DUP or illness severity (PANSS Total) at baseline.

Discontinuation data

Seventy-point-seven percent (41/58) of the sample completed the study. The mean duration of participation was 274 (± 116.09) days. During the course of the study, one patient was discontinued due to a general medical condition and one due to ongoing substance abuse. Only one patient was withdrawn due to side-effects. Seven participants withdrew their consent, three relocated, and four participants were discontinued due to non-response (see figure 10.20).

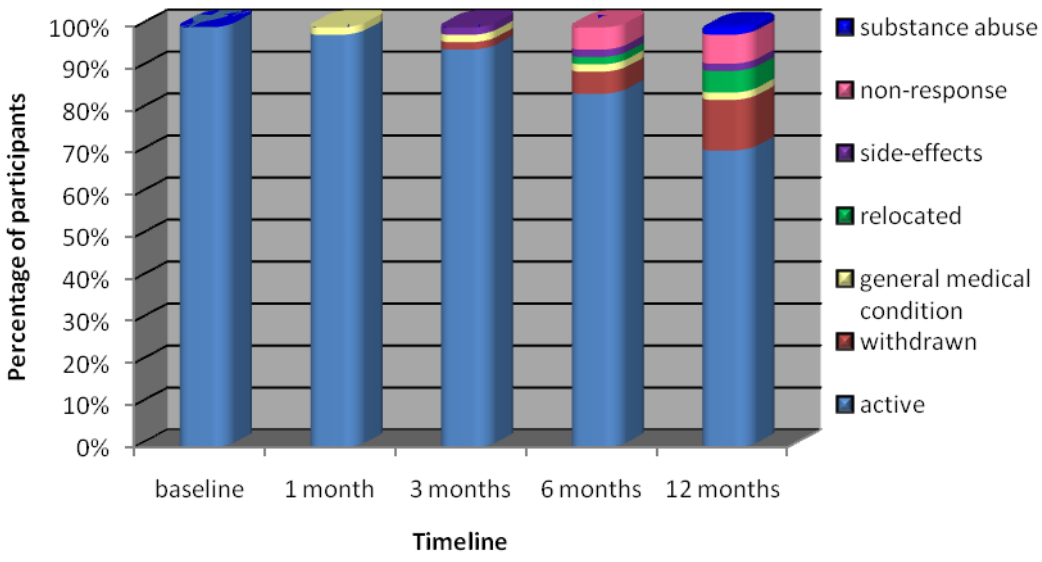

Figure 10.20: All cause discontinuation

Baseline descriptive statistics for the participants completing the study, and for those who discontinued, are displayed in table 10.2. The groups were too small to calculate statistical differences between the groups, therefore no statistical specifiers such as degrees of freedom and level of significance are specified.

Table 10.2: Completers vs non-completers

	n	%	Mean PANSS score	Mean MCCB Cognitive Composite Score
Completers	41	70.69	100.78, ± 15.35	9.86, ± 14.1
Non-responders	4	6.89	119.25, ± 11.11	-2.00, ± 3.61
Withdrawn consent	7	12.07	96.75, ± 15.6	9.83, ± 10.74
Poor tolerance	1	1.72	85	17

Details on treatment, treatment response, and side-effects are discussed in chapter 11.

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CHAPTER 11

RESULTS: PSYCHOPATHOLOGY AND TREATMENT EFFECTS

Severity of illness at baseline

Patients were markedly ill at baseline, with a mean PANSS[1] Total score of 100.5 (± 15.89), and a CGI[2] of severity (CGI-s) score of 5.28 (± 0.64). Although differences in PANSS Total scores at baseline did not reach statistical significance (p=0.07), there was a trend in the CGI-s suggesting that male participants may have been more severely ill (see figure 11.1)

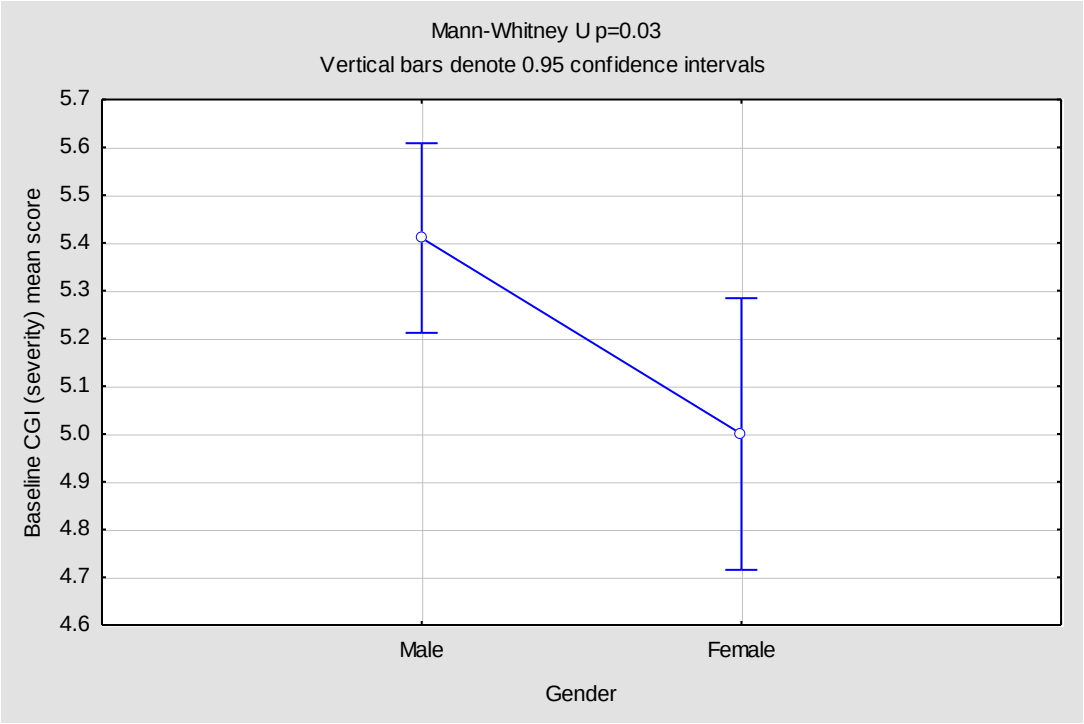

Figure 11.1: Gender differences in illness severity at baseline

Treatment and response

During the course of the study, the mean dose of FD administered was 22.48 (± 0.47) mg/month, with a modal dose of 10mg 2 weekly IMI. See chapter 9 for details of treatment protocol.

Participants improved significantly over time, with a 53.9% reduction in symptoms (PANSS Total) from baseline to one year (see table 11.1).

Table 11.1: Change in psychopathology over time

		Mean PANSS score			
	N	**Total**	**Positive**	**Negative**	**General**
Baseline	58	100.50 (± 15.89)	24.98 (± 4.01)	28.00 (± 5.47)	47.52 (± 9.02)
1 month	56	80.11 (± 15.26)	18.18 (± 4.12)	23.96 (± 5.23)	37.96 (± 8.14)
3 months	54	57.96 (± 12.68)	12.27 (± 3.62)	18.55 (± 4.89)	27.14 (± 6.01)
6 months	48	49.63 (± 11.96)	10.06 (± 2.98)	15.54 (± 4.89)	24.02 (± 6.13)
12 months	41	45.34 (± 11.28)	8.89 (± 2.08)	14.03 (± 4.45)	22.44 (± 6.06)

The greatest improvement in PANSS Total scores occurred early, with 36.96% of the total improvement observed within the first month, 77.12% within the first 3 months, and 92.22% within the first 6 months. This reduction were a reflection of improvement in positive (PANSS P), negative (PANSS N) and general (PANSS G) symptoms.

After six months of treatment, no further significant improvement in psychopathology scores occurred (see figure 11.2).

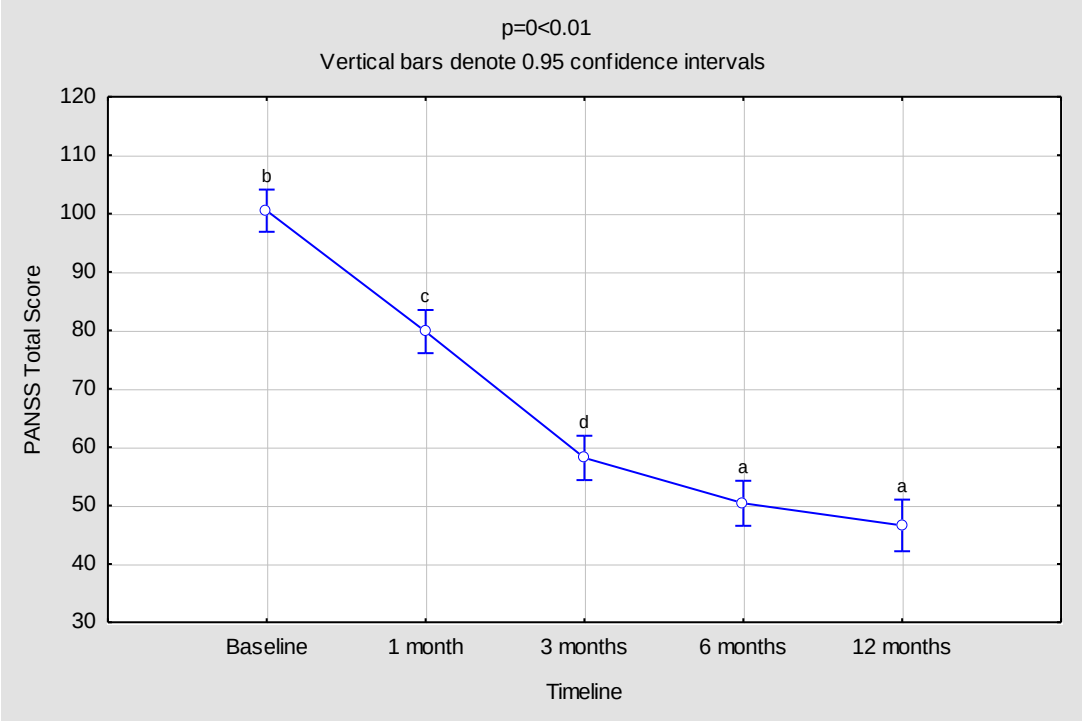

Figure 11.2: Decrease in psychopathology over time

The improvement in psychopathology, as measured by the PANSS, was mirrored in other measures of illness, such as the change in CGI scores (see figure 11.3). Participants were rated as much improved as early as one month (CGI-c 2.64, ± 0.08).

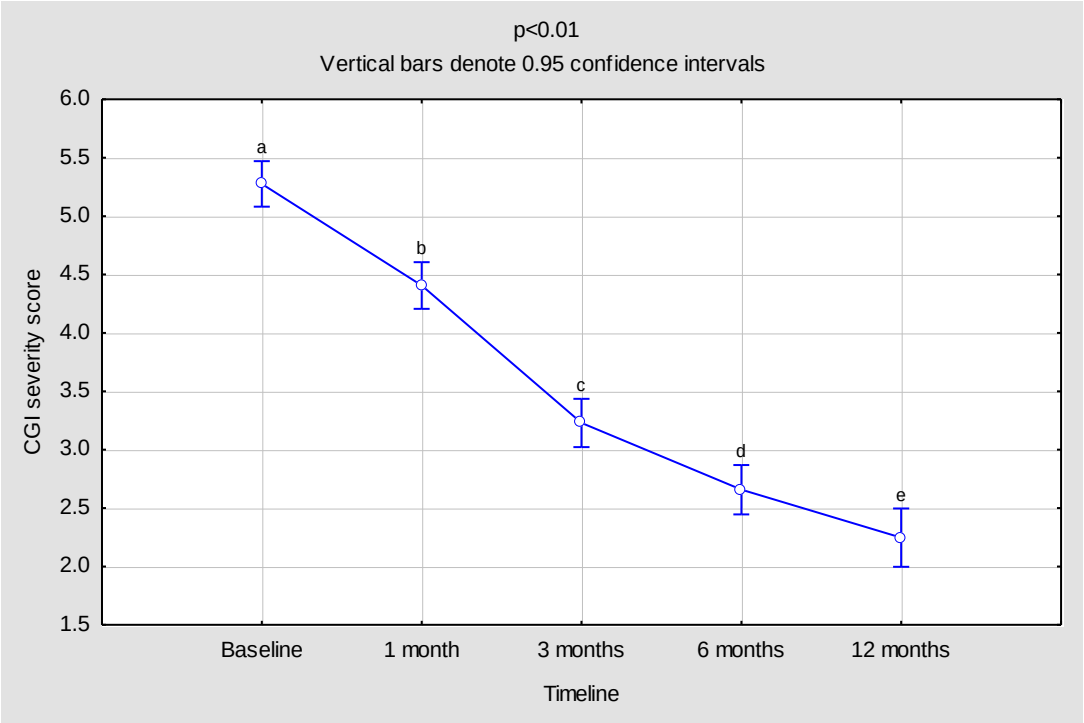

Figure 11.3: Decrease in severity of illness over time

Various studies have used factor analytic approaches to identify a PANSS Cognitive factor as one of the dimensions of psychopathology[1,3-10]. We calculated the PANSS Cognitive factor (PANSS C) according to Lancon et al.[11] and Good et al.[12]. Lancon et al established their cognitive factor in schizophrenia as a group (independent of duration of illness, previous treatment, etc.) consisting of PANSS items P2 (conceptual disorganization), N5 (difficulty in abstract thinking), G10 (disorientation) and G11 (poor attention). Good et al. suggested PANSS C to be of specific relevance in

FEP, with the factor consisting of items P6 (suspiciousness/ persecution), N5 (difficulty in abstract thinking), N6 (lack of spontaneity and flow of conversation), G2 (anxiety) and G10 (disorientation). In our sample, there was a positive correlation between the two estimates of the PANSS C score at all time points (see figure 11.4).

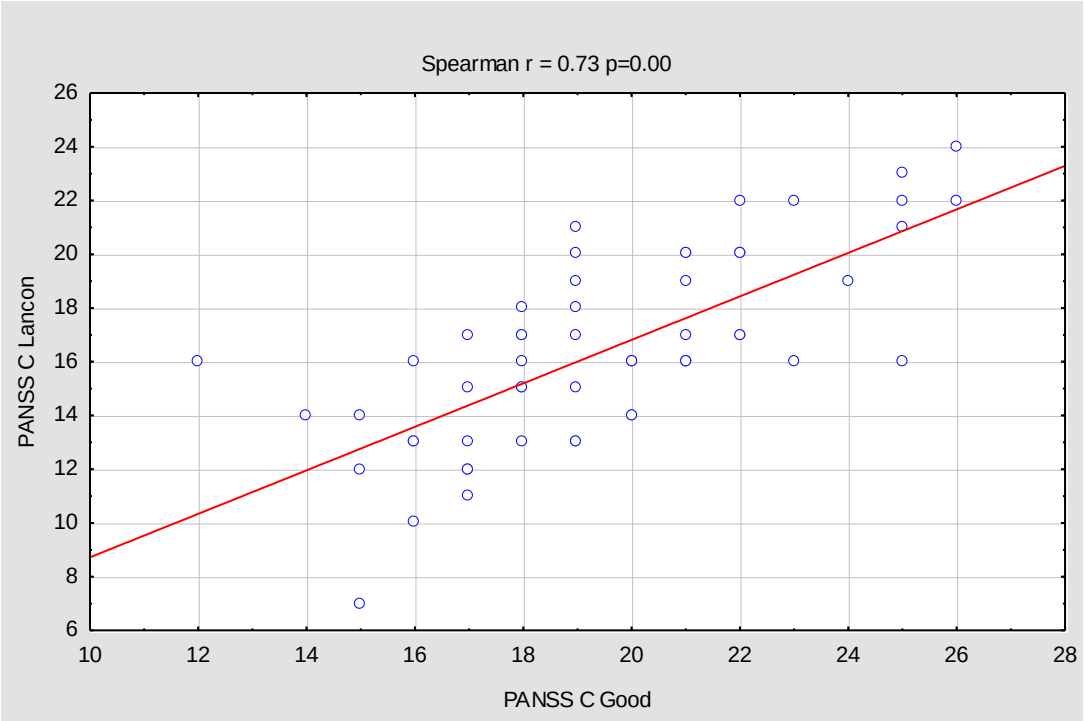

Figure 11.4: Correlation between PANSS C Lancon and PANSS C Good at baseline

No differences in mean PANSS C were found between genders, or language of assessment. The PANSS C had highly significant, inverse correlations ($p<0.01$) with all MCCB[13] cognitive domains at baseline (Speed of Processing, r=-0.68; Attention and Vigilance, r=-0.49; Working Memory, r=-0.63; Verbal Learning, r=-0.49; Visual Learning r=-0.53; Reasoning and Problem Solving, r=-0.44; Social Cognition, r=-0.43; Cognitive Composite Score, r=-0.72).

The PANSS C continued to decline over time (see figure 11.5 and table 11.2), while also showing a decline in strength of correlation with cognitive domains. By one year, PANSS C had no significant correlations with MCCB domains of Attention and Vigilance, Visual Learning, and Reasoning and Problem solving.

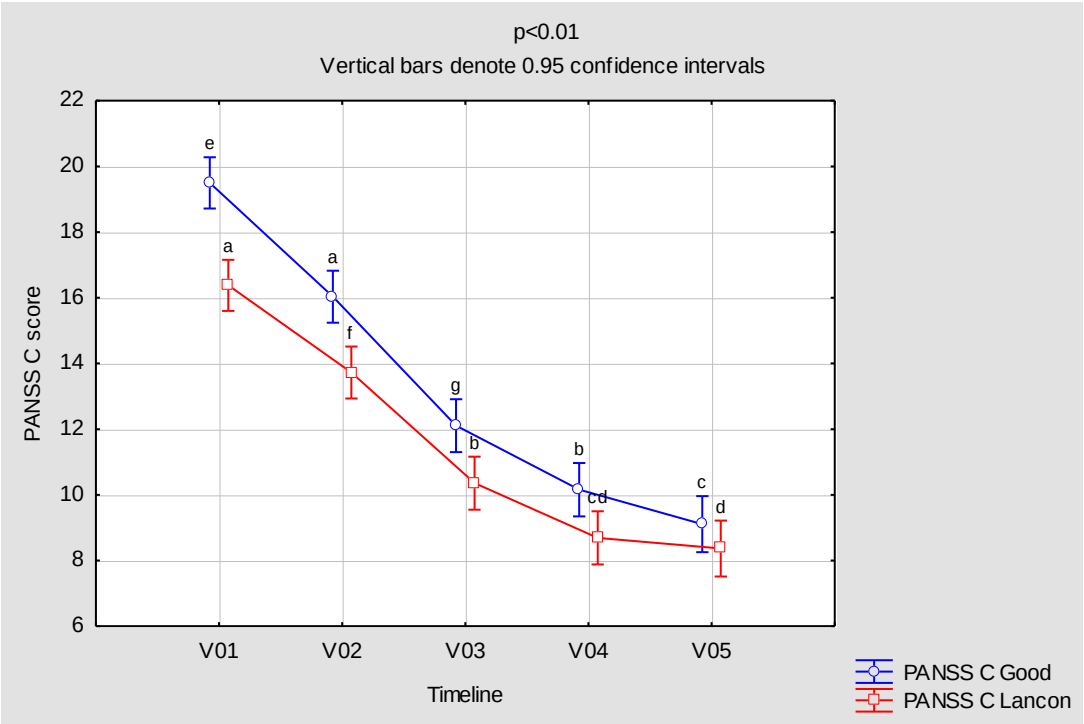

Figure 11.5: Change in PANSS C mean score over time

* The letters in the above graph indicate differences in mean scores for the specific cognitive factor over time, as well as interactions between the two cognitive factors.

