The clinical course and outcomes of first episode psychosis: A study of the acute, medium and long-term outcomes in a cohort rigorously treated in the early phase of illness.

Dissertation presented by

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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained herein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that production and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification. This dissertation includes four original papers published in peer reviewed journals. The development and writing of the papers were the principal responsibility of myself and for each of the cases where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contributions of the co-authors.

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SUMMARY

The period surrounding the first episode of psychosis represents a critical period in the natural course of the illness. There are several studies on the nature of the clinical presentation, the effects of treatment, course, and the outcome of the illness. However, there remain several knowledge gaps. This PhD sought to address some of those gaps. The overall aim was to assess the acute, medium- and long-term clinical and functional outcomes of participants with first-episode schizophrenia spectrum disorders who received intensive treatment with a long-acting injectable antipsychotic over a period of 24 months.

We reported a well-established finding that psychotic symptoms in patients with first-episode schizophrenia spectrum disorders respond well to antipsychotic treatment. Overall, outcomes were favourable, with 70% achieving symptom remission, 56% functional remission and 61% rating their quality of life as good or excellent (although only 29% met all three of our criteria for recovery simultaneously). Symptom remission may be an important stepping stone to recovery, insofar as very few patients (9%) who did not achieve symptom remission were able to achieve functional remission and a good subjective quality. Our finding on longitudinal assessment of changes in insight was that in contrast to clinician-rated insight, significant impairments in patient-rated insight persisted despite assured treatment. This suggests that insight impairment is more trait- than state-related. We found that depressive symptoms during the early phase of illness are intrinsic to psychosis and responded well to antipsychotic treatment. Regarding negative symptoms, we replicated the two-factor structure, namely an experiential and an expressive domain, although the two subdomains appear closely related rather than being independent entities. Premorbid correlates and treatment response trajectories were similar for the two subdomains. We found that secondary negative symptoms affect the subdomains differentially. Depression affects the experiential subdomain, whereas extrapyramidal symptoms affect the expressive subdomain. A link between lipid metabolism and negative symptoms is suggested in that

post-hoc testing indicated that reductions in HDL-cholesterol levels were associated with less improvement in both expressive and experiential subdomain scores. Taken together, our findings support the use of long-acting injectable antipsychotics as a first line treatment in schizophrenia spectrum disorders, perhaps particularly in resource constrained settings such as our own.

OPSOMMING

Die tydperk rondom die eerste episode van psigose verteenwoordig 'n kritieke tydperk in die natuurlike verloop van die siekte. Daar is verskeie studies oor die aard van die kliniese beeld, die gevolge van behandeling, verloop en uitkoms van die siekte. Daar heers egter nog steeds verskeie kennis-gapings. Hierdie PhD het gepoog om van die leemtes aan te spreek. Die oorkoepelende doel was om die akute, medium- en langtermyn kliniese en funksionele uitkomste van deelnemers met skisofrenie spektrum steurnisse in die eerste episode te evalueer, wat oor 'n tydperk van 24 maande intensiewe behandeling ontvang het met 'n langwerkende inspuitbare antipsigotiese middel.

Ons rapporteer ŉ goed bevestigde bevinding, dat pasiënte met skisofrenie spektrum steurnisse, se psigotiese simptome tydens die eerste episode goed reageer op antipsigotiese behandeling. Oor die algemeen was die uitkomste gunstig, met 70% wat simptomatiese remissie behaal het, 56% funksionele remissie, terwyl 61% hul lewensgehalte as goed of uitstekend beskou het (alhoewel slegs 29% gelyktydig aan al drie ons kriteria vir herstel voldoen het). Remissie van simptome kan 'n belangrike stap tot herstel wees, in soverre baie min pasiënte (9%) wat nie simptoom-remissie behaal het nie, was in staat om funksionele remissie en 'n goeie subjektiewe kwaliteit te behaal. Ons bevinding oor die longitudinale koers van veranderinge met betrekking tot pasiënt insig, was in teenstelling met die insig soos deur 'n dokter gegradeer was, daar het deurgaans ŉ beduidende gestremdheid rakende pasiënt gegradeerde insig geheers, ondanks versekerde behandeling. Dit dui daarop dat insig gestemdheid meer persoonlikheidseienskap as siektetoestandeienskap verwant is. Ons het gevind dat depressiewe simptome tydens die vroeë fase van die siekte inherent gekoppel is aan psigose en goed gereageer het op antipsigotiese behandeling.

Wat die negatiewe simptome aanbetref, het ons die twee-faktor struktuur gereproduseer, naamlik 'n ervarings- en ekspressiewe domein, alhoewel hierdie twee sub-domeine nou verwant voorgekom het, dit eerder as twee onafhanklike entiteite gesien kan word.