Table 11.2: Mean PANSS C scores at different assessments			
	N	**Good**	**Lancon**
Baseline	58	19.56, ± 3.12	16.46, ± 3.51
1 month	56	16.19, ± 3.12	13.89, ± 3.21
3 months	54	12.19, ± 3.13	10.41, ± 3.22
6 months	48	10.17, ± 2.55	8.67, ± 2.63
12 months	41	9.00, ± 2.18	8.18, ± 2.55

Mood symptoms

Mood symptoms were evaluated by the PANSS depression factor (PANSS D) as described by Kay[14], as well as the CDSS[15].

The PANSS D consists of the combined scores of G1 (somatic concern), G2 (anxiety), G3 (guilt), and depression (G6). The mean PANSS D score at baseline was 9.17 (± 3.59). This score declined significantly over the first three months of the study (see figure 11.6 and table 11.3).

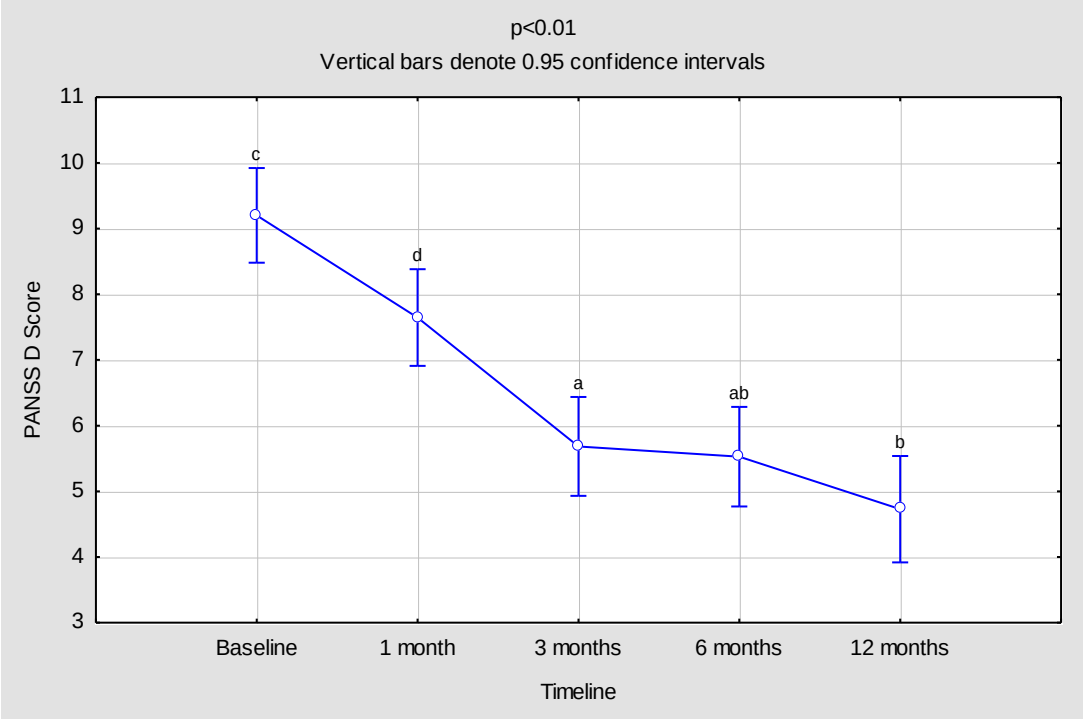

Figure 11.6: Change in mean PANSS D score over time

Table 11.3: PANSS D scores at different assessments		
	N	**Mean PANSS D score**
Baseline	58	9.17, ± 3.59
1 month	56	7.62, ± 3.51
3 months	54	5.66, ± 2.01
6 months	48	5.61, ± 2.21
12 months	41	4.86, ± 1.68

PANSS D demonstrated a positive correlation with mean CDSS score from baseline to 3 months (baseline, r=0.69; 1 month, r=0.38; 3 months, r=0.34; p<0.01), but not at 6 months and at one year. PANSS D at baseline showed an inverse correlation with age at baseline (r=-0.28; p=0.03), and an inverse

correlation with insight (PANSS G12) at baseline (r=-0.37; p<0.01), one month (r=-0.38; p<0.01) and six months (r=0.35; p=0.02). At one month, there was a positive correlation between PANSS D and MCCB Speed of Processing (r=0.32; p=0.02), while at three months, a positive correlation between PANSS D and MCCB Social cognition was found (r=0.34; p=0.01).

The mean CDSS score at baseline was 3.22 (± 0.38). The mean CDSS score had positive correlations with mean PANSS G scores from baseline to six months (baseline r=0.42, p<0.01; 1 month r=0.46, p<0.01; 3 months r=0.35, p=0.01; 6 months r=0.40, p<0.01) and mean PANSS Total scores at baseline (r=0.27; p=0.04), 1 month (r=0.34; p=0.01) and 6 months (r=0.33; p=0.02). One 24 year old male participant presented at baseline with a suicide attempt (PANSS Total score of 120). None of the other participants displayed any suicidal behavior during the course of the study, even though participants did obtain mild ratings on the CDSS suicide item indicating frequent thoughts of being better off dead, or occasional thoughts of suicide. Although as a group CDSS ratings remained below 7 (cut off for depression) for the duration of the study (see figure 11.7), some individuals did obtain higher ratings. This necessitated the addition of selective serotonin reuptatke inhibitors (SSRIs) in 11 patients. Five of these participants started antidepressants at six months. All received fluoxetine or citalopram 20mg/d, but in three participants, the dose had to be increased to 40mg/d.

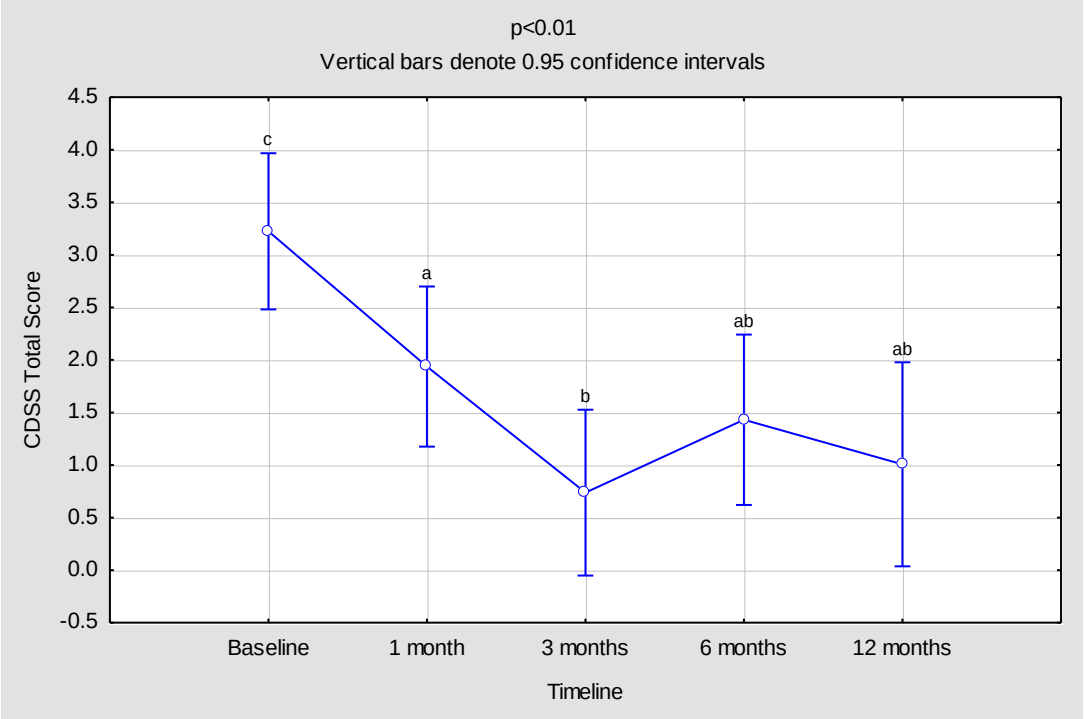

Figure 11.7: Change in CDSS mean score over time

The presence of baseline depressive features (CDSS) had inverse correlations with quality of life ratings (WHOQOL) of Psychological Health (r=-0.35; p=0.05) and Social Relationships (r=-0.50; p<0.01) at one year, while the PANSS D at baseline had a significant inverse relationship with Social Relationships (r=-0.51; p<0.01) at one year. The presence of depressive symptoms (CDSS) at 6 months also demonstrated inverse correlations with quality of life ratings of Physical Health (r=-0.40; p<0.03), Psychological Health (r=-0.46; p<0.01) and Environment (r=-0.33; p=0.03).

Response, remission and relapse data

Of the 41 participants who completed the study, only six (14.6%) did not achieve remission (remission criteria[16] met for six consecutive months), despite an initial good response to treatment. Three participants relapsed during the course of the study, as indicated by an increase of 25% in PANSS Total score from the previous lowest score obtained. Two of the participants relapsed due to substance abuse; one at 6 months (remission criteria met at 9 months), and one at 12 months. One participant relapsed at 9 months due to non-compliance (remission criteria met at 12 months).

Side-effects

Side-effects that did occur were, on the whole, of mild intensity. No serious side-effects were reported on for the duration of the study. Participants were evaluated for the presence of EPSE with the ESRS[17]. The prevalence of isolated EPSE in the sample (N=58) was as follows: parkinsonism 3.45%, dystonia 3.45% and akathisia 5.17%. Dystonia in combination with parkinsonism occurred in 3.45%, as did akathisia in combination with parkinsonism. EPSE therefore occurred in 18.97% of the sample. However, side effects were mild, and temporary, occurring within the first three months of initiation of treatment. Dystonic reactions were mild and occurred within 3-10 days after the initiation, or dose increase of FD. It responded well to a single dose of biperidine. Akathisia responded well to the addition of

propranolol 20mg tds *per os*, while parkinsonism responded well to a decrease in dose of flupenthixol to previously tolerated levels.

Four participants (6.89%) were withdrawn due to poor response to treatment, with an inability to increase the flupenthixol, due to the presence of EPSE. Only one subject was withdrawn due to side-effects. This 16 year old lady had a DUI of 332 days and DUP of 57 days. She previously abused methamphetamine, heroine, cannabis and alcohol, but was abstinent for four months prior to the onset of her DUI. She presented with thought disorder and prominent decreased tempo of thought, followed by the onset of a refusal to eat, insomnia, and crying. She received chlorpromazine 25mg/d *per os* for one day, then 50mg/d *per os* for five days during the week prior to inclusion in the study. She had a baseline PANSS Total score of 85. Her BMI was 14 at baseline. She received flupenthixol 1mg/d *per os* for two days, then 2mg/d *per os* on days 3 to 10. She received FD 10mg IMI on day 8, and developed akathisia three days later. Oral flupenthixol was decreased to 1mg/d *per os* and lorasepam up to 8mg/d *per os* added. Both were stopped on day 11 and propranolol 40mg tds *per os* initiated. The akathisia disappeared, but mild cogwheel rigidity in her left arm was evident by day 16. She received a second dose of FD 10mg IMI on day 19. She was withdrawn from the study on day 33 due to persistence of EPSE.

Functional outcome and quality of life

The baseline social and occupation functioning, as measured by the mean SOFAS[18] score, improved significantly from 42.07 (± 9.81) at baseline, to 63.26 (± 7.59) at 6 months. Only modest gains occurred between six months and one year (63.97, ± 6.66) (see figure 11.8).

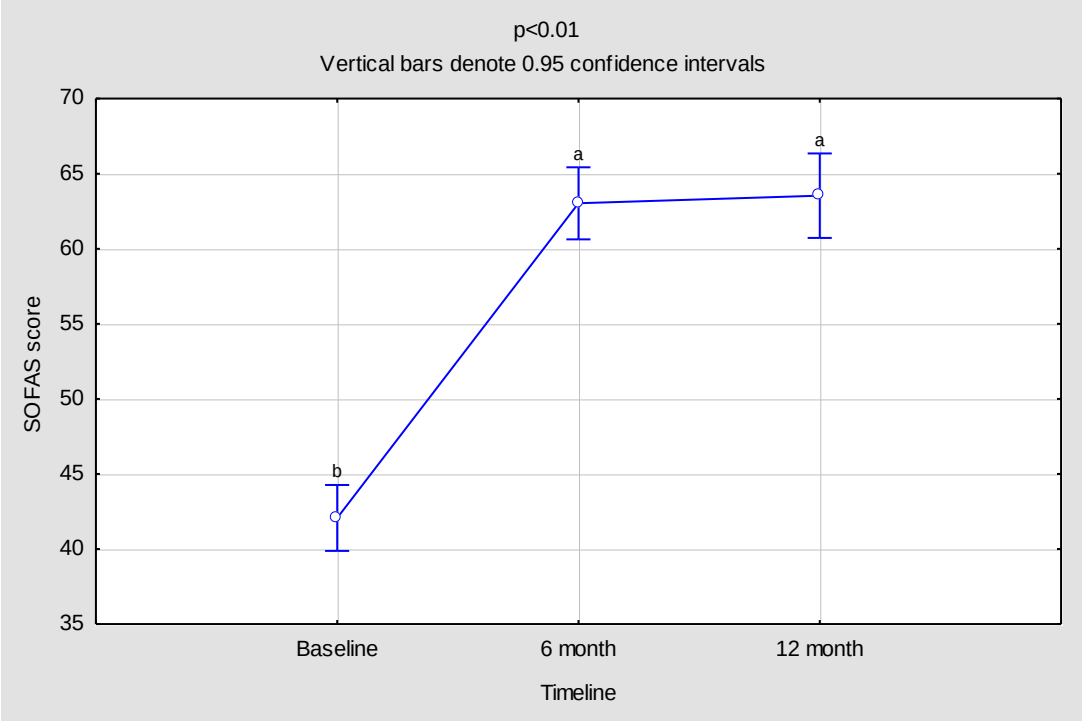

Figure 11.8: Change in SOFAS mean score over time

There was an inverse correlation between mean SOFAS score at baseline and mean PANSS Total score (r=-0.51; p <0.01) which persisted at six months (r=-0.55; p=0.01), and at one year (r=-0.69; p<0.01). The presence of negative symptoms (PANSS N) at baseline had an inverse correlation with functioning at six months (r=-0.37; p=0.01), while there were significant inverse relationships between functioning at one year and

PANSS N (r=-0.39, p=0.03), PANSS G (r=-0.38; p=0.03) and PANSS Total (r=-0.42; p=0.02) scores. Baseline, as well as 6 month cognitive functioning (mean MCCB Cognitive Composite Score) correlated with mean SOFAS scores at 6 months (r=0.31, p=0.05; and r=0.32, p=0.03 respectively), but at baseline and one year, there was no correlation between cognition and SOFAS.

Baseline quality of life ratings (WHOQOL-BREF)[19] indicated that participants were not satisfied with their quality of life (QOL), with the least satisfaction expressed with regard to Social Relations and Environment. WHOQOL-BREF ratings, with changes over time, are tabulated in table 11.4.

Table 11.4: WHOQOL Domain transformed mean domain scores

	N	Physical Health	Psychological Health	Social Relations	Environment
Baseline	57	48.10, ± 14.83	53.39, ± 17.21	44.53, ± 25.94	45.75, ± 19.44
6 months	48	56.89, ± 13.54	57.54, ± 14.99	59.02, ± 24.37	58.73, ± 16.07
12 months	32	57.77, ± 15.87	60.59, ± 13.76	62.88, ± 22.65	65.19, ± 15.33

We found no gender differences in the perception of QOL at baseline and at 6 months (p set at 0.05). However, females were significantly less satisfied with their environmental circumstances at one year than their male counterparts (54.33, ± 11.63 and 69.43, ± 14.67 respectively; p<0.01). QOL, with regard to Physical Health, Social Relationships, and Environment, did improve over time, with most gains evident during the first 6 months of the study. However, there was no significant change over time with regard to

Psychological Health (see figure 11.9). Non-significant improvements in Physical Health, Psychological Health, Social Relations and Environment continued during the course of the study.

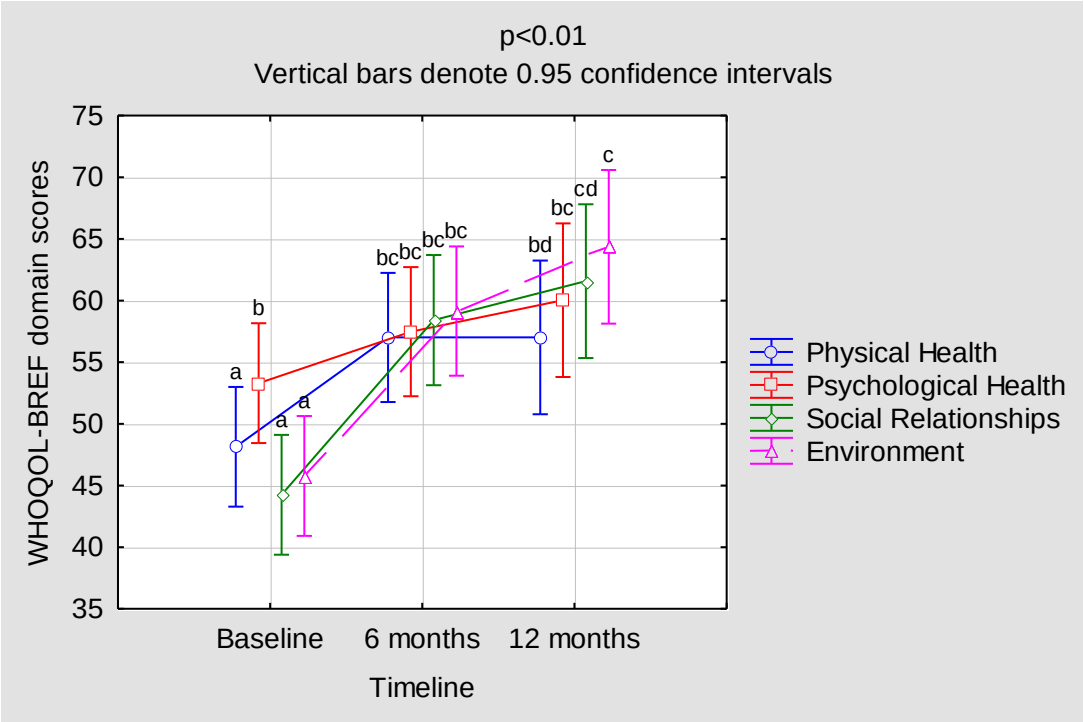

Figure 11.9: Change in WHOQOL-BREF mean scores over time

The severity of positive symptoms (PANSS P) at baseline had significant inverse correlations with Physical Health (r=-0.32; p=0.03), Psychological Health (r=-0.30, p=0.04) and Social Relationships (r=-0.33; p=0.03), as well as with Social Relationships at 6 months (r=-0.30; p<0.05). However, illness severity (PANSS Total), as well as cognitive functioning (MCCB Cognitive Composite Score) at 6 months failed to demonstrate significant correlations with QOL ratings (p set at 0.05). At six months, social and occupational functioning (SOFAS) had positive correlations with Physical Health (r=-.34; p=0.02), Psychological Health (r=0.44; p<0.01), Social Relationships

(r=0.34; p=0.02) and Environment (r=0.41; p<0.01). Baseline premorbid level of adjustment (PAS) had a positive correlation with Psychological Health (r=0.75; p<0.01), while years of education had a positive correlation with Social Relationships (r=0.40; p=0.02).

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CHAPTER 12

RESULTS: COGNITIVE DATA

Premorbid intelligence

We used the WAIS[1] Vocabulary Subscale score as estimation of premorbid intelligence. Our sample did display evidence of impaired premorbid intelligence, with a baseline mean Z-score of -2.20 (± 0.91). There was a statistically significant difference between baseline and one year Z-scores (p≤0.01) (see figure 12.1).

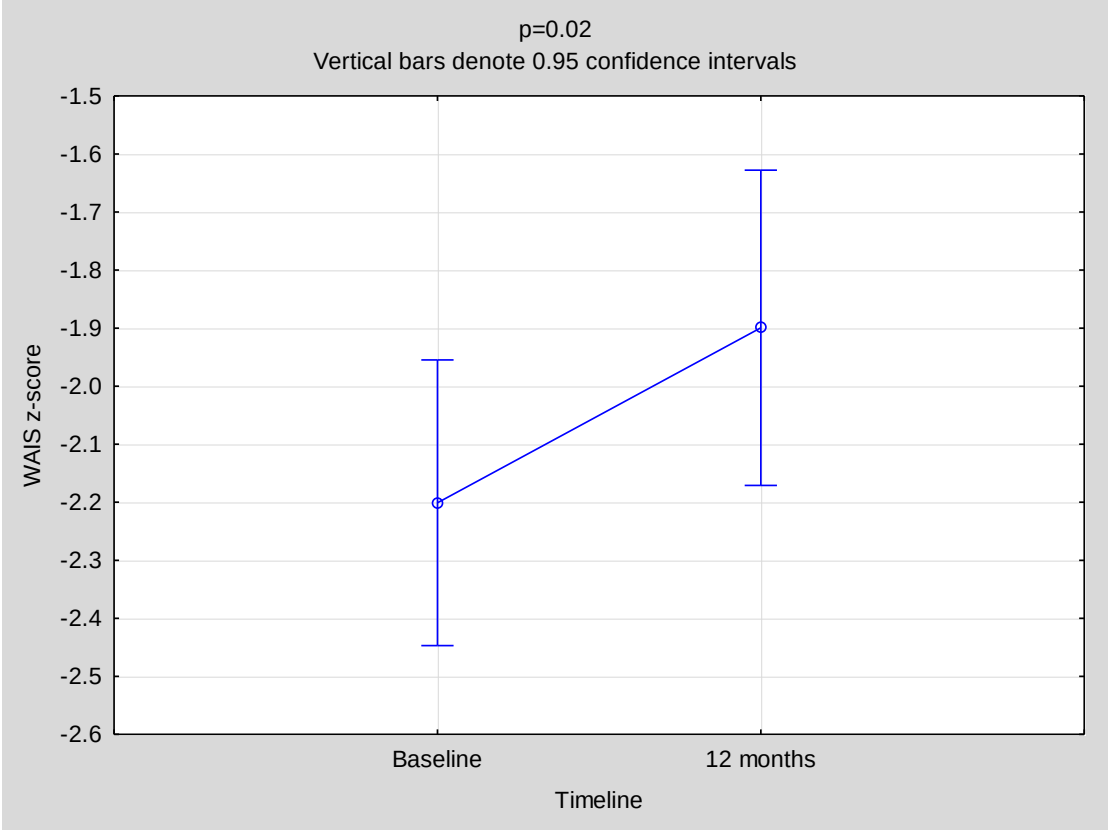

Figure 12.1: Difference in WAIS Vocabulary scale Z-score over time

There was a significant inverse correlation between the PANSS Cognitive factor and WAIS Vocabulary score at baseline ($r=-0.51$; $p<0.01$). A highly significant, positive correlation was demonstrated between premorbid IQ estimation at baseline and overall cognition (MCCB[3] Cognitive Composite Score) at both baseline ($r=0.46$, $p<0.01$) and at one year ($r=0.05$, $p<0.01$). There was also a highly significant, positive correlation between premorbid IQ estimation at one year and overall cognition at one year ($r=0.66$, $p<0.01$), but not between overall cognition at baseline and premorbid IQ estimation at one year.

Neurocognitive results: Baseline and change over time

The MCCB[3] was used for objective measurement of neurocognitive impairment. Although 58 participants were included in the initial sample, total scores could not be computed for all participants due to some assessments having missing data. The primary cause for incomplete data was the psychopathology of the patients, e.g. distractibility, and persecutory ideation toward computerized assessments. Socio-cultural factors, such as computer illiteracy (i.e. participants' difficulty with maneuvering the mouse during the CPT-IP[4]), were also detrimental to the assimilation of data.

The change in the neurocognitive composite score (MCCB Cognitive Composite Score) from baseline to one year is reflected in figure 12.2 and table 12.1.

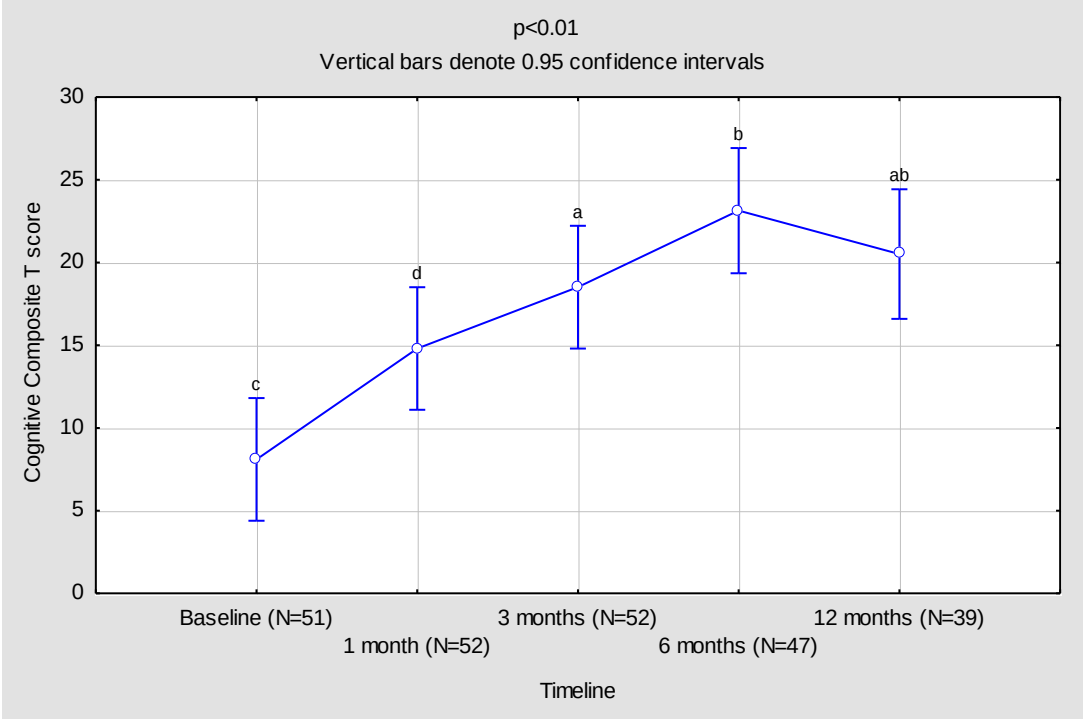

Figure 12.2: Cognitive Composite T-score mean improvement over time

Improvement in the Cognitive Composite Score occurred early, with 54.1% of the improvement from baseline to one month, while 81.5% of the improvement occurred within the first three months. No significant further improvement occurred after six months.

Note that the Cognitive Composite Score may not be a very sensitive index of change within an individual cognitive domain, as it represents an average level of cognitive performance across cognitive domains that are often only

weakly to moderately intercorrelated. Furthermore, the MCCB computer scoring program does not provide a domain T-score if any of the individual test scores is missing in Speed of Processing and Working Memory. Similarly, the program does not calculate an overall composite if any of the seven domain T-scores are missing.

The changes in neurocognitive domains from baseline to one year are represented in table 12.1, figure 12.3 and figure 12.4. Changes in individual measures are presented in table 12.2.

Table 12.1: Change in neurocognitive composite and domain scores over time

	Baseline		**12 months**		**F Test** *
	N	**T-score mean (SD)**	N	**T-score mean (SD)**	
Speed of Processing	57	12.42 (16.41)	40	25.78 (12.67)	22.92
Attention and Vigilance	52	23.98 (12.05)	40	34.73 (10.98)	30.23
Working Memory	58	21.10 (15.93)	39	29.92 (13.58)	18.77
Verbal Learning	58	31.95 (8.18)	40	36.23 (7.65)	7.58
Visual Learning	58	25.55 (14.26)	40	36.08 (12.37)	12.06
Reasoning and Problem solving	58	30.41 (8.84)	40	36.90 (8.76)	10.46
Cognitive Composite	51	9.71 (15.01)	39	20.97 (13.49)	30.68

* $p<0.001$

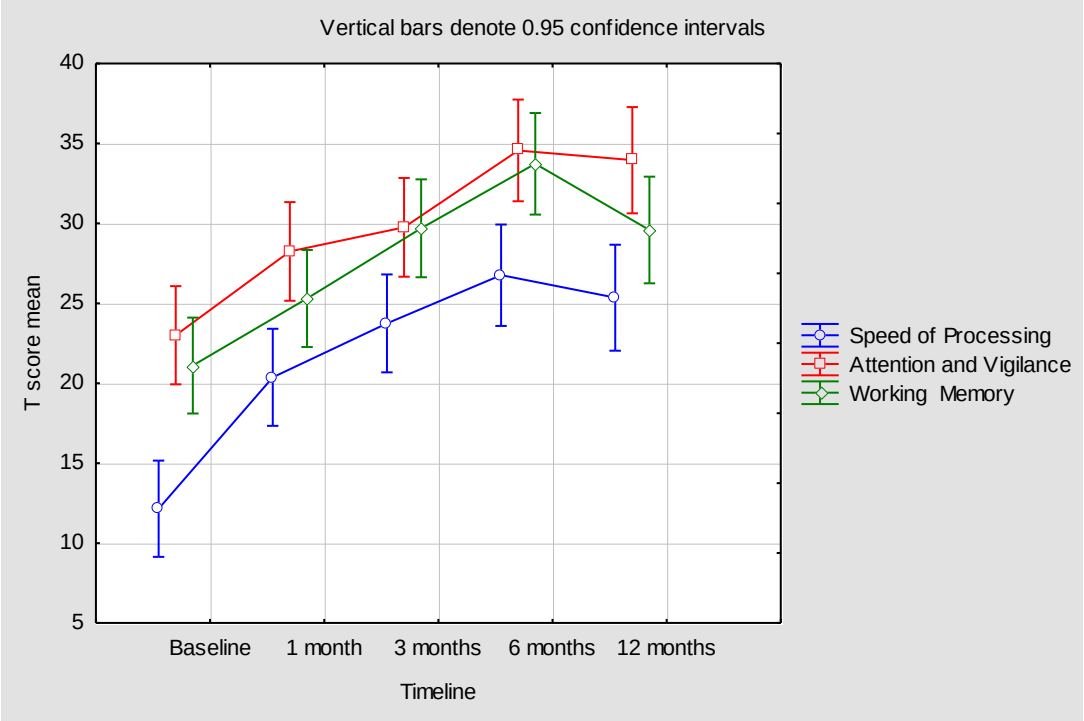

Figure 12.3: Speed of processing, Attention and Vigilance, and Working Memory T-score means improvement over time

Speed of Processing was the most severely impaired domain at baseline (T-score mean 12.42, ±16.41). Improvement in Speed of Processing occurred early, with 73.9% of total improvement occurring within the first 3 months of the 12 month period. Individual measures, contributing to Speed of Processing, are the Trail Making Test (TMT)[5]: Part A, Brief Assessment of Cognition in Schizophrenia (BACS)[6]: Symbol-Coding and Category Fluency (Fluency)[7]: Animal Naming. Fifty-one-point-fourteen-percent of improvement in the TMT occurred within one month, 66.34% by 3 months, and 92.92% by 6 months. No significant gains occurred after 6 months (F test 25.33; $p<0.01$). Eighty-one-point-zero-nine-percent of the improvement in BACS occurred by 3 months (F test 18.00; $p<0.01$), after which improvement reached a plateau. Fluency improved early, and quickly, with 65.35% of improvement within the first month (F test 5.63; $p<0.01$).

A significant improvement was evident in Attention and Vigilance, as measured by the Continuous Performance Test- Identical Pairs (CPT-IP)[4] . Fifty-eight-point-one-percent of the improvement occurred within three months from baseline, with no improvement after six months (F test 28.81; $p<0.01$).

Working Memory showed significant improvement up to six months from baseline, with 71.3% of gains occurring within the first three months. Tests used as measures of Working Memory include the Wechsler Memory Scale – 3rd ed. (WMS-III)[8] :Spatial Span (non-verbal memory) and Letter-Number Span[9] (LNS) (verbal memory). Both of these measures showed improvement up to the 3 month mark, with 65.5% (F test 12.06; $p<0.01$) and 64.8% (F test 11.86; $p<0.01$) of total improvement respectively occurring within this time frame.

Although these three domains all had a decrease in T-scores from 6 months to one year, these changes were small and not significant. This may be an artefact due to the attrition rate of participants and the resultant decrease in sample size over time.

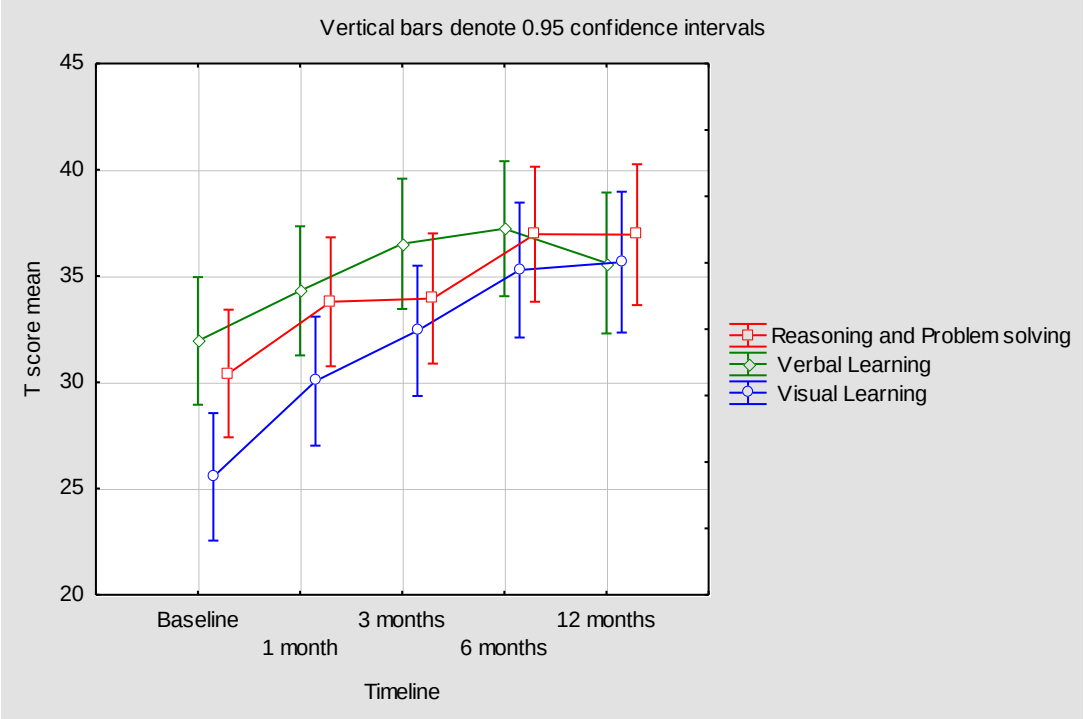

Figure 12.4: Reasoning and Problem solving, Verbal Learning, and Visual Learning T score means improvement over time

A 51.05% improvement in Reasoning and Problem solving, as measured by the Neuropsychological Assessment Battery (NAM)[10]: Mazes, occurred within the first month. By the third month, 72.86% of the overall improvement was attained, whereas no further significant gain was evident after six months (F test 11.85; p<0.01).

Verbal Learning, represented by the Hopkins Verbal Learning Test-Revised (HVLT-R)[11], was the least affected of all cognitive domains at baseline (T-score mean 31.95, ± 8.18). Similar early gain was achieved, with 79.96% of all improvement occurring within the first three months (F test 7.44; p<0.01).

Visual Learning was the only cognitive domain in which continued improvement (as measured by the Brief Visuospatial Memory Test-Revised [BVMT-R][12]) was evident. At 3 months, 67.46% of improvement took place, while at 6 months 95.95% of improvement had occured (F test 10.96; $p<0.01$).

Changes in individual measures and domain scores were small, but for the most part positive and significant. T-score means indicate that at baseline, participants performed 2 to 4 standard deviations below the mean, while at endpoint (12 months), participants performed 1.5 to 3 standard deviations below the mean.

Table 12.2: Neurocognitive T-scores of individual measures

	Baseline		1 month		3 months		6 months		12 months	
Variable	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
TMT	57	19.74 (18.19)	56	28.32 (13.82)	54	30.74 (12.13)	47	36.04 (14.30)	40	36.83 (12.64)
BACS	58	15.57 (15.69)	56	21.73 (15.54)	54	25.22 (12.31)	47	27.47 (11.77)	40	25.58 (13.07)
HVLT-R	58	32.00 (8.12)	56	34.39 (7.16)	54	36.44 (6.99)	47	37.68 (8.51)	40	36.23 (7.65)
WMS-III	58	27.03 (14.39)	56	31.16 (14.29)	54	34.46 (12.37)	47	38.38 (12.41)	40	33.83 (14.03)
LNS	58	25.93 (13.42)	56	28.71 (12.74)	54	31.83 (10.59)	47	35.04 (10.49)	39	32.85 (11.65)
NAB	58	29.89 (9.53)	56	33.82 (8.31)	54	33.83 (7.91)	47	37.29 (10.02)	40	36.80 (8.76)
BVMT-R	58	25.43 (13.60)	56	30.11 (14.31)	54	32.09 (13.77)	47	36.11 (13.68)	40	35.18 (13.35)
Fluency	58	31.55 (10.29)	56	35.36 (10.42)	54	35.74 (9.46)	47	37.38 (6.98)	40	36.33 (7.33)
CPT-IP	52	23.98 (12.05)	52	28.54 (11.01)	52	30.16 (11.40)	47	35.04 (9.79)	40	34.45 (11.09)

Abbreviations: TMT, Trail Making Test: Part A; BACS, Brief Assessment of Cognition in Schizophrenia: Symbol-Coding; HVLT-R, Hopkins Verbal Learning Test-Revised; WMS-III, Wechsler Memory Scale – 3rd ed.: Spatial Span; LNS, Letter-Number Span; NAB, Neuropsychological Assessment Battery: Mazes; BVMT-R, Brief Visuospatial Memory Test-Revised; Fluency, Category Fluency: Animal Naming; CPT-IP, Continuous Performance Test- Identical Pairs.