Premorbiede korrelate en behandelings-verwante trajekte was soortgelyk vir die twee sub-domeine. Ons het gevind dat sekondêre negatiewe simptome die sub-domeine differensieël beïnvloed. Depressie het die ervarings sub-domein beïnvloed, terwyl ekstrapiramidale simptome die ekspressiewe sub-domein beïnvloed het. Assosiasies tussen lipied metabolisme en negatiewe simptome was aangedui, aangesien post-hok-toetse ‘n verhouding tussen verlagings in HDL-cholesterol vlakke en minder verbetering in beide ekspressiewe- en ervarings domein tellings getoon het. Ter opsomming, ons bevindinge het die gebruik van langwerkende inspuitbare antipsigotiese middels, as ’n eerste linie van behandeling vir skisofrenie spektrum steurnisse ondersteun, miskien veral in hulpbron beperkte instellings, soos ons eie.

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This dissertation is dedicated to the memory my late grandfather, Reverend Kotedi Makakaba, who would have been proud to see its completion.

TABLE OF CONTENTS

Declaration i

Summary ii

Opsomming iii

Acknowledgements iv

Chapter 1 1

Chapter 2 19

Chapter 3 27

Chapter 4 36

Chapter 5 45

Chapter 6 53

CHAPTER 1

INTRODUCTION

This chapter provides an overview of the literature of select topics relevant to this thesis. Further, it describes the aims and objectives of the thesis and gives details of methodology of the parent study. In conclusion, it provides a brief description of the subsequent chapters.

THE BURDEN OF SCHIZOPHRENIA

The global burden of disease has seen a shift from communicable to non-communicable diseases including mental disorders, giving rise to new challenges on health systems (Murray et al., 2012). The burden of mental health disorders is related to disability rather than mortality (Whiteford et al., 2015). Schizophrenia is a heterogenous mental disorder with the long-term course and outcome varying from patient to patient. The course of illness is typically characterized by multiple relapses and enduring social and occupational impairments, and may require life-long treatment (Andreasen et al., 2005). Individuals living with schizophrenia have a shorter life expectancy than the general population and are at an increased risk of cardiovascular diseases and suicide (Saha et al., 2007).

EARLY INTERVENTION AND RATIONALE FOR LONG-ACTING ANTIPSYCHOTIC MEDICATION

Early intervention in schizophrenia refers to strategies aimed at reducing morbidity by identifying the illness as early as possible and providing intensive treatment in the early, critical stage of illness (Wyatt and Henter, 2001). The early phase of illness is a “critical period” to influence the long-term trajectory of the individual and has implications for prevention of illness-associated impairments and determining the long-term prognosis (Birchwood et al., 1998, Wyatt and Henter, 2001). This “critical period” is where the illness is at its most aggressive, and where relapse and illness progression is most likely to occur (Birchwood et al, 1998). There is consensus that effective treatment of first episode psychosis with antipsychotic medication is essential to limit the negative consequences of persistent psychosis, however, non-adherence to oral antipsychotic medication is common

during the early stages of the disease (Novak-Grubic and Tavcar, 2002) and is very likely to lead to symptom recurrence (Zipursky et al., 2014). Symptomatic relapses are associated with poorer long-term outcomes, disease progression, and treatment refractoriness (Emsley et al., 2013a, Emsley et al., 2013b, Wiersma et al., 1998). Long-acting antipsychotic medications were developed specifically to address the problem of non-adherence in schizophrenia and they are effective in reducing the risk of relapse (Correll et al., 2016). They are also associated with added advantages, including lower steady state blood levels required and reduced fluctuation of serum levels (Ereshefsky and Mascarenas, 2003), reduced patient and carer burden of adherence and promotion of regular interaction between patients and clinicians (Kane and Garcia-Ribera, 2009).

PROBLEM STATEMENT

Longitudinal studies of first-episode cohorts of schizophrenia spectrum disorder patients present an opportunity to examine factors influencing the outcome the illness by assessing patients at the same phase of illness without confounding effects of previous treatment and illness chronicity. Results of previous studies are diverse and only a few studies have conducted longitudinal assessments beyond 24 months (Henry et al., 2007). Interpretation of the literature is limited by differences in diagnostic criteria and assessment instruments, varying pre-study treatment exposure, non-standardised treatment and infrequent follow-up assessments. Further, many studies did not account for an important confounding variable such as treatment adherence. The cohort of patients with first-episode schizophrenia spectrum disorders that was collected in the Stikland hospital catchment area, and from which the present studies are drawn, provided an opportunity to address several of the factors potentially confounding much of the literature to date. Participants were either antipsychotic naïve or had received only minimal antipsychotic exposure; they were comprehensively evaluated with validated instruments; investigators were trained to use the main instruments at the study initiation and throughout its duration; inter-rater reliability testing was conducted, and assessments were repeated at regular timepoints over the first

two years of treatment; treatment was standardised and the use of a long-acting formulation provided assured adherence and allowed us to calculate total antipsychotic exposure with precision.