Spearman correlations between MCCB Cognitive Composite Scores and PANSS[13] symptom factors are listed in table 12.3.

Table 12.3: Spearman correlations between neurocognitive composite scores and clinical ratings

		Cognitive Composite score at baseline	Cognitive Composite score at 12 months
PANSS score at baseline	**Total**	-0.58 **	-0.21
	Positive	-0.27	0.18
	Negative	-0.63 **	-0.36 *
	General	-0.46 **	-0.23
	PANSS C	-0.65 **	-0.29
	PANSS D	0.04	-0.02
	PANSS G12	-0.48 **	-0.13
PANSS score at 12 months	**Total**	-0.22	-0.53 **
	Positive	-0.05	-0.57 **
	Negative	-0.32	-0.53 **
	General	-0.26	-0.43 *
	PANSS C	-0.30	-0.54 **
	PANSS D	-0.05	-0.12
	PANSS G12	-0.21	-0.58 **

* $p<0.05$ ** $p<0.01$

Symptom severity (PANSS Total) explained 33.64% of the variance in cognitive symptoms (MCCB Cognitive Composite Score) at baseline and 28.09% at 12 months. Negative symptoms explained 39.69% of cognitive symptoms at baseline. At 12 months, positive symptoms explained more of the variance in cognition than negative symptoms (32.49% vs 28.09% respectively).

However, PANSS C[14] predicted only 42.25% of the variance in cognitive symptoms at baseline, and 29.16% at 12 months. PANSS D[15] had no significant correlation with overall cognition, or any cognitive domains, at either baseline, or at 12 months. Insight (PANSS G12) showed a highly significant, inverse correlation with cognitive symptoms (MCCB Cognitive Composite Score) at both baseline and at one year.

Spearman correlations between neurocognitive domain scores and PANSS symptom factors are listed in table 12.4.

Table 12.4: Spearman correlations between cognitive domain scores and clinical ratings

		Domain score at baseline					
		SPO	**AV**	**WM**	**VerL**	**VisL**	**RP**
PANSS score at baseline	**Total**	-0.56 **	-0.43 **	-0.56 **	-0.50 **	-0.37 **	-0.32 *
	Positive	-0.24	-0.23	-0.26	-0.29	-0.12	-0.03
	Negative	-0.64 **	-0.48 **	-0.60 **	-0.50 **	-0.44 **	-0.44 **
	General	-0.46 **	-0.37 **	-0.48 **	-0.40 **	-0.30 *	-0.28 *
	PANSS C	-0.52 **	-0.56 **	-0.53 **	-0.47 **	-0.48 **	-0.36 **
	PANSS D	0.13	0.05	0.08	0.04	-0.10	0.01
	PANSS G12	-0.43 **	-0.39 **	-0.37 **	-0.36 **	-0.28 *	-0.23
		Domain score at baseline					
		SPO	**AV**	**WM**	**VerL**	**VisL**	**RP**
PANSS score at 12 months	**Total**	-0.41 **	-0.14	-0.45 *	-0.34	-0.48 **	-0.20
	Positive	-0.26	-0.22	-0.47 **	-0.49 **	-0.31	-0.01
	Negative	-0.39 *	-0.22	-0.50 **	-0.28	-0.42 *	-0.24
	General	-0.40 *	-0.09	-0.35 *	-0.31	-0.46 **	-0.16
	PANSS C	-0.59 **	-0.21	-0.46 **	-0.41 *	-0.56 **	-0.28
	PANSS D	-0.12	-0.13	-0.27	0.07	-0.07	0.19
	PANSS G12	-0.26	-0.28	-0.25	-0.57 **	-0.40 *	-0.13

* p<0.05 ** p<0.01

Abbreviations: SPO, Speed of Processing; AV, Attention and Vigilance; WM, Working Memory; VerL, Verbal Learning; VisL, Visual Learning; RP, Reasoning and Problem solving

Positive symptoms (PANSS P) at baseline showed no significant correlations with any of the cognitive domains. However, at one year, positive symptoms

had highly significant, inverse correlations with Working Memory and Verbal Learning. Negative symptoms (PANSS N) at baseline showed highly significant, inverse correlations with all cognitive domains. However, at one year, the only significant correlations between negative symptoms and cognition were in the domains of Working Memory and Visual Learning. General psychopathology scores (PANSS G) demonstrated significant, inverse correlations with all cognitive domains at baseline, while at one year, the only significant correlations were with Speed of Processing, Working Memory and Visual Learning. PANSS C had a highly significant, inverse correlation with all cognitive domains at baseline, while at one year PANSS C had significant inverse correlations with Speed of Processing, Working Memory and Visual Learning. PANSS D had no correlations with cognitive domains at baseline, or at 1 year.

Insight (PANSS G12) showed highly significant, inverse correlations with each of Speed of Processing, Attention and Vigilance, Working Memory, and Verbal Learning at baseline, while at one year insight had a highly significant inverse correlation with Verbal Learning. There were significant inverse correlations between insight and Visual Learning at both baseline and at one year.

Social Cognition

Social cognition was evaluated by means of the Mayer-Salovey-Caruso Emotional Intelligence Test[16] (MSCEIT™).

There was no difference between genders or ethnic groups at either baseline or one year. However, there was a significant difference (p=0.02) in Social Cognition at baseline between participants assessed in English (26.59, ± 6.19) or Afrikaans (32.14, ± 8.95) (see figure 12.5).

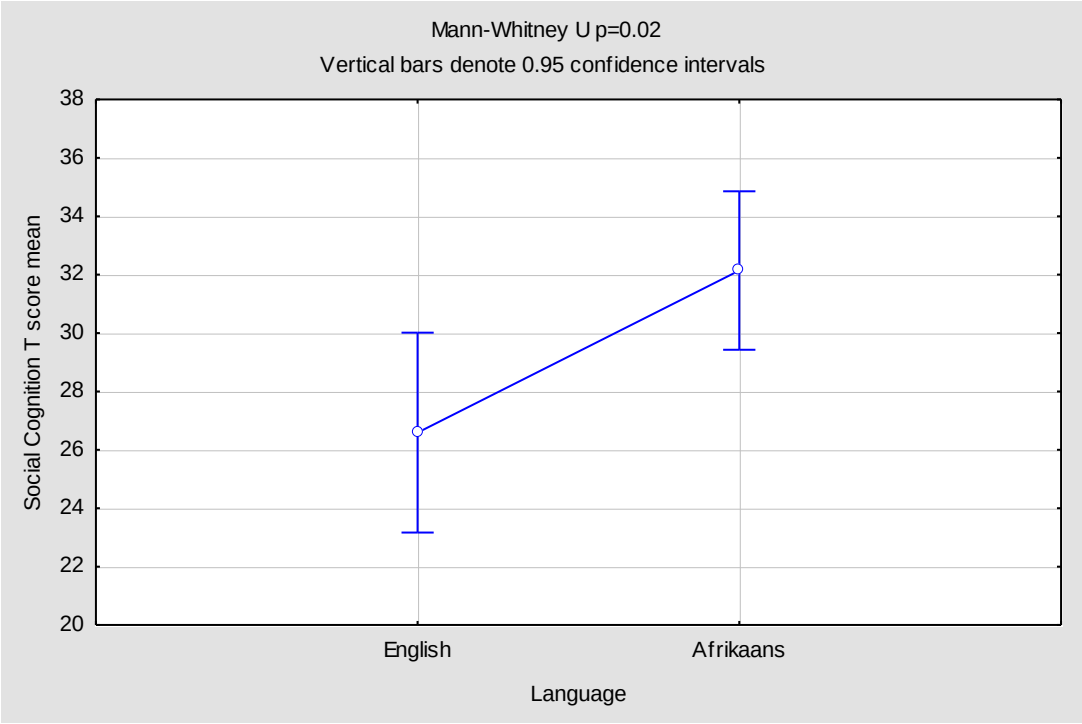

Figure 12.5: Baseline differences between language and Social Cognition

This difference in Social Cognition between English and Afrikaans groups persisted at one year (28.29, ± 9.07 and 35.17, ± 13.73 respectively;

p=0.04). Age had a statistically significant positive correlation with the Managing Emotions Branch (MEB) at 1 year (r=0.38; p=0.02).

The ability of female participants to regulate the self (Emotion Management Task; REMT) was significantly better than that of male participants (83.44, ± 8.63 and 77.57, ± 6.74 respectively; p=0.01) at baseline (see figure 12.6). This gender difference disappeared by 1 year.

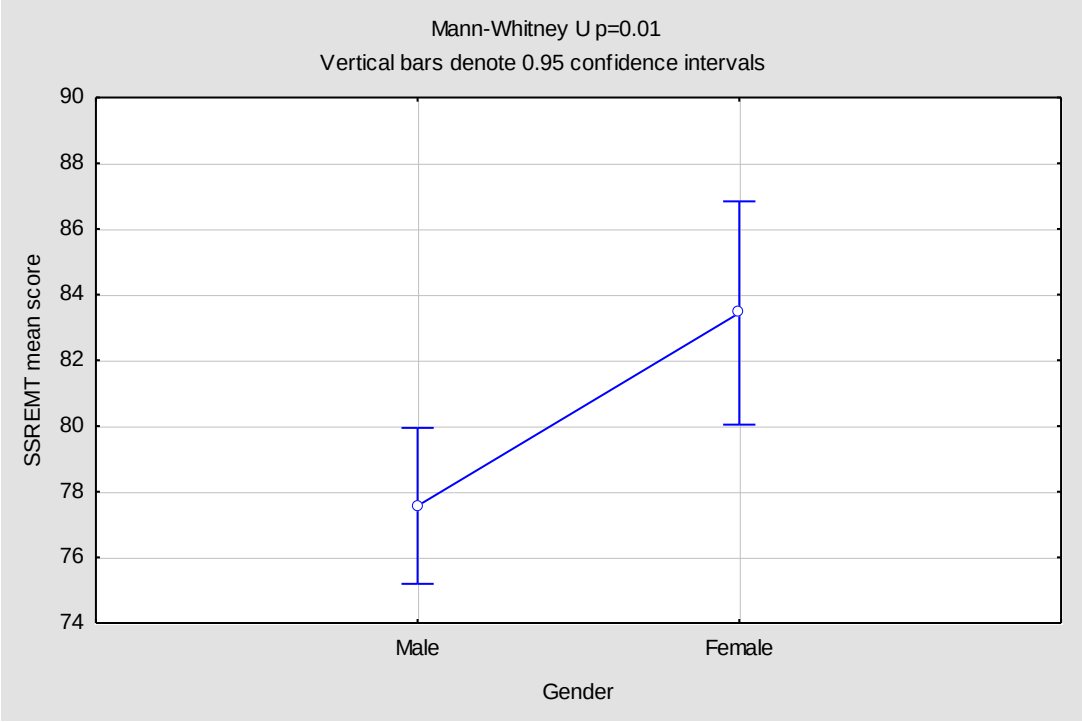

Figure 12.6: Difference between genders in self-regulation at baseline

Although Social Cognition improved from a mean T-score of 30.00 (± 8.39) at baseline to 32.25 (± 12.22) at one year, the change was not significant. Thirty-four-point-six percent of the improvement occurred within one month,

and 51.71% by 3 months. However, improvement over time was significant for both MEB and the Social Management Task (RMT) (see table 12.5).

Table 12.5: Change in Social Cognition and individual measures over time

	Baseline		12 months		F Test; p value
	N	T-score mean (SD)	N	T-score mean (SD)	
Social Cognition	58	30.00 (8.39)	40	32.25 (12.22)	2.89; 0.02
MEB	58	76.99 (7.52)	40	79.73 (10.14)	3.05; 0.02
RMT	58	79.84 (9.37)	40	81.12 (11.50)	2.63; 0.04
REMT	58	79.49 (7.84)	40	82.19 (9.53)	1.52; 0.19

Abbreviations: MEB, Managing Emotions Branch; RMT, Social Management Task; REMT Emotion Management Task

Spearman correlations between Social Cognition and PANSS symptom factors are listed in table 12.6.

Table 12.6: Spearman Correlations between Social Cognition and clinical ratings

		Social Cognition scores at baseline				Social Cognition scores at 12 months			
		Total	**MEB**	**RMT**	**REMT**	**Total**	**MEB**	**RMT**	**REMT**
PANSS score at baseline	**Total**	-0.44 **	-0.51 **	-0.15	-0.27	-0.21	-0.24	-0.14	-0.17
	Positive	-0.12	-0.18	-0.1	-0.14	-0.08	-0.17	-0.14	-0.17
	Negative	-0.38 **	-0.46 **	-0.39 **	-0.30 *	-0.15	-0.14	-0.08	-0.13
	General	-0.40 **	-0.46 **	-0.41 **	-0.33 *	-0.17	-0.24	-0.13	-0.28
PANSS score at 12 months	**Total**	-0.30	-0.29	-0.27	-0.22	-0.39	-0.38 *	-0.40 *	-0.15
	Positive	-0.17	-0.19	-0.08	-0.18	-0.33	-0.43 * *	-0.43 *	-0.26
	Negative	-0.25	-0.26	-0.27	-0.19	-0.27	-0.29	-0.34	-0.07
	General	-0.35	-0.34	-0.29	-0.25	-0.44 *	-0.41 *	-0.39 *	-0.19

* p<0.05 ** p<0.01

At baseline, negative and general symptoms had a highly significant inverse correlation with Social Cognition, and specifically with MEB and RMT. However, at one year, negative symptoms did not correlate with Social Cognition, while positive symptoms had a highly significant, inverse correlation with MEB and RMT. Self regulation showed no significant correlation with clinical psychopathology at one year.

Insight

Insight was evaluated by the PANSS insight item (G12), as objective measure, as well as the Birchwood Insight Scale (BIS)[17], as subjective measure.

The mean baseline PANSS G12 score was 5.03 (± 1.03) which is indicative of moderately severe impairment in insight, where participants show only a vague or shallow recognition of illness. There was a significant, inverse correlation between PANSS D and PANSS G12 at baseline (r=-0.37; p<0.01).

Participants with poor insight were more likely to be hospitalized (see figure 12.7)

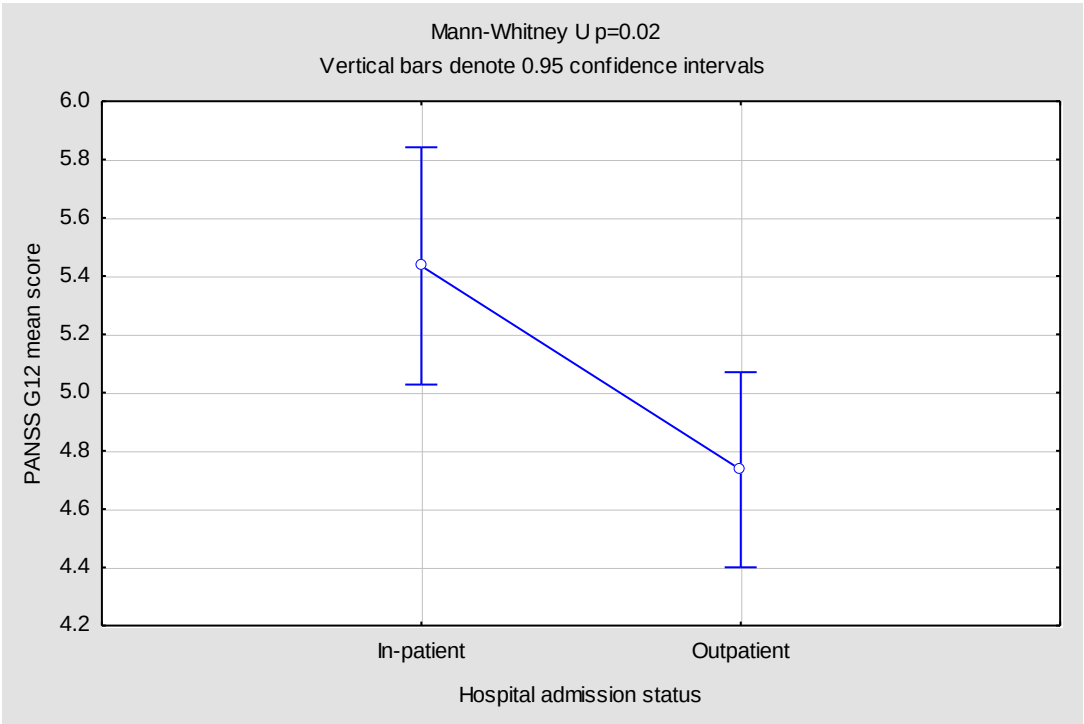

Figure 12.7: Difference between hospital admission statuses with regard to insight

Although there was a significant, inverse correlation between insight and hospital admission status (r=-0.34; p=0.01), the duration of admission did not correlate with insight.

There was a significant improvement in insight after acute stabilization (p<0.01), with PANSS G12 decreasing from 5.03 (± 1.03) at baseline to 3.05 (± 0.95) at 12 months (see figure 12.8).

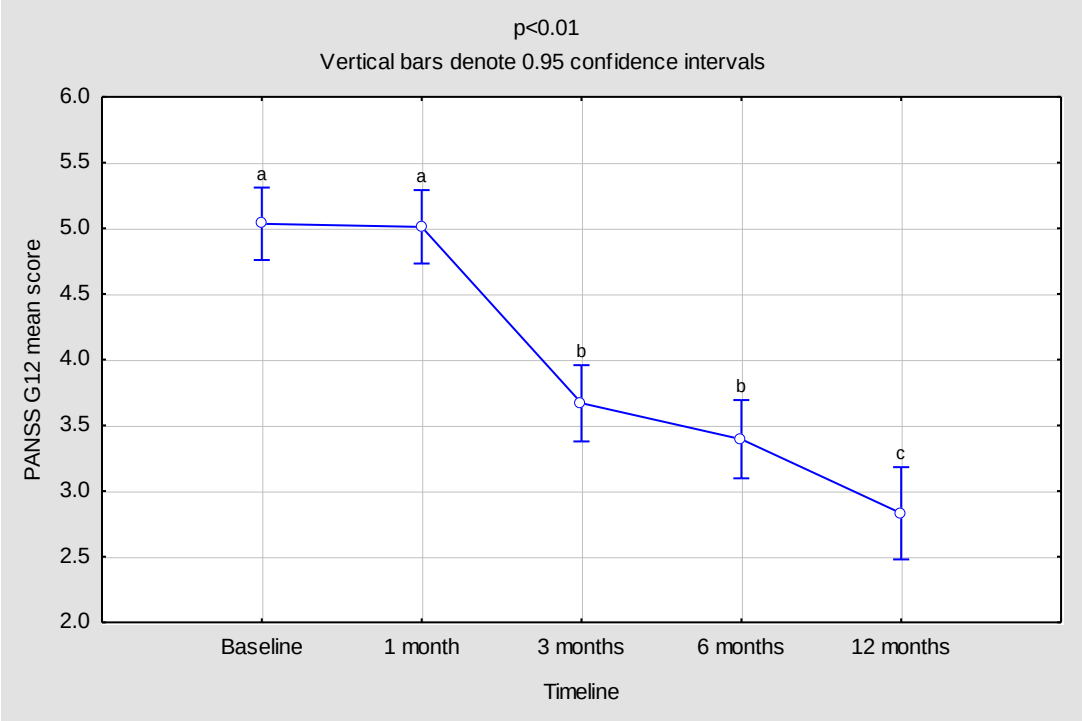

Figure 12.8: Improvement in insight over time

The participants BIS total scores are depicted in figure 12.9.