ASPECTS OF THE ILLNESS THAT WERE SELECTED AS THE FOCUS OF THIS PhD THESIS

This PhD study was nested within the longitudinal study described above. The symptom expression of schizophrenia is diverse and complex. In addition to the well-recognised core positive, negative and disorganised domains of psychopathology, cognitive and insight impairments are prominent, and functionality is compromised (American Psychiatric Association, 2013). Rather than attempting to assess all these components in relation to treatment outcome, we focussed on specific aspects. Selection of the specific aspects was based on gaps that we identified in the literature and those that our cohort might best interrogate. The topics were chosen by the PhD candidate and supervisor, in consultation with the other members of our schizophrenia research team. The present dissertation provides further clarification on aspects of the treatment outcome in first-episode schizophrenia spectrum disorders by focusing on longitudinal examination of insight, depression, and negative symptoms. It also contributes on the potential measures of recovery from schizophrenia.

Insight

Insight impairment is observed among 50-75% of individuals with schizophrenia spectrum disorders (Amador et al., 1994) and is associated with negative outcomes such as poor treatment adherence (Velligan et al., 2017), severity of symptoms, and other markers of poor clinical outcomes (Lysaker et al., 2018). Many patients display unawareness of their illness (i.e. anosognosia), and this impairment is considered a symptom of the illness rather than a psychological coping strategy (American Psychiatric Association, 2013). Given the need for long-term treatment and the potentially grave consequences of treatment discontinuation, a

detailed understanding of the nature of insight impairment and its changes over time is necessary for promoting optimal outcomes. Therefore, insight is important in the evaluation of the long-term trajectory of first episode psychosis and is an important determinant of treatment outcome. The concept of insight is considered a multidimensional construct consisting of three domains, illness awareness, symptoms attribution to the illness, and recognition of the need for treatment (Wiffen et al., 2010). Whilst these three subdomains are interrelated, they relate to other outcome measures such as quality of life, depression, psychotic and negative symptoms, and overall functioning in different ways (Cuesta et al., 2011, Misdrahi et al., 2014, Palmer et al., 2015, Rocca et al., 2010, Saeedi et al., 2007). Several studies have reported varied treatment related improvements in insight (Cuesta et al., 2000, Crumlish et al., 2005, Mintz et al., 2004, Wiffen et al., 2010). However, the degree to which the different components of insight are amenable to treatment is unknown.

Recovery

To date, there is no widely accepted or validated definition for recovery. The primary goal for the treatment of schizophrenia has for many years been the reduction of clinical symptoms, behavioural control and relapse prevention. More recently, advances in pharmacological and psychosocial interventions led to heightened outcome expectations and attempts to “raise the bar”. Operationally defined criteria for remission were introduced, with a severity threshold of mild levels at most for the core positive, negative and disorganised symptoms, and without significantly influencing behaviour (Andreasen et al., 2005). While these criteria were widely implemented in clinical and research settings, it was recognised that outcome goals should not just focus on psychopathology. Measuring outcome by symptom remission only does not fully describe problems and deficits experienced by people living with schizophrenia such as overall daily functioning and quality of life. Accordingly, there is now consensus that symptom remission is only one of several meaningful treatment goals (Carpenter and Koenig, 2008). It has been suggested that outcome measures should be multidimensional, culturally relevant, and consist of more than one parameter (Shrivastava

et al., 2010). Assessing the rates, correlations, and predictors of recovery across psychopathology, clinician-rated social and occupational functioning, and patient-rated quality of life may better describe recovery in patients with schizophrenia spectrum disorders. Our cohort allowed us to investigate the temporal relationships between changes in psychopathology, social and occupational functioning and self-rated quality of life.

Depressive symptoms

Depressive symptoms are a discrete symptom domain in schizophrenia (Chiappelli et al., 2014) and have been associated with both favourable and poorer outcomes. Previous longitudinal studies of depressive symptoms during the first episode of psychosis (Cotton et al., 2012, Koreen et al., 1993, Sands and Harrow, 1999, Sonmez et al., 2013, Sonmez et al., 2016, Upthegrove et al., 2010) are complicated by significant methodological limitations such as prior exposure to antipsychotic medication, reliance on retrospective information, non-standardized treatments, lack of appropriate instruments to assess depression, variable follow-up intervals, substance abuse, and inclusion of patients with chronic illness. Depressive symptoms may remit on antipsychotic medication; however, additional antidepressant medication may be required in some patients where symptoms persist or emerge in the post-acute phase (Hafner et al., 2005, Oosthuizen et al., 2006). This suggests that depressive symptoms in schizophrenia may have both state and trait related features (Chiappelli et al., 2014). Examination of the trajectories and predictors of depressive symptoms during acute and stable phases of the illness may help distinguish between depressive symptoms that are intrinsic to psychosis from those that occur independently.

Negative symptoms

Negative symptoms of schizophrenia are associated with markers of poor outcome (Albert et al., 2011, Katschnig, 2000) and represent an unmet therapeutic need (Fusar-Poli et al., 2015). Several studies have confirmed that they are distinct from positive and disorganized symptoms (Arndt et al., 1991, Emsley et al., 2003, Grube et al., 1998). In the first episode of

illness, 50-90% of patients with schizophrenia spectrum disorders show negative symptoms (Lyne et al., 2015, Lyne et al., 2012). According to the National Institute of Mental Illness initiative on Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH MATRICS) consensus statement, the negative symptom domain includes alogia, asociality, avolition, blunted affect, and anhedonia (Kirkpatrick et al., 2006). The classification of negative symptoms has evolved from a unitary to a two-factor structure comprising two semi-independent factors, namely: experiential deficits consisting of avolition, asociality and anhedonia; and the expressive deficits consisting of blunted affect and alogia (Liemburg et al., 2013, Messinger et al., 2011). Longitudinal examination of the trajectories and correlates of these subdomains can contribute to better understanding of the course of illness and optimize treatment outcomes. Furthermore, it may be that these subdomains represent distinct therapeutic targets.

AIM AND OBJECTIVES

The overall aim was to assess the acute, medium- and long-term clinical and functional outcomes of participants with first-episode schizophrenia spectrum disorders who received intensive treatment with a long-acting injectable antipsychotic over 24 months.

OBJECTIVES

The objectives of the study address the overall aim by:

1. Examining changes in insight over 24 months using both patient- and clinician-rated assessment instruments.
2. Assessing the rates, trajectories, correlations, and predictors of recovery across three domains, i.e., core psychopathology, clinician-rated social and occupational functioning, and patient-rated quality of life.
3. Assessing the prevalence, trajectory, clinical concomitants, and predictors of depressive symptoms.

4. Replicating the two-factor model for negative symptoms in schizophrenia and exploring the associations of the two subdomains with demographic, premorbid, and treatment related variables.

DESCRIPTION OF THE PARENT STUDY

The doctoral research described here was conducted as part of a longitudinal single-site cohort study which included first episode schizophrenia spectrum disorder patients treated according to a standardized protocol over 24 months.

Participants

Participants were recruited during their first admission to hospitals and community clinics situated in a well demarcated catchment area of the Eastern and Northern districts of the Greater Cape Town municipality, the Winelands, and Cape West Coast. Inclusion criteria were men and women, inpatients and outpatients, aged 18 to 45 years, with a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria were lifetime exposure to more than four weeks of antipsychotic medication, serious or unstable medical condition, and psychosis arising from acute substance intoxication and intellectual disability.

Treatment

Patients were treated according to a fixed protocol with flupenthixol decanoate, a depot antipsychotic. There was a 7-day lead-in with oral flupenthixol (1-3 mg per day) followed by flexible doses of flupenthixol decanoate intramuscular injections (two-weekly). The starting dose of flupenthixol decanoate was 10 mg two-weekly intramuscular injection (IMI), with six weekly increments of 10 mg two-weekly IMI permitted, to a maximum of 30 mg two-weekly IMI. Permitted concomitant medications include lorazepam, anticholinergics, propranolol, antidepressants, and medications for medical conditions. Additional oral flupenthixol tablets

were prescribed at the discretion of the investigator for acute exacerbation of psychotic symptoms between visits. Prohibited medications included other antipsychotics, mood stabilizers, and psychostimulants. The study was registered on the South African National Clinical Trials Register, trial number DOH-27-0710-1957 and was approved by the Stellenbosch University Human Research Ethics Committee. Findings on treatment rates and response patterns and tolerability have been published (Chiliza et al., 2015, Chiliza et al., 2016).

Physical examination

Full medical history was taken, and all patients underwent full physical examination, and the following measures were recorded: height, weight, blood pressure, fasting blood glucose and lipogram, and urine drug screen.

OUTLINE OF THE THESIS

This thesis consists of four manuscripts with the PhD candidate as first author, three of which have been published and one that is under review at an international peer reviewed journal. These articles are presented as chapters corresponding to each objective of interest.

Chapter 2 describes changes in insight over the first 24 months of treatment in schizophrenia spectrum disorders (sub-study I). *This first-author manuscript was published in Schizophrenia Research.*

Chapter 3 describes the early recovery in the first 24 months of treatment in first-episode schizophrenia-spectrum disorders (sub-study II). *This first-author manuscript was published in NPJ Schizophrenia.*

Chapter 4 describes the longitudinal course and concomitants of depressive symptoms in schizophrenia spectrum disorders (sub-study III). *This first-author manuscript was published in Psychiatry Research.*

Chapter 5 describes the trajectories and correlates of the two negative symptoms subdomains in schizophrenia spectrum disorders (sub-study IV). *This first-author manuscript was published in Schizophrenia Research*.