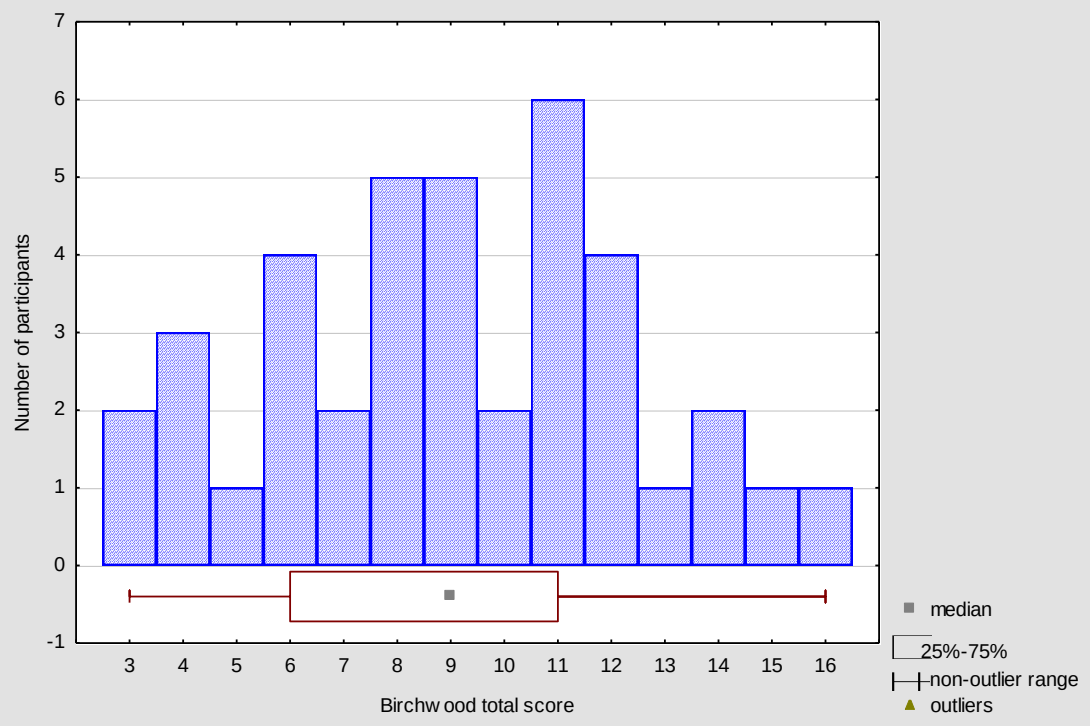

Figure 12.9: Birchwood Insight Scale scores at baseline

Participants' mean BIS score was 9.03 (± 3.34), suggesting "good insight". If we examine the number of participants with "good" (>9) versus those with "poor" (≤9) insight, 22 (56%) of the participants who completed the scale had poor insight, with 17 (44%) considered having good insight. Although there was a small improvement in mean BIS score over time to 9.45 (± 2.01) at one year, the change was not significant.

There were no significant differences in levels of insight between age groups, different levels of education, genders or language groups at baseline. However, at one year, females had better insight than males (10.7, ± 3.40 versus 8.20, ± 2.44; p=0.03).

Correlations between BIS scores and PANSS G12 at baseline, 6 months and 1 year did not reach a level of significance (p set at 0.05). However, PANSS Total and PANSS G scores at baseline had significant positive correlations with BIS scores at 12 months (see table 12.7).

Table 12.7: Spearman correlations between insight and clinical ratings

		BIS score at baseline	BIS score at 12 months
PANSS score at baseline	**Total**	0.13	0.51**
	Positive	0.07	0.19
	Negative	0.09	0.27
	General	0.17	0.54**
	PANSS C	0.12	-0.02
	PANSS D	0.10	0.33
PANSS score at 12 months	**Total**	-0.21	-0.06
	Positive	-0.14	-0.09
	Negative	-0.47	0.03
	General	-0.09	-0.10
	PANSS C	-0.02	-0.02
	PANSS D	-0.16	0.04

* p<0.05 ** p<0.01

Although correlations between the BIS scores and MCCB Cognitive Composite Scores were not significant at any visit (p set at 0.05), PANSS G12 scores showed highly significant (p<0.01) inverse correlations with MCCB Cognitive Composite Scores at all visits (baseline r=-0.48; 1 month r=-0.41; 3 months r=-0.42; 6 months r=-0.52 and 12 months r=-0.58).

There were no significant correlations at baseline between insight and premorbid adjustment (PAS), social and occupational functioning (SOFAS), DUI/DUP, hospital admission status, or estimation of premorbid intelligence (WAIS).

Subjective reports of cognitive impairment

The Subjective Scale to Investigate Cognition in Schizophrenia[18] (SSTICS) was used as quantitative measure to assess participants with regard to the cognitive deficits they experienced.

The mean SSTICS Global score at baseline was 35.23 (± 18.19) (N=39), where zero would indicate no impairment, while the maximum score that can be obtained is 84. Participants assessed in English reported more cognitive impairment at baseline (51.67, ± 20.79) than those assessed in Afrikaans (27.93, ± 11.00) (see figure 12.10). At one year (N=37), there was no difference between the groups.

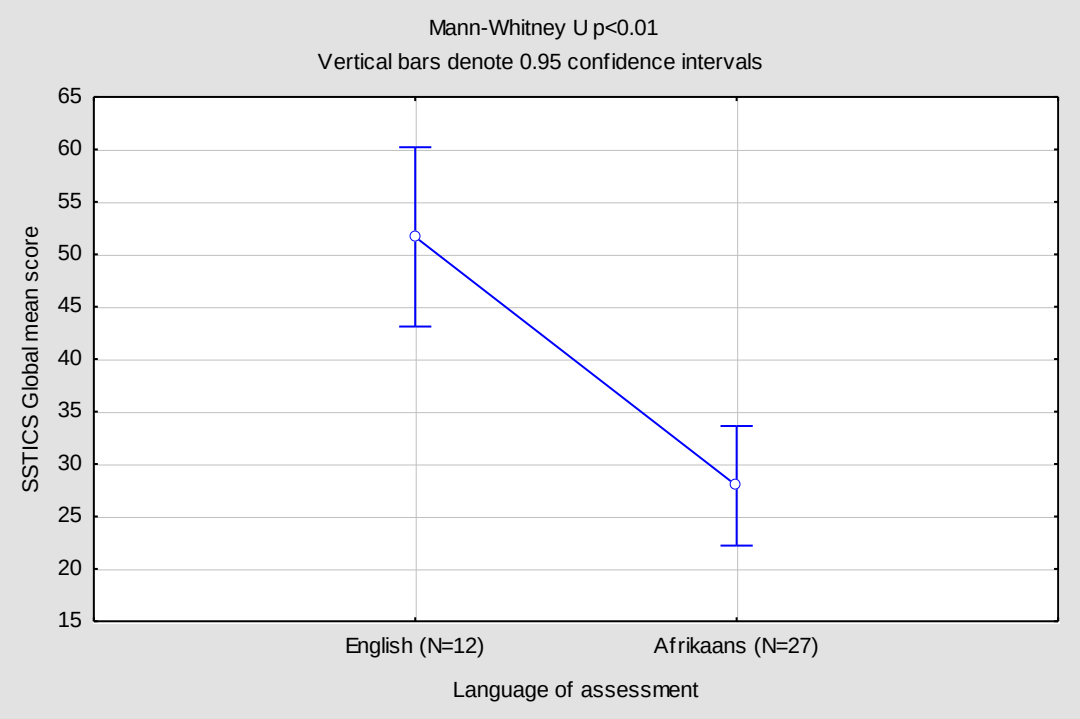

Figure 12.10: Language differences in cognitive complaints at baseline

No significant differences between gender groups were present at baseline. However, at one year, male participants reported more subjective impairment than female participants (30.21, ± 15.84 versus 17.33, ± 12.89 respectively; p=0.03) (see figure 12.11).

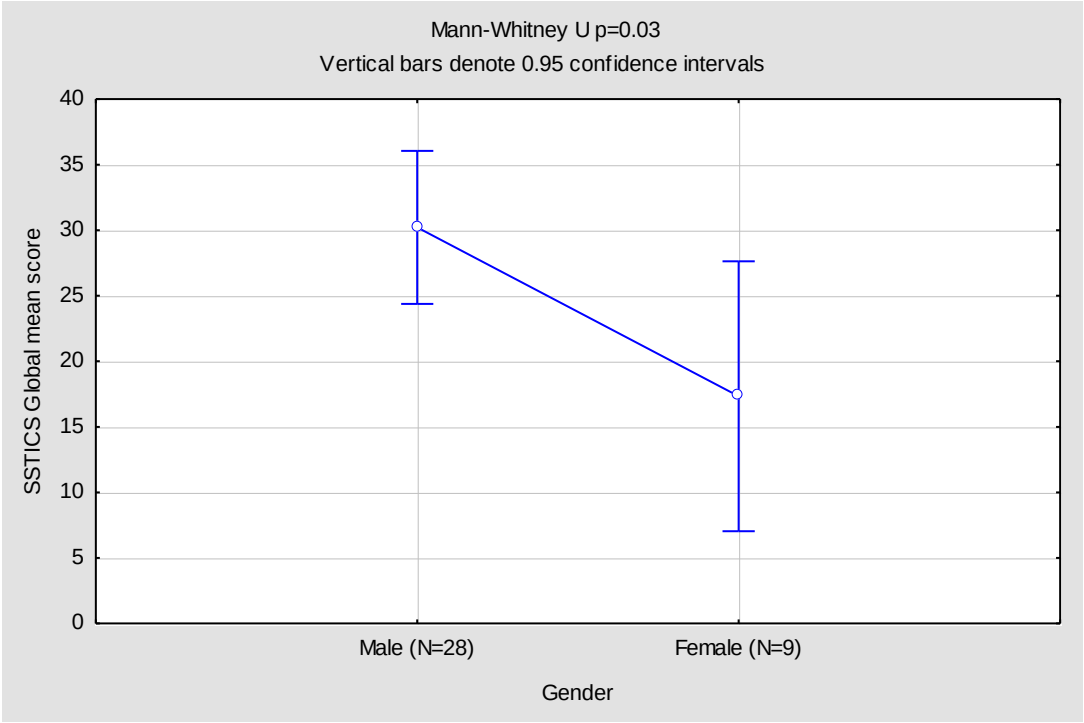

Figure 12.11: Gender differences in cognitive complaints at 12 months

Male participants therefore presented with 15.33% more cognitive complaints at one year than did female participants.

A significant ($p<0.01$) decrease in complaints of cognitive impairment occurred over time, most notably between one and 3 months (see figure 12.12 and table 12.8).

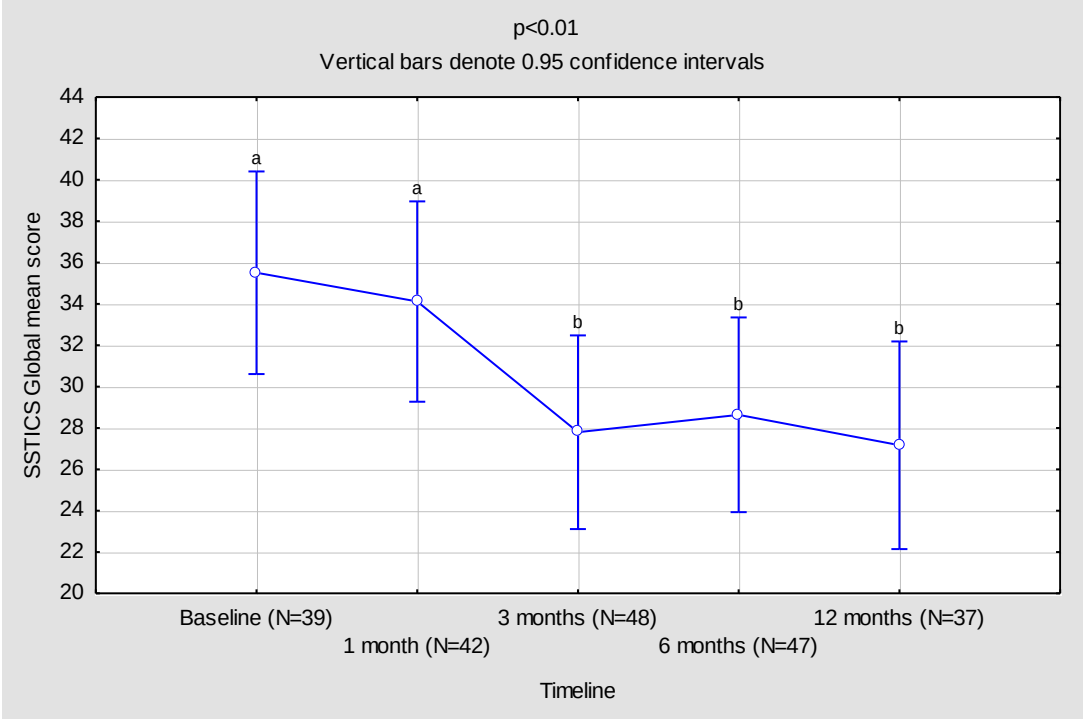

Figure 12.12: Change in cognitive complaints over time

As mentioned (p 248) this questionnaire was only used after the initial six months of the study, therefore not all participants completed the questionnaire at baseline, one and three month assessments. This would explain the apparent discrepancy in number of participants completing the SSTICS at a given time point

Table 12.8: Change in subjective reports of cognitive impairment over time

	Baseline (N=39)	**12 months (N=37)**	**F Test; p value**
Variable (maximum score)	**Mean (SD)**	**Mean (SD)**	
Sustained Executive Function (16)	8.00 (3.97)	6.11 (4.15)	4.09; <0.01
Memory of information (16)	5.46 (3.73)	4.05 (3.19)	3.32; 0.01
Consciousness of effort (16)	7.77 (3.90)	6.35 (3.54)	2.83; 0.03
Daily Life (16)	6.10 (4.16)	4.65 (3.18)	2.46; 0.05
Distractibility (12)	5.05 (3.49)	4.46 (2.66)	3.06; 0.02
Alertness (4)	1.41 (1.31)	1.08 (1.23)	2.06; 0.09
Global (84)	35.23 (18.19)	27.08 (16.02)	5.05; <0.01

Sustained Executive Function and Consciousness of effort improved up to one month, thereafter, no significant decrease in complaints occurred. Problems with regard to Memory of information (working memory and explicit memory) and Distractibility decreased up to 3 months, with no significant change thereafter. Of the individual measures, Alertness and Daily Life did not improve significantly over the 12 months of the study.

No correlations were present between subjective cognitive impairment and each of the following: insight, QOL, and hospital admission status, DUI/DUP, mood symptoms (CDSS and PANSS D), or severity of illness at baseline (PANSS and CGI-s).

Spearman correlations between subjective cognitive complaints and objective neurocognitive measures and clinical ratings are listed in tables 12.9 to 12.11.

Table 12.9: Spearman correlations between SSTICS individual measures, MCCB scores, and PANSS ratings at baseline

	SEF	MEM	COE	DL	DIST	ALERT	Global
PANSS P Total	-0.20	-0.05	-0.20	-0.03	-0.03	0.02	-0.11
PANSS N Total	0.04	0.23	0.20	0.14	0.13	-0.01	0.12
PANSS G Total	0.17	0.20	0.16	0.28	0.16	0.15	0.19
PANSS Total Score	0.09	0.24	0.15	0.25	0.19	0.11	0.18
PANSS C factor	-0.21	-0.33	-0.42 **	-0.20	-0.21	-0.08	-0.31
PANSS D factor	0.12	-0.14	0.07	0.18	-0.05	0.06	0.01
Speed of Processing	0.02	-0.01	0.04	-0.02	0.16	0.15	0.04
Attention and Vigilance	-0.22	-0.23	-0.43 **	-0.32	-0.22	-0.08	-0.32
Working Memory	-0.15	-0.14	-0.21	-0.08	-0.08	-0.10	-0.15
Verbal Learning	-0.14	-0.22	-0.34 *	-0.24	-0.13	-0.12	-0.28
Visual Learning	-0.10	-0.19	-0.22	-0.29	-0.11	-0.21	-0.24
Reasoning and Problem Solving	-0.22	-0.08	-0.26	-0.27	-0.04	-0.08	-0.24
Social Cognition	-0.26	-0.15	-0.43 **	-0.26	-0.11	0.02	-0.25
Cognitive Composite	-0.23	-0.36 *	-0.32	-0.24	-0.13	-0.02	-0.32 *

* p<0.05; ** p<0.01

Abbreviations: SEF, Sustained Executive Function; MEM, Memory of information; COE, Consciousness of effort; DL, Daily Life; DIST, Distractibility; ALERT, Alertness

We found a highly significant, inverse correlation at baseline ($p<0.01$) between Consciousness of effort and PANSS C ratings, as well as between Consciousness of effort and cognitive domains of Attention and Vigilance and Social Cognition (see table 12.9).

Table 12.10: Spearman Correlations between SSTICS individual measures, MCCB scores, and PANSS ratings at 1 month

	SEF	MEM	COE	DL	DIST	ALERT	Global
PANSS P Total	0.13	-0.07	0.03	0.12	0.10	0.24	0.14
PANSS N Total	0.17	0.06	0.11	0.32 *	0.18	0.10	0.21
PANSS G Total	0.38 *	0.22	0.35 *	0.25	0.37 *	0.11	0.42 **
PANSS Total Score	0.34 *	0.18	0.25	-0.28	0.31 *	0.15	0.37 *
PANSS C factor	0.25	0.12	0.13	0.12	0.33	0.11	0.24
PANSS D factor	0.21	0.07	0.17	0.12	0.13	-0.03	0.14
Speed of Processing	-0.46 **	-0.43 **	-0.41 **	-0.33 *	-0.40 **	-0.56 **	-0.52 **
Attention and Vigilance	-0.28	-0.25	-0.20	-0.21	-0.35 *	-0.25	-0.35 *
Working Memory	-0.45 **	-0.25	-0.37 *	-0.34 *	-0.29	-0.55 **	-0.45 **
Verbal Learning	-0.41 **	-0.40 **	-0.27	-0.35 *	-0.34 *	-0.44 **	-0.45 **
Visual Learning	-0.38 *	-0.42 **	-0.31	-0.26	-0.41 **	-0.47 **	-0.46 **
Reasoning and Problem Solving	-0.44 **	-0.35 *	-0.35 *	0.01	-0.31 *	-0.56 **	-0.48 **
Social Cognition	-0.11	0.05	0.21	-0.28	0.11	-0.20	-0.00
Cognitive Composite	-0.44 **	-0.36 *	-0.27	0.25	-0.32	-0.54 **	-0.46 **

* $p<0.05$; ** $p<0.01$

Abbreviations: SEF, Sustained Executive Function; MEM, Memory of information; COE, Consciousness of effort; DL, Daily Life; DIST, Distractibility; ALERT, Alertness

At one month, subjective cognitive complaints correlated inversely with the domains of Speed of Processing, Working Memory, Visual Learning and

Reasoning and Problem solving. Global PANSS symptoms had a positive correlation with Global subjective cognitive impairment. MCCB Cognitive Composite Score correlated significantly, and inversely, with Sustained Executive Function and Alertness. No correlation between subjective impairment in cognition and PANSS C, or with PANSS D, was found (see table 12.10).

At three months, PANSS D had a strong positive correlation with Sustained Executive Function ($r=0.35$, $p=0.02$), while Verbal Learning had a strong, inverse correlation with Sustained Executive Function ($r=0.33$, $p=0.02$). No other correlations between subjective and objective cognitive measures were present. PANSS Total scores showed highly significant ($p<0.01$) inverse correlations with Distractibility ($r=0.39$), Alertness ($r=0.46$) and Daily Life (0.40).

At six months, correlations between PANSS G, Speed of Processing, and individual measures of the SSTICS remained significant ($p<0.01$). Furthermore PANSS D had significant positive correlations with subjective cognitive impairments reported (see table 12.11).

Table 12.11: Spearman Correlations between SSTICS individual measures, MCCB scores, and PANSS ratings at 6 months

	SEF	MEM	COE	DL	DIST	ALERT	Global
PANSS P Total	0.25	0.24	0.31	0.27	0.28	0.11	0.27
PANSS N Total	0.32 *	0.13	0.22	0.23	0.21	0.13	0.19
PANSS G Total	0.40 **	0.34 *	0.39 **	0.37 *	0.36 *	0.01	0.38 **
PANSS Total Score	0.38 **	0.28	0.36 *	0.35 *	0.33 *	0.10	0.33 *
PANSS C factor	0.22	0.21	0.20	0.18	0.11	-0.18	0.15
PANSS D factor	0.33 *	0.30 *	0.43 **	0.35 *	0.31 *	0.30 *	0.38 **
Speed of Processing	-0.41 **	-0.31 *	-0.32 *	-0.28	-0.19	0.10	-0.31 *
Attention and Vigilance	-0.28	-0.36 *	-0.13	-0.20	-0.17	-0.10	-0.22
Working Memory	-0.31 *	-0.23	-0.32 *	-0.26	-0.13	0.01	-0.23
Verbal Learning	-0.18	-0.25	-0.11	-0.16	-0.17	-0.00	-0.17
Visual Learning	-0.11	-0.14	-0.01	-0.04	-0.13	-0.07	-0.02
Reasoning and Problem Solving	-0.03	-0.11	-0.06	-0.00	-0.01	-0.09	-0.03
Social Cognition	-0.11	-0.11	-0.16	-0.14	-0.16	-0.06	-0.09
Cognitive Composite	-0.30 *	-0.33 *	-0.24	-0.24	-0.24	-0.15	-0.26

* $p<0.05$; ** $p<0.01$

Abbreviations: SEF, Sustained Executive Function; MEM, Memory of information; COE, Consciousness of effort; DL, Daily Life; DIST, Distractibility; ALERT, Alertness

There were significant, positive correlations present between PANSS D and Consciousness of effort ($r=0.42$, $p<0.05$) and between PANSS D and Daily

Life ($r=0.42$, $p<0.05$) at 12 months. There were no other significant correlations between clinical ratings and subjective cognitive impairment present. However, Social Cognition was inversely correlated with Daily Life ($r=-0.13$, $p<0.05$) and Distractibility ($r=-0.22$, $p<0.01$), while MCCB Cognitive Composite Score showed an inverse correlation with Memory of information ($r=-0.24$, $p<0.05$).

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CHAPTER 13

DISCUSSION

The aim of this study was to investigate cognitive deficits in patients with first episode psychosis (FEP), and the response of these impairments to treatment with a depot formulation of the first generation antipsychotic (FGA) flupenthixol.

To date, this study is one of the largest FEP studies in South Africa, with the largest number of participants completing the one year follow-up period. Only three other South African studies, investigating some of the cognitive aspects of schizophrenia, could be traced by the author (those of Mattson et al.[1], Emsley et al.[2], and Skuy et al[3].) The author believes this to be the first longitudinal study investigating both cognition in FEP, and the response thereof, to ultra low doses of an injectable FGA, to be undertaken in South Africa.

The literature indicates that differences in population constructs and the variables within schizophrenia itself are important factors influencing the presentation, treatment response and patient outcome of the illness, that are unique to differing global settings[4]. Continued investigation to provide additional comparable data on these aspects of the illness is, therefore, important. This study confirmed the findings of similar investigations held elsewhere, and presented some findings not previously documented.

GENERAL

Gender and age (refer pp 257-259, 282, 314, 323)

Disparity between the genders in schizophrenia has been reported on and attributed to biological and environmental influences[5,6]. The disparity between gender representation in our sample and the 2007 population estimate for the Western Cape[7] is as follows: 67% male vs. a 51.9% provincial representation; and 33% female vs. a 49.9% provincial representation. The mean age for the Western Cape population is 27.1 years for males, and 28.3 years for females; whereas the mean in our sample was 22.43 years, and 25.35 years, respectively

Various studies have reported onset of illness to occur between 15 and 30 years of age, and the literature suggests a trend toward males being younger at onset, and more severely ill, than females[6,8,9]. However, this belief is not supported by all reports[5,6,8-10]. The findings of our study mirrored the mean age of onset[11,12], however, we were unable to confirm that males were more severely ill at baseline than females.

We did not find any significant differences in objective measures of neurocognitive functioning between the genders at any stage of the study, though females displayed some advantages in social cognitive skills at baseline, and males reported more subjective cognitive impairment at one year.

Ethnicity (refer pp 259-263)

This study was conducted at the Stikland and Tygerberg hospitals. As the majority of the patients who present at these locations are of Mixed (African-Caucasian) ethnic lineage, this study's cohort is a representative sample of the ethnicity of this catchment area's population, although it does not fully reflect the ethnic composition of the Western Cape Province. This composite differential is demonstrated as follows: the study sample was 78% Mixed ethnic origin vs. a 50.2% provincial population; 12% Black African vs. a 30.1% provincial population; and 10% White vs. an 18.4% provincial population[13].

Differences in presentation between ethnic groups, as previously reported[14], were not supported by the results of this study; nor could any significant differences be demonstrated in severity of illness and cognition between these groups at baseline, or in response to treatment at the end of the one year trial period. Although a significant difference in premorbid IQ estimation was evident, this may not be of any clinical significance, but may rather reflect the presence of demographic and psychopathological differences at baseline. Results on ethnic differences should however be interpreted with great caution, due to the small number of participants in the White and Black African groups.

Language (refer pp 259-261, 313)

“Education and ethnicity cannot be discussed without taking language into account”[15] (pg 251).

The linguistic cross-section of this study’s sample, compared to that of the Western Cape Province, was as follows: Afrikaans 79% vs. a 55.3% provincial usage; Xhosa 10.3% vs. a 23.7% provincial usage; and English 8.6% vs. a 19.3% provincial usage[7].

South Africa’s 11 official languages are reputed to be the highest number of languages recognized on a national level in any country in the world. However, only two of these languages (Afrikaans and English) are the primary mediums through which mainstream education is delivered. For this reason, all assessments in this study were conducted in the patients’ preferred language of either Afrikaans or English, being a reflection of their language of education.

Participants, who preferred to be assessed in English, were more severely ill at baseline than those assessed in Afrikaans. This could be due to selection bias, as well as differences in educational level attained. The difference in premorbid IQ between language groups appeared to be an effect of educational level attained and not of ethnicity, or language *per se*. Although no difference in objective assessment of neurocognitive functioning was evident at baseline, participants assessed in English reported more

subjective cognitive impairment, than those assessed in Afrikaans. Although participants assessed in English displayed more impairment in social cognition at both baseline and one year, this may be a reflection of cultural differences. It should also be taken into consideration that bilingualism can alter normal performance expectations[16].

In this study sample, three late-bilingual male participants (i.e. who learned their second language after the age of 6 years) “switched” spontaneously from their mother tongue (Afrikaans) to their second language (English) during the onset of their psychotic episode, subjectively experiencing communication to be easier, and thought processes to be more coherent, in their second language. This ‘preserved’ second language functioning was evident in objective clinical assessments. One such case has been documented elsewhere by Schoeman et al.[17], and Southwood et al.[18].

Language disruption in schizophrenia appears to differ between genders. Male patients performed significantly worse than healthy male controls on domains of phonology (least affected), semantics, and grammar. Conversely, language function has been described as relatively preserved in female patients when compared to healthy female controls, with phonology most affected[19].

Abuse of illicit substances (refer pp 265-267)

Numerous studies have indicated that individuals with FEP display a significantly higher rate of substance abuse than their non-psychotic peers, with a median lifetime prevalence estimate of at least 40%[20-23]. At baseline, five of 58 participants in our study (8.6%) tested positive for illicit substances. Although this is slightly higher than the prevalence of illicit substance use in the general South African population, it is representative of the prevalence for the population of the Western Cape[24-26].

Figures from North American studies that compared the estimated lifetime prevalence for illicit substance use in individuals with schizophrenia, reported a range between 47% in the Epidemiologic Catchment Area Study[27] (ECA), and 59% in the USA National Comorbidity Study[28] (NCS), compared to 16% in the general population. Other studies of the same nature reported figures as high as 65% to 80% (four times that of the general population) [29],[30]. In the CATIE trials 60% of the sample was found to abuse substances, with 37% of the group reported as being current substance users[31]. Yet, on the other side of the Atlantic, studies in the United Kingdom reported significantly lower figures that ranged between 7% and 27%[32-34].

Substance abuse in our sample increased from 8.6% at study outset to 51.2% at 12 months. However, this may not be a reflection of the 'real use' by patients. While we used urine drug screening and reports from participants and their family members to evaluate substance use, these do

not necessarily reflect variations in the degree of substance abuse that may occur over time. This is also in contrast to certain studies which have indicated that substance abuse by individuals with FEP declined after entry into a treatment program[23,35,36]. Other studies have reported that at least 50% of patients continued their substance abuse unabated[37].

The most common substance of abuse during the course of this study was cannabis (>70%), followed by methaquolone (>40%) and methamphetamines (>60%). Although our study sample did not reflect the high prevalence of estimated methamphetamine use in the Cape Town population[38], cannabis use within the sample did correlate with international study documentation that this appears to be the most common illicit substance of abuse in schizophrenia[39]

There is some disparity in the literature on differences in clinical symptomatology and severity of illness between patients who use illicit substances and those who do not[21,40,41]. Some studies reported differences, specifically fewer negative symptoms and more severe positive symptoms in substance abusers, whereas others did not find any significant differences between these groups. In our particular case, no significant differences were found [31,42].

Due to the small number of participants using illicit substances at the outset of our study we were unable to comment on the previously reported differences in age, mood symptoms, social functioning, compliance, side-

effects and relapse between so-called dual diagnosis patients, and those who were psychotic but did not use illicit substances[21,31,43-48].

There are reports in the literature that claim an effect of substance abuse on cognitive performance in schizophrenia patients; however this view is not universally held. While some studies reported adverse effects on memory and attention[49], and impaired verbal fluency[50], others have reported enhancement of attention span[51], psychomotor speed[52], memory[53], verbal fluency[53], and visual spatial construction[54-56].

Our study found no evidence to support differences in cognitive performance between the participants who used illicit substances, and those who did not. Our results therefore support those of Pencer and Addington[50] who, in a two year prospective cross-sectional and longitudinal study of FEP (N=266), found no significant associations between cognitive functioning and the use of different substances of abuse. However, they did note a relationship between illicit substance use and the presence of more positive symptoms. Not surprisingly though, the participants in our study, without comorbid substance did have better insight, which concur with findings by Addington and Addington[57].

Social circumstances such as unemployment, religious orientation, and availability of illicit substances may have contributed to substance use in our sample. However, we cannot disregard the possibilities of attempts at self-

medication[58-60], or of a shared biological and genetic vulnerability[61,62] existing between schizophrenia and substance abuse.

Developmental history and premorbid functioning (refer pp 263-265, 267-279)

Longitudinal studies have demonstrated that individuals with schizophrenia differ from their peers, even in early childhood, in attaining developmental milestones[10,63], cognitive functioning[64,65], educational achievement[10,63,66,67], neurological and motor development[68,69], social competence[67,70], and psychological disturbances[70].

It has been suggested of late that some of the problems evident in social functioning do not reflect premorbid symptoms and signs, but may possibly be part of the early prodromal period pre-dating psychosis. In the classic long-term follow-up study by Ciompi et al.[71], 50% of individuals with schizophrenia experienced an acute onset of symptoms, whereas 50% of individuals had a long prodromal phase. The presence of this long DUI, defined as the interval between the onset of the disorder and the administration of the first pharmacological treatment, is often reflected in poor social and vocational functioning[72,73], and is considered a poor prognostic factor in schizophrenia [74].

The average DUI of our study sample was 1.5 years, thus considerably shorter than the 5 year average[75] reported in studies elsewhere. This is in

agreement with the belief that subjects with mental illness in developing countries have better social support structures, therefore being able to be 'absorbed' in society for longer periods than their counterparts in the first world[76,77], but it can also reflect readily accessible mental health services in our area. It must be noted that, in determining the DUI, information was obtained from participants and their relatives, and was not harvested from specific rating scales. Results may therefore have been influenced by so-called 'recall bias'. Furthermore subtle changes during the prodromal period may not have been noted by these untrained individuals.

Agerbo et al. found that individuals suffering from schizophrenia are more likely to be single, less likely to be married and more likely to divorce if they do[78]. In our study sample 31.58% of the females were involved in (or had experienced) long-term relationships, compared to 5.13% of the male participants. Findings that females with schizophrenia tend to have better social functioning than males[5,6,79-81] and experience a milder course of illness[8,82], can possibly be attributed to the later onset of illness in this gender group. This would enable females to develop more social roles prior to the onset of illness, and thereby maintain a greater degree of functioning throughout. It is possible that the single status of the male participants in our study may simply have been a reflection of their younger age and different social role expectations.

Competitive employment rates for individuals with schizophrenia are lower than the general population[78,83,84]. A review by Marwaha and Johnson

reported employment rates in the UK between 4% and 27% (mean 13.7%) for individuals with schizophrenia[85]. In Australia, unemployment rates of individuals with schizophrenia is ten times higher than that of the general population (50.2% vs 5.1% respectively)[23,86], with similar rates documented in Canada (43%)[87] and Singapore (39%)[88].

Whereas no significant differences in status of employment between ethnic groups were found in this study, the unemployment figure within the sample (78%) was four times higher than that for this catchment area[89] (20.3%). Seventy-eight percent of the participants were unemployed, 12% were gainfully employed, while, 9% were learners. These figures differ significantly from those of the EPPIC[90] study in which 29% of the FEP sample was employed, 25% was receiving a form of educational instruction, and 39% was unemployed. These differences could be a reflection of the high unemployment rate (29.4%) in South Africa, however, it may also be a reflection of the "social drift" hypothesis[91], and therefore be a reflection of current functional status, and not of highest functional status.

Decreased work functioning could also be attributed to poor scholastic or social circumstances. The median number of school years completed for this sample was 10 years. Seventy-nine percent of the participants conformed to the provincial average of 8-12 years of completed schooling. It therefore appears that the high unemployment rate in our sample cannot be attributed to educational level only. It is noteworthy that there was a positive correlation between cognitive functioning, and social and occupational functioning in this

sample. We can therefore conclude that factors impacting on cognitive function, will also impact on social and vocational functioning.

It is interesting to note that Afrikaans speaking participants reported more satisfaction with regard to social relations than those participants who preferred to be assessed in English. This may reflect the social isolation minority groups experience in our catchment area, and may not necessarily be as a consequence of language *per se*. Participants with better social and occupational functioning also report better quality of life. Those participants with more prominent positive symptoms were less satisfied with their environment, which, once again, could be a reflection of aspects of their illness (such as delusions), and not of 'real-life' issues.

Duration of untreated psychosis (refer pp 276-279)

The literature has evidenced that FEP patients experience an alarming delay between the times of the first psychotic symptom manifestation to initiation of treatment[4,92-94]. This so-called 'duration of untreated psychosis' (DUP) averages 1-2 years, with a median duration of 3-4 months[95-98]. It has been proposed that the DUP has a biological, toxic effect with deterioration of brain function. Therefore it is likely that a longer DUP is a poor, but modifiable prognostic factor[99-101].

Our study found a DUP of 166.69 (± 168.33) days, which is shorter than the average duration of DUP reported in both high income and Low and Middle

Income (LAMI) countries[99,102-105]. Several studies have reported schizophrenia to have a more benign course, and better prognosis in LAMI countries[4,106-108]. A recent systematic review found a significant difference ($p<0.01$) in DUP between the DUP of LAMI countries (125 weeks) and the DUP of high income countries (63 weeks)[109]. It appears that differences in DUP reflect the nature of the psychosis, and not a delay in treatment as such, as evidenced by a re-analysis of data from the original Northwick Park Study[93,104]. Furthermore, increased DUP was also found to be related to smaller social support networks and a less insidious onset[103,105,110].

Our finding of participants with a short DUP being more likely to be hospitalized could potentially be attributed to a more acute onset of illness. Participants with more disruptive behavior are more difficult to accommodate in the informal settlements common to our catchment area, and therefore less likely to be tolerated than in more rural areas. Furthermore, social and community support is relatively good in our catchment area, and patients of Mixed ethnic origin are less marginalized and isolated. However, this social tolerance does not hold true for Xhosa speaking patients[111].

We did not find any correlation between DUP and gender, DUP and psychopathology, DUP and clinical improvement, or DUP and cognitive functioning, and therefore could neither support, nor contradict, previous results[99,100,112,113].

Being reliant on consensus agreement, our assessment of DUP may be less reliable than studies that employed specific DUP rating scales such as the Retrospective Assessment of Onset of Schizophrenia (IRAOS)[114].

TREATMENT

Efficacy of treatment (refer pp 279-280, 302-303)

The participants in our study were markedly ill at baseline with PANSS Total scores around 100, and CGI[115] ratings of >5. As we recruited from both acute in-patient units and outpatient services, we consider this sample as being representative of all patients with FEP in our catchment area.