Chapter 6 synthesizes the four studies, discusses the implications of the findings, and provides conclusions drawn from these findings.

CONTRIBUTIONS OF THE CANDIDATE

The candidate has been a core member of the schizophrenia research team that conducted the ongoing study, since the year 2013. During that time, he was involved in:

- Drafting of the study protocol under the guidance of my supervisor.
- Formulating research questions across all the studies.
- Conducting clinical assessments and managing the patients.
- Participating in the weekly schizophrenia research team meetings to assess the study progress.
- Participating in weekly academic meetings of the schizophrenia research team.
- Conceptualising and planning each manuscript.
- Participating in the planning of the statistical analysis.
- Interpreting the results of the studies.
- Drafted manuscripts for submission, managed co-author inputs, submitted manuscripts for review, and addressed reviewers' comments.

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CHAPTER 2

Changes in insight over the first 24 months of treatment in schizophrenia spectrum disorders. *This first-author manuscript was published in Schizophrenia Research.*

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Changes in insight over the first 24 months of treatment in schizophrenia spectrum disorders

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ABSTRACT

Background: While insight in schizophrenia improves with treatment, significant impairments often persist. The degree of persistence is not well characterised.
Aims: We assessed patient and clinician-rated changes in insight in acutely ill, minimally treated first-episode schizophrenia spectrum disorder patients over 24 months of standardised treatment with a depot antipsychotic.
Method: This single arm open label longitudinal cohort study included 105 participants with first-episode schizophrenia, schizophreniform or schizoaffective disorder. Insight was assessed at months 0, 6, 12 and 24 using the patient-rated Birchwood Insight Scale (BIS) and clinician-rated global insight item of the Positive and Negative Syndrome Scale (PANSS). Changes in insight over time were assessed using linear mixed-effect models for continuous repeated measures. Relationships between insight and psychopathology, functionality, cognition and quality of life were assessed with regression models.
Results: There was significant improvement over time for the PANSS insight item ($p < 0.0001$). However, the only significant improvement for the BIS was with the Need for Treatment subscale ($p = 0.01$). There were no significant improvements noted for the Symptom Attribution ($p = 0.7$) and Illness Awareness ($p = 0.2$) subscales, as well as the BIS Total score ($p = 0.6$). Apart from depressive symptoms at baseline, there were no significant predictors of patient-rated insight.
Conclusions: Clinicians should note that, even when treatment is assured and response is favourable, fundamental impairments in patient-rated insight persist.

1. Introduction

Impaired insight is a common and prominent feature of schizophrenia, with 50–80% of patients believing that they are not ill (Amador et al., 1994; Dam, 2006). The concept of insight has evolved over decades, with contemporary research recognising its multidimensional nature, including recognition of having a mental disorder, symptom attribution and awareness of need for treatment (Wiffen et al., 2010a, 2010b). The clinical importance of insight impairment lies in its association with poor treatment adherence (Velligan et al., 2017), heightened symptom severity and worse clinical outcomes (Lysaker et al., 2018). Although studies exploring insight have largely been cross-sectional, several longitudinal studies have been conducted. Prospective evidence suggests that insight is not a static phenomenon, and that there is improvement with treatment (Wiffen et al., 2010a, 2010b; Segarra et al., 2012; David et al., 1995; Cuesta et al., 2000; Mintz et al., 2004; Crumlish et al., 2005; Parellada et al., 2011; Pijnenborg et al., 2015; Gharabawi et al., 2006; Mohamed et al., 2009). This improvement is reportedly modest (Wiffen et al., 2010a, 2010b) and mostly occurs during in the early phase of treatment (Segarra et al., 2012; Mintz et al., 2004; Parellada et al., 2011). Impairments may persist in the stable phase of illness (Wiffen et al., 2010a, 2010b; Cuesta et al., 2000; Parellada et al., 2009). Consequently, insight is regarded as having both state and trait-like properties (Wiffen et al., 2010a, 2010b; Parellada et al., 2011). However, the degree to which insight impairment improves with treatment, and whether different components of insight are more amenable to treatment remains unclear.