The participants in this study were treated with an ultra low dose of flupenthixol decanoate (FD). The mean administered dose was 22.48, ± 0.47mg/month (28.10mg/d CPZE[116,117]). This very low dose of antipsychotic was effective in treating the symptoms of schizophrenia, as measured by PANSS Total score reduction, in the majority of the patients. In our study, improvement in both psychopathology and cognitive symptoms occurred early - within the first month. The majority of improvement occurred within the first three months, and leveled out after six months with no significant gains thereafter. Our findings support documented research indicating that patients with FEP generally respond better to antipsychotic agents than those who have had multiple episodes[118,119]. Evidence for this is the lower dose of antipsychotic treatment needed to achieve positive symptoms

remission in FEP than in chronic patients[120-125], and a higher response and remission rate[126,127]

The effectiveness of the very low dose of FD used in this study in reducing positive symptoms, negative symptoms, general psychopathology symptoms, and mood symptoms, compares favorably to studies with higher doses of flupenthixol[128-136], as well as with the effectiveness documented for other FGAs and SGAs[137-143]. This finding should, however, be interpreted with caution, as this was a single arm, open-label study, which did not have the comparison between different treatments as an objective.

We performed an extensive search of the available literature, and were only able to trace one other study (Ruhrmann et al.[136]) that specifically compared the response of cognitive symptoms to treatment with flupenthixol vs. a SGA. In this six month randomized double-blind study of 144 chronic schizophrenic patients, comparing oral flupenthixol 6.23 (±2.86) mg/d with risperidone 3.56 (±1.20) mg/d, flupenthixol demonstrated non-inferiority with regard to effectiveness on negative symptoms (PANSS N) and cognitive symptoms (PANSS C). Unfortunately, the authors of this study did not conduct any neuropsychological assessments to which we could compare our findings.

A three year longitudinal, randomized, open-label trial, investigated the neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in 104 patients with FEP. Participants completed clinical and cognitive

evaluations at baseline, 6 months, and one year. Although the degree of cognitive improvement was small, all three of the treatment arms demonstrated significant improvement in cognitive functioning over the one year period. No significant difference with regard to effectiveness between the groups was evident[144].

The significant improvements in negative and cognitive symptoms during the course of our study are notable. This supports findings by Davis et al.[145] and Mishara and Goldberg[146], that FGAs may benefit cognitive function and negative symptoms.

It is possible that the very low dose of flupenthixol used in our study was less likely to cause secondary negative symptoms than standard doses of FGAs[147]. It is also possible that FD, is indeed effective in treating core negative symptoms[148-150]. However, it is worthwhile to again note that flupenthixol does resemble some SGAs with regard to receptor profile[151,152], with improved efficacy against negative symptoms and depressed mood, when compared to agents such as fluphenazine.

Seventy-point-seven percent of our sample completed the study. The ACDR of 29.31% (17/58) compares favorably with ACDRs noted for low dose haloperidol[122], long-acting risperidone[153], clozapine[154,155], olanzapine[154,155], and others[156-158]. The ACDR in our study was lower than those reported in international trials such as EUFEST (41.57%)[156-158], CATIE (74%)[159,160], and the CAFE study (70.25%)[161,162]. The mean time to discontinuation in our

sample was 274 (± 116.09) days; being almost double the median time to discontinuation of 4.6 months reported in CATIE [156-158].

During the course of our study, only four patients were withdrawn due to inadequate response. Thirty-six participants (85.37%) in the completer sample of our study achieved remission[163], which is higher than remission rates recorded elsewhere for FEP treated with long-acting injectable risperidone. In a open-label study of 50 FEP patients, newly diagnosed with schizophreniform disorder or schizophrenia, patients were treated with injectable, long-acting risperidone 25-50 mg every 2 weeks for two years[153]. Remission was achieved in 64% of the patients.

High relapse rates within the first few years of illness have been noted[164]. However, in our study, only one participant relapsed as a result of non-compliance. The first few years of illness has also been described as the "critical period"[165] in determining long-term outcome. It has been proposed that suboptimal outcomes with regard to response, remission and relapse rates may have as much to do with non-adherence[166-168] as with inadequate treatment. Since cognitive impairment, a core deficit in FEP, has been linked to poor treatment adherence[169-171], there are clearly arguments in favour of the use of long-acting injectable antipsychotics in the treatment of FEP[172,173].

Tolerability (refer pp 292-293)

In our study, side-effects, if present, where of mild intensity, with EPSE reported in 18.97% of the sample. However, these side-effects were temporary and occurred within the first three months after initiation of treatment, and responded well to symptomatic treatment or dose reductions. Only one patient had to be withdrawn due to the development of akathisia. None of the participants developed tardive dyskinesia.

Our experience with flupenthixol supports previous findings which suggest that flupenthixol is well tolerated, with a low incidence of mild adverse effects[174]. Contradictory reports with regard to EPSE rates exist, ranging from as low as 0.8% with 3mg/d or less[175] *per os*, to as high as 28% with doses of around 30mg 3 weekly[175] IMI. Post-marketing surveillance trials[131,132] have reported treatment related side-effects in 4.6% of 658 patients, 7.8% being FEP, after ten weeks of treatment with either FD (mean dose equivalent of 9.2 mg/d) or oral flupenthixol (mean daily dose 6.3 mg/d). Flupenthixol appears to compare very favorably to low dose haloperidol with regard to the incidence of EPSE[176]

COGNITION

Premorbid intelligence (refer pp 258-262, 300-301)

We used the WAIS-III[177] Vocabulary subscale as estimation of premorbid intelligence. This subscale has been proven to be relatively resistant to brain impairment, and therefore be an indication of crystallised intelligence[178], although some researchers have criticised this “hold” approach as being simplistic and inaccurate[179].

Although our study found a Z-score mean of -2.20 (± 0.91) at baseline, we cannot conclude that our sample performed worse than the general population as there are no data available for population norms in our catchment area, nor did we have a control group. However, it should be noted that the Z-scores of individual participants followed a normal distribution.

Although the WAIS-III was standardized for English-speaking South Africans[180-182], the norm group in which the scale was standardized does not reflect the ethnic distribution of our sample. The impact of language as a mediator of cognitive test performance, which can affect test scores significantly, should be borne in mind[183]. Test-takers whose first language is not English, may understand the wording and instructions of items, but the interpretation and meaning of words can vary significantly across cultures, as well as between first and second language speakers of English, which

could significantly affect test scores. Although we used the Afrikaans translation of this test in assessing the Afrikaans speaking participants, criticism has been raised as to the non-equivalence of the translation due to outdated words, difference in difficulty level, and different meanings of words included[184]. However, after careful consideration and consultation, this was still deemed the most appropriate measure of premorbid intelligence for use in our study. The deliberation on this matter raised the concern that it is crucial for local norms to be developed.

Lastly, it is also possible that our sample represents a subgroup of individuals with schizophrenia who indeed had a lower level of premorbid functioning, or had significant deterioration. It would be worthwhile in future studies for researchers to stratify the participants according to IQ performance [185], and to compare this with records of school performance.

This study found a significant inverse correlation between premorbid IQ estimation and the PANSS Cognitive factor at baseline, as well as a highly significant positive correlation between premorbid IQ estimation at baseline and overall cognition (MCCB Cognitive Composite Score) at both baseline and one year. This means that participants with a lower premorbid IQ at baseline, presented with more cognitive problems (a higher PANSS C and lower MCCB Cognitive Composite Score). It has been suggested that early in the course of schizophrenia, general cognitive ability (as measured by IQ) is a more sensitive and reliable predictor of functional outcome, up to ten years later, than measures of specific cognitive ability[186,187].

The inverse correlation between age and IQ estimation at baseline, are likely to reflect the educational level of participants, and not age *per se*[188]. Although we found a statistical significant improvement in IQ estimation from baseline to one year, this is more likely a reflection of symptomatic improvement, as well as practice effects[189,190].

Neurocognition (refer pp 303-311, 259-260)

In our study, all cognitive domains were significantly impaired at baseline with performance of the sample below the 5th percentile. This supports the notion of multiple cognitive domain impairments and therefore a generalized cognitive deficit being present in schizophrenia, and, specifically so, in FEP[191-198]. We are in agreement with Keefe's proposal to include cognitive impairment in the diagnostic criteria for schizophrenia.

Previous studies have reported more specific impairments in verbal learning and memory, speed of processing, and attention and vigilance to be present in FEP.

In our study, Speed of Processing was confirmed as the cognitive domain with the lowest mean T-score at baseline. Impairment in speed of processing has been regarded as a central cognitive deficit in schizophrenia[199] that influences performance in a number of different cognitive domains[200-202]. According to Townsend et al.[203], individuals with FEP generally performed in

the average range across the majority of tasks, with the exception of speeded processing tasks that appear to be more affected.

In our study, individual measures most impaired at baseline was BACS[204]: Symbol-Coding, these findings concur with previous reports of WAIS[177] Digit Symbol processing speed performance being significantly worse than performance in other domains[205]. The majority of improvement (>70%) in Speed of Processing occurred within the first three months of treatment. This improvement in Speed of Processing was larger than for any other cognitive domain. Since this domain has been reported to be more sensitive to side effects of medication[206], it appears that flupenthixol does not have a detrimental effect in the doses administered in this study.

Attention and Vigilance has a close association with Speed of Processing. In our study, improvement in Attention and Vigilance followed the same trend as improvement in Speed of Processing, with >50% of improvement within the first three months of treatment, and then leveling out after six months. Reviews have found impairment in this domain to be associated with social deficits, decreased community functioning and difficulties in skills acquisition[207,208]. Furthermore, poor performance in this domain has also been linked to poor treatment adherence[209], which increases the risk for relapse.

In our sample Working Memory was second to Speed of Processing as the domain most significantly affected, at both baseline and at one year,

remaining below the 5th percentile. Working memory, a core component of cognitive impairment in schizophrenia[210,211], has been shown to have strong correlations with other cognitive domains[211], such as attention, planning and memory[211], as well as with IQ[212]. Working memory performance has been linked to employment status[213] and job tenure[214]. It has been proposed that decreased encoding speed, rather than the ability to maintain information over time, underlies working memory dysfunction[202].

Improvement in these three domains (Speed of Processing, Attention and Vigilance, and Working Memory) was small. These three domains are inter-related, with significant overlap. Our findings support evidence for the impairment in central executive processes subserved by the dorsolateral PFC in schizophrenia[215].

More than half of the improvement in Reasoning and Problem Solving, important in the ability to adapt to rapidly changing environments, occurred during the first month of treatment.

In our study, Verbal Learning appeared to be the least affected and most stable neurocognitive domain. As we used alternate forms of the HVLT-R[216] it is unlikely that a ceiling effect can explain the limited improvement in verbal learning. Furthermore, it is also possible that the apparently limited cognitive improvement despite clinical improvement could be due to relative cognitive decline. Cognitive decline could also have been present prior to presentation and inclusion in our study[63,217,218].

The only neurocognitive domain in which we found evidence for continuous improvement over time was Visual Learning. In our study, contrary to previous reports, Visual Memory were more impaired than Verbal Memory at baseline[197].

Although changes in individual measures and domain scores were small, they were, for the most part, positive and significant. T-score means indicate that at baseline, participants performed 2 to 4 SDs below the mean, while at 12 months participants performed 1.5 to 3 SDs below the mean. Our results therefore concur with previous reports of relative cognitive stability, and an absence of cognitive decline, in the early years of illness[219-221].

It is notable that improvement in cognitive functioning occurred early. More than 50% of the improvement occurred within the first month of treatment, more than 80% of the improvement within the first three months of treatment, with no further significant improvement after six months. Although the possibility of practice-related improvement has been mentioned as an explanation for increased cognitive scores found during early phases of the illness[190,222], our use of alternate forms of instruments, wherever possible, in this study would have limited this effect.

In accordance with previous reports[220,223], we found no difference in cognitive performance between genders. Yet, this contradicts reports that have demonstrated differential degrees of impairment with male participants

performing worse than females across all neuropsychological functions, and significantly worse on test scores of attention, verbal memory and executive functioning[224]. Gruzelier et al.[225] and Lewine et al.[8] reported that although gender difference is preserved in schizophrenia, and is similar to that in the general population, these differences are often masked by clinical psychopathology and age effects.

Although we found no correlation between age and cognitive impairment at baseline, a positive correlation between age and cognition was evident at one year. This would be in keeping with previous findings[226] that patients affected at a younger age have a worse outcome, and more severe cognitive impairment. However, this finding, as well as the finding that participants assessed in Afrikaans demonstrated better cognitive performance at one year, may reflect the educational attainment of the participants in our sample.

The interplay between neurocognitive symptoms and psychopathology (refer pp 286-288, 309-312)

Symptom severity (PANSS[227] Total) explained 33.64% of the variance in cognitive symptoms (MCCB Cognitive Composite Score) at baseline and 28.09% at 12 months. Traditionally, cognitive symptoms were seen as a product of other symptoms clusters of schizophrenia. It is only more recently that cognition has become firmly established as an independent domain[228]. Latter day studies have acknowledged that considerable variability in the

severity and pattern of cognitive deficits can be present; these partially reflect the clinical heterogeneity of the disorder[195,196,220,229].

In keeping with studies elsewhere[196,230,231] we found no correlation between cognitive deficits at baseline and the presence of positive symptoms. At one year we found that the presence of positive symptoms had a highly significant inverse correlation with cognitive functioning, thus explaining one-third of the variance in cognitive impairment. This was specifically relevant with regard to working memory[232-234] and verbal learning[235], in support of previous studies.

Cross-sectional associations between cognitive impairment and the severity of negative symptoms have been documented in the literature[236-238]. In our study, negative symptoms explained 39.69% of cognitive deficits at baseline. Highly significant correlations were present between negative symptoms and each of the neurocognitive domains at baseline; however, from 6 months onwards only Working Memory and Visual Learning had significant correlations with the severity of negative symptoms. Although we found no correlation between the presence of depressive symptoms and cognitive performance at both baseline and at one year, we cannot exclude the influence of poor motivation, and the relationship thereof with negative symptoms[239,240], on cognitive functioning in our sample.

We found that general psychopathology correlated with a variety of cognitive domains at both baseline and at one year. The proportion of the variance in cognition explained by the severity of these symptoms is approximately 20%. In summary, we support the notion that cross-sectional correlations between neurocognitive impairment and psychopathological symptoms are undoubtedly weak, and concur with the proposal that cognition is a separable domain and not caused by psychosis.

In our study the PANSS Cognitive factor (PANSS C) was the strongest predictor of cognitive functioning at baseline, displaying highly significant inverse correlations with all cognitive domains. At one year the influence of the PANSS C was surpassed by those of positive symptoms, and PANSS C had significant inverse correlations with Speed of Processing, Working Memory and Visual Learning. Since both the PANSS C factors we used (Lancon et al.[241], and Good et al.[242]) include PANSS P items (P2 and P6 respectively), it could be argued that an improvement in cognitive functioning is due to a decrease in positive symptoms, thereby explaining the decline in strength of correlation of PANSS C with cognitive domains over time. However, PANSS C factors previously identified reflect characterisitics of participants included in the studies, and therefore may not be the ideal representation of our sample.

Depression and insight (refer pp288-291, 309-312, 317-321)

It was reported by Kay and Lindenmeyer[243] that the presence of depressive symptoms during the acute psychosis may be a good prognostic factor, whereas persistence of depressive features is considered the opposite[244].

In our study, the mean PANSS D[245] score at baseline was 9.17 (± 3.59) and declined significantly over the first three months to 5.66 (± 2.01). Although, as a group, the CDSS[246] scores remained low, 11/58 (18.97%) of the sample developed clinically significant symptoms which necessitated treatment with an antidepressant. Previous studies have reported symptoms of depression to be common in schizophrenia, with prevalence rates ranging from 7 to 70%[247], with a modal prevalence rate of 25%[248].

In our study, depressive symptoms had an inverse correlation with age, affecting younger participants more. The presence of depressive symptoms did not correlate with overall cognitive functioning. We also did not find any correlation between verbal memory performance and depression as reported in studies such as that of Brebion et al.[249].

The presence of depressive symptoms has the potential to instill a less realistic outlook in participants regarding their illness and treatment, thereby with the potential to contributing to non-compliance and relapse. On the other hand, poor insight can contribute to problems with therapeutic engagement and treatment adherence. Even so, only three of the

participants relapsed during our study: two due to ongoing substance-abuse, and one because of non-compliance.

Objective measure of insight indicated that the participants in our study had a moderate to severe impairment in insight, with only a vague or shallow recognition of their illness. Subjective reports of insight confirmed that 56% of our participants had poor insight; worse than previously reported[258].
In our study, the presence of depressive symptoms had a significant inverse correlation with objective measures of insight (PANSS G12). This is in agreement with studies reporting that increased awareness of illness contribute to depressive symptoms, low self-esteem, and poor quality of life [250-252] [253-256].

As in studies elsewhere[259] we found a highly significant inverse correlation between objective insight ratings and cognitive composite scores (MCCB Cognitive Composite Score) at all visits, with insight contributing to 23.04% of the variance in overall cognition at baseline, and 33.64% at 12 months. In a meta-analysis Mintz et al.[255], reported a correlation of 0.25 between positive symptoms and insight, and 0.23 between negative symptoms and insight. From this it can be argued that impaired insight is part of psychopathology and cognitive impairment in relatively equal measures. However, we found no correlation between subjective measurements of insight (Birchwood[260] scores) and cognitive functioning in our sample.

At baseline there were no significant differences in levels of insight between age groups, different levels of education, genders or language groups in our sample. However, females displayed better insight at one year than did their male counterparts. Concordant with results of a Dublin Study[261], participants in our sample with poor insight were more likely to require hospitalization.

The moderating effect of stigma has to be borne in mind, where the presence of stigma and negative societal views attached to schizophrenia can make the diagnosis more distressing and contribute to a worsened outcome[257,252]. An interesting future exercise would be to evaluate community perceptions in our catchment area, as well as the perceptions of individuals with schizophrenia, specific to stigma and mental health in order to correlate this information with measures of depression and insight.

Social cognition (refer pp 313-316)

Social cognition is the ability to perceive, process, and interpret social and emotional information in oneself and others, and have the ability to implement this in behaviour[262]. As such, social cognition has emerged as an important concept that contributes to functional recovery in schizophrenia[263-265].

In our study social cognition of participants was clearly impaired with a score 2 SDs below average of the norms. Although there was an improvement in social cognition from baseline to one year, this change was not significant.

We found no difference between genders and ethnic groups with regard to social cognition. However, participants assessed in Afrikaans performed better than participants assessed in English. The performance of the Xhosa-speaking participants who preferred to be assessed in English may have been adversely affected due to poor understanding of nuances and subtleties in the case vignettes in the MSCEIT™ [266], a test that was developed in the USA and possibly not culturally relevant for the use in all South African sub-populations.

Negative symptoms had a highly significant inverse correlation with social cognition, while the PANSS Cognitive factor did not correlate with social cognition. Furthermore, the presence of depressive symptoms in our sample also had an inverse correlation with social cognition. This could cause participants to be less realistic, and more pessimistic, about their illness, treatment, and social circumstances, thereby also explaining the inverse correlation with quality of life ratings. However, we could not determine a causal relationship between depression and social cognition.

Older participants were better at managing their emotions after one year. This may be a reflection of illness severity as there was a significant inverse correlation between symptoms severity and the ability to manage emotions at this time point – with a highly significant inverse correlation between positive symptoms and the ability to manage emotions.