The aim of the study was to assess changes in insight in acutely ill, minimally treated patients with a first-episode of schizophrenia spectrum disorder, over the first 24 months of flupenthixol decanoate depot treatment. Insight was assessed according to both patient and clinician-rated assessment instruments. We also investigated baseline and endpoint insight and its relationships to psychopathology,

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functionality, quality of life, neurological signs and cognitive status. We hypothesised that: 1) all measures of insight would improve with treatment; 2) substantial insight impairments would persist, and that 3) endpoint insight domains would have specific relationships with clinical, cognitive and neurological features of the illness. Previous studies did not necessarily take into account factors such as illness chronicity, prior medication exposure, level of psychotic symptoms and treatment adherence. Also, instruments to assess insight were not always optimal. In the present study we were able to address several of these potential confounds. By selecting a first-episode, minimally treated cohort we were able to assess the illness in its most symptomatic state and without effects of previous treatment and illness chronicity; the standardised treatment approach avoided possible differential effects of individual antipsychotics; and using depot antipsychotic removed the possible confound of covert non-adherence – of importance given that poor insight leads to a greater likelihood of patients rejecting medication (Lysaker et al., 2018).

2. Methodology

2.1. Study design

This was a single arm open label longitudinal study of a cohort of first episode psychosis patients investigating treatment outcome, its predictors and concomitants. Ethics approval was obtained from the Human Research Ethics Committee (HREC) of Stellenbosch University (SU) Faculty of Medicine and Health Sciences. The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice (GCP) (International Conference on Harmonization, 1996) and, although not a clinical trial assessing safety and tolerability of treatment, was registered at the South African National Clinical Trials Register (DOH-27-0710-1957; http://www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx).

2.2. Selection of study participants

In total, 105 patients were recruited between April 2007 and March 2011 from first hospital admissions and community clinics in the Greater Cape Town area. Written, informed consent was obtained from the patients. Where they were hospitalized involuntarily, or considered too ill to provide informed consent, assent was obtained together with consent from their legal guardian. Participant consent was then obtained once their condition had improved. Inclusion criteria were: men and women, inpatients or outpatients, aged 16–45 years, experiencing a first psychotic episode, and meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (American Psychiatric Association, 1994) diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria included: lifetime exposure to a period > 4 weeks of antipsychotic medication, previous treatment with a long-acting depot antipsychotic, serious or unstable general medical condition, intellectual disability and overt substance abuse.

2.3. Treatment

We chose flupenthixol decanoate as the best tolerated depot that is freely available in the public health sector in South Africa. There was a one-week lead-in period of oral flupenthixol 1 to 3 mg/day followed by long acting flupenthixol decanoate injections every two weeks for the duration of the study. The initiation dose was 10 mg 2-weekly. Additional oral flupenthixol was prescribed at the discretion of the investigator. Permitted concomitant treatment included medication for general medical conditions, lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms and propranolol for akathisia. No benzodiazepines, propranolol or anticholinergics were permitted in the 12 h prior to assessments. Medications not permitted included other antipsychotics, mood stabilizers and psychostimulants.

2.4. Clinical assessments

Diagnostic assessment was performed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Diagnoses were reviewed and revised by the investigators throughout the study. Insight was measured at baseline and after 6, 12 and 24 months using the Birchwood Insight Scale (BIS) (Birchwood et al., 1994). The BIS is a self-reported measure assessing clinical insight and comprises eight questions, each scored on a 4-point scale, with higher scores indicating better insight. The scale assesses three dimensions of insight: symptom attribution, illness awareness, and need for treatment, in addition to providing an overall total score. The G12 Insight item on the Positive and Negative Syndrome Scale (PANSS) was extracted. This item represents a clinician-rated assessment of global impairment of judgement and insight on a scale of 1 (no impairment) to 7 (extreme impairment). Psychopathology was assessed using the PANSS total score (Kay et al., 1987) and additional assessments included the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994), the Calgary Depression Scale for Schizophrenia (CDSS) total score (Addington and Addington, 1993), the World Health Organization Quality of Life Questionnaire-Brief Version (WHOQOL-BREF) domains for physical health, psychological, social relationships and environment (WHOQOL Group, 1998), the Neurological Evaluation Scale (NES) total score (Buchanan and Heinrichs, 1989), the Extrapyramidal Symptom Rating Scale (ESRS) total score (Chouinard and Margolese, 2005) and the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery (MCCB) composite score (Nuechterlein and Green, 2006).

2.5. Statistical analyses

Analyses were conducted using Statistica 13 software (Dell). We assessed the distribution of the data by inspecting histograms and normal probability plots. Linear mixed-effect models for continuous repeated measures (MMRM) were constructed to assess the changes in BIS total and subscale scores and PANSS insight item over time, with age, gender and highest level of education as covariates. All of the variables were entered as fixed effects, except participant number which was entered as a random effect. Within analyses Fisher's Least Significant Difference (LSD) tests were used for multiple comparisons of post-hoc tests. Endpoint scores were calculated as last observation carried forward on all patients with at least one post-baseline BIS assessment ($n = 81$). All patients included in the endpoint analyses had therefore received at least 6 months of antipsychotic treatment during the study. Pearson correlation coefficients were used to assess relationships between insight and other symptoms at baseline and end-point. Correlations at the $p = 0.1$ level were used to select predictor variables for best subsets general regression models with BIS subscale and total scores and PANSS insight item as predictor variables and age, gender and level of education as covariates. Dependent variables were PANSS total score, CDSS total score, SOFAS, WHOQOL-BREF domains, NES Total score and MCCB Composite score. All tests were 2-tailed.

3. Results

The sample of 105 comprised 78 (74%) men and 27 (26%) women with a mean (s.d.) age of 24.5 (6.7) years. Eighty-one (77%) were of mixed ethnicity, 15 (14%) black and 9 (9%) white. DSM-IV diagnosis was schizophrenia ($n = 73$ [70%]), schizophreniform ($n = 31$ [29%]) and schizoaffective disorder ($n = 1$ [1%]). Mean duration of untreated psychosis was 37 (45) weeks. Thirty-three (31%) were hospitalized at the start of the study. Sixty-one (58%) patients were antipsychotic naïve and the other 44 (42%) had received antipsychotics for a mean

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of 6 (7) days. Eighty-one (77%) participants completed at least 6 months of treatment, and 64 (61%) completed 24 months of treatment. Of the 24 patients excluded from the endpoint analyses, reasons for discontinuation were, respectively, poor efficacy 4 (4%), poor tolerability 7 (7%), consent withdrawal 2 (2%), relocation 2 (2%), lost to follow-up 7 (7%) and other 4 (4%). The excluded participants did not differ from the rest of the sample in terms of age, sex, baseline BIS total and subscale scores and PANSS insight item. Mean endpoint flupenthixol dose was 12.9 (7.4) mg 2-weekly. Table 1 provides baseline and endpoint scores for psychopathology, cognition, functionality, quality of life, neurological signs and insight scores. PANSS total scores indicate that the patients were moderately to markedly ill at baseline (92.6 [15]), and only mildly ill at endpoint (52.5 [17.6]). Similarly, measures of functionality, quality of life, neurological signs and cognition indicate pronounced impairments at baseline, and substantial improvements at endpoint.

Fig. 1 shows the least squares means and 95% confidence intervals (CIs) by MMRM over 24-months of treatment for the BIS total and subscale scores and the PANSS insight item. There was a significant time-effect for the PANSS insight item ($F(3, 309) = 57.9$, $p < 0.0001$) with LSD tests indicating significant improvement from baseline to month 6 [mean (CI) change −1.64, (1.30–1.98), $p = 0.0001$], but no further improvement thereafter. There was also a significant effect for time for the BIS Need for Treatment subscale ($F(3, 309) = 3.7$, $p = 0.01$), with LSD tests indicating significant improvement at month 12 [mean (0.46, (0.17–0.74), $p = 0.001$)]. There were no significant time effects for BIS Symptom Attribution ($F(3, 309) = 0.5$, $p = 0.7$) and Illness Awareness ($F(3, 309) = 1.4$, $p = 0.2$) subscales as well as the BIS Total score ($F(3, 309) = 0.6$, $p = 0.6$).

According to the recommended cut-off scores of ≤2 for the BIS subscale scores (Birchwood et al., 1994) the numbers (%) of patients classified as having poor insight at baseline and endpoint respectively, were: Symptom Attribution subscale 65 (62%) and 55 (68%); Illness Awareness subscale 78 (74%) and 62 (77%); Need for Treatment subscale 64 (61%) and 44 (54%). The numbers (%) of patients with baseline and endpoint BIS total scores of ≤6 were, respectively, 62 (59%) and 44 (54%), and PANSS Insight item scores ≥4 (moderate impairment) were 96 (91%) and 22 (27%).The BIS total score was significantly correlated with the PANSS insight item at baseline ($r = -0.35$, $p = 0.0001$) but not at endpoint ($r = -0.20$, $p = 0.08$).

The correlations between the insight scores and clinical, functional, quality of life, cognitive and neurological scores at endpoint are provided in Table 2. The general regression models identified the following independent baseline and endpoint predictors of the insight measures: CDSS score [$\beta = 0.26$ (CI = 0.69–0.44), $p = 0.008$] predicted BIS total at baseline ($R^2 = 0.11$, $p = 0.008$); there were no significant predictors of BIS endpoint score ($R^2 = 0.007$, $p = 0.4$). PANSS total score [$\beta = 0.37$ (CI = 0.19–0.56), $p = 0.0001$], CDSS score [$\beta = -0.29$ (CI = 10.46–0.12), $p = 0.0009$] and WHOQOL-BREF social relationships [$\beta = 0.28$ (CI = 0.11–0.46), $p = 0.001$] predicted PANSS insight item at baseline ($R^2 = 0.30$, $p = 0.0001$); and PANSS total [$\beta = 0.57$ (CI = 0.33–0.81), $p = 0.0001$], WHOQOL-BREF environment [$\beta = 0.27$ (CI = 0.07–0.47), $p = 0.009$] and NES total [$\beta = 0.22$ (CI = 0.05–0.40), $p = 0.008$] predicted PANSS insight item at endpoint ($R^2 = 0.53$, $p < 0.0001$).