At baseline, the ability of female participants to regulate the 'self' was significantly better than that of the male participants. However, this gender difference disappeared by one year and may be a reflection of the younger age of the male participants. Nevertheless, previous studies have found both affected and non-affected females to have an advantage over males with regard to processing emotional prosody and semantics [267]. These findings may contribute to females with schizophrenia being less compromised than males with regard to social functioning.

Although social cognition did not improve significantly over time, the opposite was true of our participants' ability to manage their emotions and social interactions. This may, in part, be explained by changes in psychopathology. At baseline, negative and general symptoms had a highly significant inverse correlation with social cognition, and specifically with managing emotions and social management tasks. At one year, positive symptoms had a highly significant inverse correlation with managing emotions and social management tasks. It appears that general symptoms contributed more to the variance in social cognition than negative and positive symptoms. At baseline 14.4% and 16% of the variance in social cognition was explained by negative and general symptoms respectively, whereas only general symptoms had a significant correlation at one year with social cognition accounting for 19.36% of this variance.

In a one year prospective study of 94 clinically stable outpatients with schizophrenia, Kee et al.[268] examined cross-sectional and longitudinal

relationships between perception of emotion and aspects of social relationships, work functioning and independent living. They found emotion processing to be a key determinant of work functioning for these individuals, independent of the presence of psychopathological symptoms. It has to be noted that only a single social cognitive measure was addressed in our study and it does not address the range of social cognitive deficits in schizophrenia. Furthermore, a performance-based assessment such as the MSCEIT™ assesses whether or not individuals are capable of performing certain behaviors in specific situations[269], and is not a reflection of broader-based domains of functional outcome such as vocational functioning[270-272].

The relationship between subjective and objective assessments of cognitive impairment (refer pp 322-331)

The first reference in the literature to individuals with schizophrenia's subjective experience of cognitive disturbances was a review of autobiographical accounts by Freedman in 1974[273]. He paved the way for what would become known as "basic symptoms"[274], so called for their representation of the basis of productive psychotic symptomatology. In other words, these are symptoms which individuals may report and are able to cope with, adapt to, and compensate for, prior to manifesting in objective noticeable symptoms and behavior.

The literature on self-reported cognitive deficits compared to objectively measured neurocognitive deficits in individuals with schizophrenia is

extremely limited. The SSTICS[275] was recently developed as a quantitative approach to measure the subjective experience of cognitive deficits in schizophrenia, and remains a work in progress. We translated and back-translated the instrument to Afrikaans, and believe this to be the first time such a quantitative approach has been used in any FEP sample, and also the first time that subjective complaints of cognitive difficulties have been compared to objective neurocognitive assessments in South Africa.

We found a 9.70% decrease in cognitive problems reported during the course of the study. Participants assessed in English reported more cognitive problems at baseline. This may either be a reflection of the amount of language dysfunction they experienced, or of their severity of illness compared to the participants assessed in Afrikaans. The domains in which the most impairment was reported were Sustained Executive Functioning and Consciousness of effort. Both these domains improved early, following the same course of improvement as psychopathology. Contrary to the baseline findings of previous reports[276], we found no correlation between subjective reports of cognitive impairment and symptom severity, the presence of positive symptoms, or the presence of negative symptoms.

We did find a highly significant, inverse correlation between Consciousness of effort and PANSS C ratings, as well as between Consciousness of effort and cognitive domains of Attention and Vigilance and Social Cognition. From this, we can deduce that the participants may have had more difficulty in paying attention to information, concentrating on it, and integrating and

applying this information as needed. These impairments would also adversely affect their focus in a social environment and the ability to make social judgments, therefore impeding their ability to accurately report on aspects of QOL. It appears that the presence of psychopathology, objective neurocognitive impairments, and social stressors, played a larger role in how the participants perceived their QOL, than did participants' subjective reports of cognitive impairments. This is evident from the fact that we did not find a significant correlation between subjective complaints of cognitive impairments and QOL. It also appeared that a more insidious, versus a more acute, onset of illness did not play a role in subjective awareness of cognitive deficits.

Although there were no significant differences between gender groups at baseline in cognitive deficits as reported by the participants, male participants presented with 15.33% more cognitive complaints at one year than females. There is no immediate explanation for this, as we would have expected females to be more aware of their deficits, based on reports in the literature, and our own findings of greater ability for emotional regulation in females.

Furthermore, participants did not report any improvement in their alertness and ability to function in daily life during the course of the study. It would therefore appear that participants in our sample did not experience cognitive problems as being of practical importance. This might be a reflection of social circumstances of, and the lack of formal cognitive demands on the

participants. However, participants who returned to attend their tertiary education, as well as the three participants who 'switched' languages, did indeed report an influence of cognitive deficits on their day-to-day life. Individual experience may therefore not be adequately reflected by the statistical findings.

Although many other significant correlations were present between domains of subjectively reported cognitive complaints and objectively assessed neurocognitive domains, our sample size was such that we decided on a conservative approach in interpretation thereof. Despite this, it should be noted that Speed of Processing and Sustained Executive Function and Alertness were the two domains that had a highly significant positive correlation up to 6 months with social cognition, while Distractibility had an inverse relation with social cognition at one year.

Research in prodromal patients has produced conflicting results, with some studies reporting subjective and objective cognitive deficits to be unrelated[277,278], while others[279,280] have found neuropsychological deficits, either self-perceived or objectively measured, to be able to contribute to prediction of transition to psychosis. In a longitudinal study of 96 individuals with DSM-III-R diagnoses of personality disorders, Klosterkotter et al. was able to correctly predict the development of schizophrenia in 77% of the participants who developed schizophrenia over an eight year period[281]. These predictions were based on an earlier presence or absence of self-

experienced disturbances of thought, speech, memory, perception and action.

We were only able to find two other studies that specifically compared subjective complaints with objective cognitive performance. In a study by Proteau et al., attentional problems were reported to be associated with poorer visual memory and planning performance as measured by the CANTAB[282], while more executive dysfunction was related to poorer visual memory scores[283]. In the study by Medalia and Lim[284], clinicians' and patients' ratings of attention, nonverbal memory and verbal memory were compared with objective neuropsychological assessment in 185 outpatients with schizophrenia. When corrected for chance findings, the agreement between classifications with regard to functioning in aspects of memory and attention, as assessed by clients, and as assessed by clinicians, vs. objective evaluations thereof, were poor. There was no significant correlation between clinicians' and patients' ratings on attention and memory, with agreement between clinicians and patients in only 57% of ratings of impaired attention and 55% of ratings of impaired memory. It is evident that the cognitive nature of these subjective complaints does not necessarily correspond with objective performances.

As insight is crucial to the awareness of cognitive deficits, it is important to recognize that what forms the basis of the SSTICS (i.e. awareness of cognitive limitations), may also be the biggest limitation of the instrument since, when an individual does not have insight, he/she will not report any

deficits. However, we found no correlation between the presence and severity of subjective cognitive complaints and insight. It is possible that insight may be modular, and therefore patients with poor insight into their symptoms may still have a degree of insight into their cognitive impairment[285].

We believe that further avenues requiring investigation are:

1) Reports of increased subjective cognitive complaints in the presence of EPSE that include akathisia, and parkinsonism[277,286,287,288];
2) Treatment of subjective cognitive complaints[289,290]; and
3) The relationship with functional outcome[291].

Functional outcome and quality of life (refer pp273-276, 294-297)

Reviews of the literature have indicated consistent and highly significant relationships between cognition and functional outcome in schizophrenia[208,292-294]. Cognitive impairment is associated with both poor premorbid, and current, social functioning, with neuropsychological deficits accounting for 5-25 % of the variance in social and vocational outcome after FEP[220,295].

The social and occupational functioning of our sample improved significantly from baseline to 6 months, after which improvement leveled out. Severity of illness demonstrated an inverse relationship with functioning for the duration of the study. More specifically, negative symptoms seemed to impact

considerably on the functioning of participants and support results of studies elsewhere[192,292].

Contrary to previous reports that documented evidence for processing speed[214,296,297], attention and vigilance[292,293], working memory[298], verbal memory[207,299, 292,300], and visual memory[202,293] to be predictors of functional outcome, we found no correlation between cognition, and social and occupational functioning. However, other studies also negated the relationship between cognition and functional outcome[53,301-303].

In our study, this lack of correlation between cognition, and social and occupational functioning may be a reflection of social circumstances. Many participants were receiving disability grants from the local government due to being diagnosed with a mental health disorder, and therefore lessened expectations by family members for the individual to find gainful employment. Furthermore, this may merely be a reflection of the high unemployment rate in the general population and not of the influence of cognition *per se*.

The SOFAS[304] is a clinician rated assessment used as an objective measure of social and occupational functioning. It is therefore largely free of individual confounding factors such as lack of insight[305,306], but may not take into account the many environmental factors, such as the presence of social support, and educational and vocational opportunities, that may facilitate or impede the patient's capacity[307] to perform a particular activity. Furthermore,

intervening factors, such as social cognition, may moderate neurocognition's impact on functional outcome[308,309]. Therefore, the best way to accurately assess functional outcome would be through direct observation in naturalistic settings. For research purposes, a combination of performance-based, proxy-measures, and objective ratings, would have to suffice[269].

In recent years, greater attention has been given to QOL in FEP, and studies have reported on the influence of various psychopathological domains, and cognitive dysfunction, on QOL[301,310].

Participants in our study expressed dissatisfaction with regard to their QOL, especially in areas of their social relationships, and their environment. We found significant positive correlations between premorbid functioning and the psychological health of participants, which may be indicative of their duration of illness. Social relationships of participants had significant positive correlation with age which may be a reflection of social cognitive skills and not necessarily the quality of relationships as a whole.

Although at baseline and at 6 months no gender differences were found with regard to QOL, females were less satisfied with their environment at one year than their male counterparts. This may reflect social factors in the community, such as limited opportunities, increased care-taking responsibilities for females (often in the absence of adequate support), and the psychological strain of being ill and dealing with stigma.

QOL with regard to Physical Health, Social Relationships, and Environment, did improve over time. A majority of these gains were evident within the first six months of this study. The severity of positive symptoms seemed to be the most important role player with regard to satisfaction in physical and psychological health at baseline, and at 6 months in social relationships. This may be a reflection of the impact of disruptive symptoms and psychosis *per se* (e.g. paranoid delusions) on relationships with others, as well as poor insight with regard to the illness as such. We noted no improvement over time with regard to participants' satisfaction with their psychological health. These findings should, however be interpreted with care, considering the impact of poor insight on the usefulness of self-report instruments[311] such as the WHOQOL-BREF[312].

We found a significant positive correlation between Reasoning and Problem solving and participants' perceptions of their physical health; and between Working Memory and their perceptions regarding their psychological health. However, literature has reported cognitive dysfunction to have a greater influence on objective QOL than subjective QOL[313], and it is therefore possible that we would have found more neurocognitive domains with significant correlations with QOL were we to use objective measures of QOL instead of subjective QOL reports.

Although social and occupational functioning had a significant positive correlation with QOL at 6 months, this did not hold true for overall cognitive functioning, or severity of illness. This may be an indication that the

presence of social stressors such as the ability/inability to function in the environment, be gainfully employed, or returning to studies, is more important than the presence of residual or mild psychotic symptoms, or objective measures of cognitive impairment.

STRENGTHS AND LIMITATIONS

This study is the first FEP study in South Africa, specifically investigating cognitive changes over time. Furthermore, it is, according to our knowledge, the first study investigating the effect of ultra low dose flupenthixol decanoate on treatment outcome, both clinical and cognitive, in FEP. We consider ensured drug delivery as one of the strengths of this study. We included participants with very limited prior antipsychotic exposure, making this a fairly homogenous cohort. The use of a ‘gold standard’ cognitive battery, the MCCB, enabled us to compare our results with those of studies conducted elsewhere in the world.

Although we took the best of care in planning, and executing this study, limitations are an inherent part of all research projects. This study is no exception. The following are the main shortcomings of this study:

1. Although our sample size is rather large, with a fairly low attrition rate, when compared to other FEP studies, the power of the study would have been enhanced, did we recruit larger numbers. This would have also enabled us to do more sub-analyses with regard to predictors of outcome.

2. This study was a single arm, open-label, unblinded study. The addition of a comparator group, receiving either placebo, or else an active comparator (preferably a SGA), would have strengthened our findings.

3. The duration of the study was sufficient for the evaluation of cognitive and clinical parameters with regard to treatment outcome. However, it is possible that subtle changes, which may influence outcome, will occur over extended periods of time, and that therefore, increasing the duration of the study would have produced additional findings of interest.

4. It is possible that the inclusion of participants with substance use/abuse in our sample may have influenced our results. However, substance abuse is highly prevalent in our population. As previously noted, patients with FEP have significantly higher rates of substance abuse than their non-psychotic peers, and excluding all patients with substance use or abuse would have biased our sample. However, we did take care not to include patients with substance induced psychoses, or substance dependence; and throughout the study we were diligent in obtaining as much accurate information as was possible regarding both past and current substance use/ abuse by participants. Evidence with regard to the effect of substances on cognitive performance is also contradictory. It is possible that substance abuse could contribute to cognitive deficits in an etiologically independent way.

5. We excluded participants with significant medical illness. However, we did not control for “subtle” problems such as disordered water homeostasis and nutritional deficiencies. The apparent association between disordered water homeostasis and cognitive impairment in schizophrenia[2], should be interpreted with caution. In their study, the authors compared 16

schizophrenic patients with severely deranged water homeostasis to 16 matched schizophrenic controls. Although patients with disordered water homeostasis obtained statistically significant poorer scores on the Wechsler Memory Scale Visual Reproduction and Trial Marking Test part A than the controls, the small sample size, the inclusion of patients ranging from 0 to 10 years of education, inclusion of patients ranging from 23 to 67 years, and the inclusion of patients ranging in duration of illness between 2 and 44 years, decreases the power of this study and could lead to a type II error.

Furthermore, in our study, after initial inclusion, two patients with underlying medical conditions were withdrawn: one with hypothyroidism and iron deficiency; the other because of the presence of akathisia, with a BMI of 14 – a condition often associated with nutritional deficiency, thus presenting the potential for increased sensitivity to the development of EPSE. These "subtle" medical problems could adversely affect cognitive performance.

6. The use of a self-report measure as a principal measure to assess quality of life, may not be a reflection of 'real-world' functioning.

7. A number of grey areas exist in the South African context that is inherently problematic to study assessments. These include cross-cultural influences and bias, and a general lack of well-standardized, culturally-relevant tests[314]. Therefore, the specific ethnic compilation of our sample may have yielded results which cannot be generalized to participants in other regions of the world. However, in a study by Harvey et al., to determine the viability of cross-national cognitive assessments in schizophrenia, a sample of 301 FEP patients was assessed in six different languages, across ten different countries. Results of this study demonstrated that differences between

countries were greater than differences between languages; that performance differences across English and other languages were only evident for tests of executive functions, vigilance, and psychomotor speed; that educational attainment had a significant influence on performance; and that executive functioning differences were non-significant. The authors concluded that the translation of tests of memory and verbal skills can lead to consistent results across translated versions of the tests, thereby supporting the validity of cross-national neuropsychological assessments[315]. Despite this, the need to develop appropriate South African translations and norms for many of the assessments should be addressed urgently. Furthermore, although the tests we used were translated and back-translated, some of the items were deemed not culturally sensitive. With this said, however, it can be argued that the use of any tests customized to suit South African norms would produce only 'localized' results that would be unable to stand up in the international arena.

Despite the limitations, we believe that this study makes a significant contribution to the literature on FEP, cognition, and treatment with assured delivery of a FGA.

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CHAPTER 14

CONCLUSION

"Madness is, contrary to the opinion of some unthinking persons, as manageable as many other distempers, which are equally dreadful and obstinate, and yet are not looked upon as incurable;….such unhappy objects ought by no means to be abandoned, much less shut up in loathsome prisons as criminals or nuisances to the society" (p93)[1].

A living proof of this 'old' statement would be John Forbes Nash Jr., the famous American mathematician and economist. Born 13 June 1928, Nash suffered his first psychotic breakdown at the age of 31. In spite of being diagnosed with paranoid schizophrenia, and repeated psychiatric hospitalizations between 1959 and 1970, Nash persevered with his studies, and emerged as a Nobel Laureate in 1994 for his early work on the game theory[2].

Recent decades have seen rapid development in technology that have helped shift the opinion of mental illnesses being 'all in the mind', to 'all in the brain'. Furthermore, contemporary treatments for serious mental illnesses are highly effective; with 70% to 90% of patients having a significant reduction in symptoms, providing the potential for improved long-term functional outcome.

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[2] Nasar S. A Beautiful Mind. London, UK: Faber and Faber; 2002

However, despite the recognition of cognitive symptoms as a core concept of schizophrenia, and the progress made in the field of neuroscience, neither the final word, nor even the “middle of the sentence”, has been spoken on the optimal management of these symptoms.

Impairment in cognitive functioning is not only an objective measurable entity, but also a distressing subjective experience, and it is clear that addressing cognition as part of the management of schizophrenia is important in terms of quality of life. Furthermore, since cognitive impairment has been proven to adversely affect compliance with treatment, thus increasing the risk for non-adherence and resultant relapses, it is of the utmost importance to develop and use strategies to counter these problems.

More than 20 years of research has established the need for psychopharmacological and psychotherapeutic interventions in addressing cognitive deficits in schizophrenia. Presently, antipsychotics remain the cornerstone in treatment of this disorder.

In this longitudinal study of FEP in South Africa, we documented the specific cognitive deficits experienced by the participants, and described the changes in response to treatment over a 12 month period. We have demonstrated that cognitive deficits are an independent domain, despite their close link to negative symptoms, as well as the impact of positive symptoms on cognition after the acute illness phase. Whereas mood symptoms were observed to affect insight, our sample did not demonstrate any direct relationship

between the presence of depressive symptoms and cognitive dysfunction. These findings re-confirm the existence of cognition as an independent domain, and focus of treatment, in schizophrenia. We have also addressed subjective versus objective experiences of cognitive impairment, as well as social cognition, functional outcome, and quality of life. We have established premorbid intelligence, or, more accurately, baseline intelligence, as one of the stronger predictors of 12 month outcome. We believe that our study has contributed to research into FEP, and advanced the development of culturally sensitive instruments of assessments and norms for evaluation of cognitive functioning in FEP.

As research and development of novel drugs is a slow and expensive process researchers and clinicians would be well-advised to consider and reconsider ‘on-the-shelf’ antipsychotic agents that have not been adequately researched. In this study, we ‘dusted off’ an ‘old’, FGA, flupenthixol decanoate, and used it in a novel application: at a very low dose, in a FEP sample. We found indications (albeit qualified) that the clinical and cognitive response to treatment was comparable to studies of SGAs, and that treatment was well tolerated – perhaps better so than has been documented in studies of haloperidol. Furthermore, the retention rate in our study, compared to FEP studies with oral preparations, confirmed the advantage in assured drug delivery in the management of FEP.

We trust that this study has contributed towards a more positive outlook on the long-term outcome of FEP. We have demonstrated that it is within our

grasp to provide effective, tolerable treatment to individuals suffering from the disease; not only in terms of suppression of positive symptoms, but also in the rehabilitation of cognitive abilities, so that individuals with schizophrenia may realize their full potential, and become Laureates in their own lives.

INDEX OF ACRONYMS AND ABBREVIATIONS

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