Finally, we assessed post-hoc whether emergent extrapyramidal symptoms influenced patients' perception of the need for treatment. We found no significant associations between BIS Need for Treatment subscale scores and anticholinergic use (ANOVA $F = 2.1$, $p = 0.15$) or endpoint ESRS total scores ($r = -0.02$, $p = 0.8$).

Table 1
Baseline and endpoint scores for psychopathology, functionality, cognition, quality of life, neurological signs and insight scores.

Variable	Baseline Mean (s.d.)	Endpoint Mean (s.d.)	T-value[a]	p[a]
PANSS (Total)	92.6 (15.0)	52.5 (17.6)	17.7	<0.0001
CDSS	2.9 (3.8)	1.1 (2.1)	4.3	<0.0001
SOFAS	44.6 (11.6)	63.7 (12.8)	−10.7	<0.0001
MCCB composite scores	22.0 (14.6)	28.5 (16.6)	−1.9	0.05
WHOQOL-BREF				
Physical health	12.0 (2.4)	12.2 (2.6)	−0.74	0.5
Psychological	13.0 (2.7)	13.4 (2.6)	−1.2	0.2
Social relationships	11.9 (4.2)	13.1 (4.2)	−2.0	0.05
Environment	11.6 (3.4)	12.1 (3.3)	−2.8	0.005
NES (Total)	14.1 (7.6)	6.6 (6.1)	7.4	<0.0001
BIS (Total)	5.8 (2.1)	6.2 (2.1)	−1.4	0.2
PANSS insight item	4.8 (1.1)	3.0 (1.1)	11.1	<0.0001

BIS, Birchwood Insight Scale; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functional Assessment Scale; MCCB, MATRICS Consensus Cognitive Battery; WHOQOL-BREF, World Health Organization Quality of Life Questionnaire-Brief Version; NES, Neurological Evaluation Scale.
[a] *t*-Test for independent samples.

4. Discussion

This study investigated changes in patient-rated and clinician-rated insight from the acute, floridly psychotic state through the first 24 months of flupenthixol decanoate treatment in patients with a first-episode of schizophrenia spectrum disorder. The most striking finding was that there were minimal improvements in patient-rated insight, while clinicians rated highly significant improvements in global insight. At endpoint, poor self-rated insight persisted in the majority of patients. This occurred despite the fact that medication adherence was assured and the clinical response was generally favourable, with improvements noted for measures of psychopathology, functionality, quality of life, neurological signs and cognition.

At first glance, our findings appear to differ from previous longitudinal studies which reported improvements in insight over the course of treatment (Wiffen et al., 2010a, 2010b; Segarra et al., 2012; David et al., 1995; Cuesta et al., 2000; Mintz et al., 2004; Crumlish et al., 2005; Parellada et al., 2011; Pijnenborg et al., 2015; Gharabawi et al., 2006; Mohamed et al., 2009). However, those studies reported only modest improvements, and substantial insight impairments persisted in the stable phase of illness (Wiffen et al., 2010a, 2010b, Segarra et al., 2012, Parellada et al., 2009). A further possible explanation for our discrepant findings is the role of adherence. We used a depot formulation which provided assured adherence, while in other studies patients with poor insight who were treated with oral antipsychotics may have been less adherent and consequently responded less well to treatment. However, counting against this possibility is that another longitudinal study using long-acting injectable risperidone reported small but significant improvements in insight over six months (Wiffen et al., 2010a, 2010b).

Finally, differences in the diagnostic composition of patient samples across studies might explain our apparently discrepant findings. For example, Parellada et al. (2011) included a more diverse group of psychotic disorders including bipolar disorder, depressive disorder with psychotic symptoms, schizoaffective disorder and brief psychotic disorder. In the subset of patients with schizophrenia and schizophreniform disorder ($n = 57$), the authors found that insight was poorer than in the other psychotic patients, and actually worsened at year two. Similarly, the Wiffen et al. (2010a, 2010b) study, in which 30% of the sample had a diagnosis of schizoaffective disorder reported a positive association between good insight and diagnosis of schizoaffective disorder. Our study included only one patient with schizoaffective disorder, while schizophrenia and schizophreniform disorder made up the rest of the sample. Taken together, these findings suggest that patients with schizophrenia and schizophreniform disorder show little, if any, improvement in insight with treatment, whereas those with an affective component to their illness (mood disorders and schizoaffective disorder) have a greater chance of insight improvement with treatment. Our findings are therefore consistent with the observation that half of persons with schizophrenia do not recognise that they have an illness,

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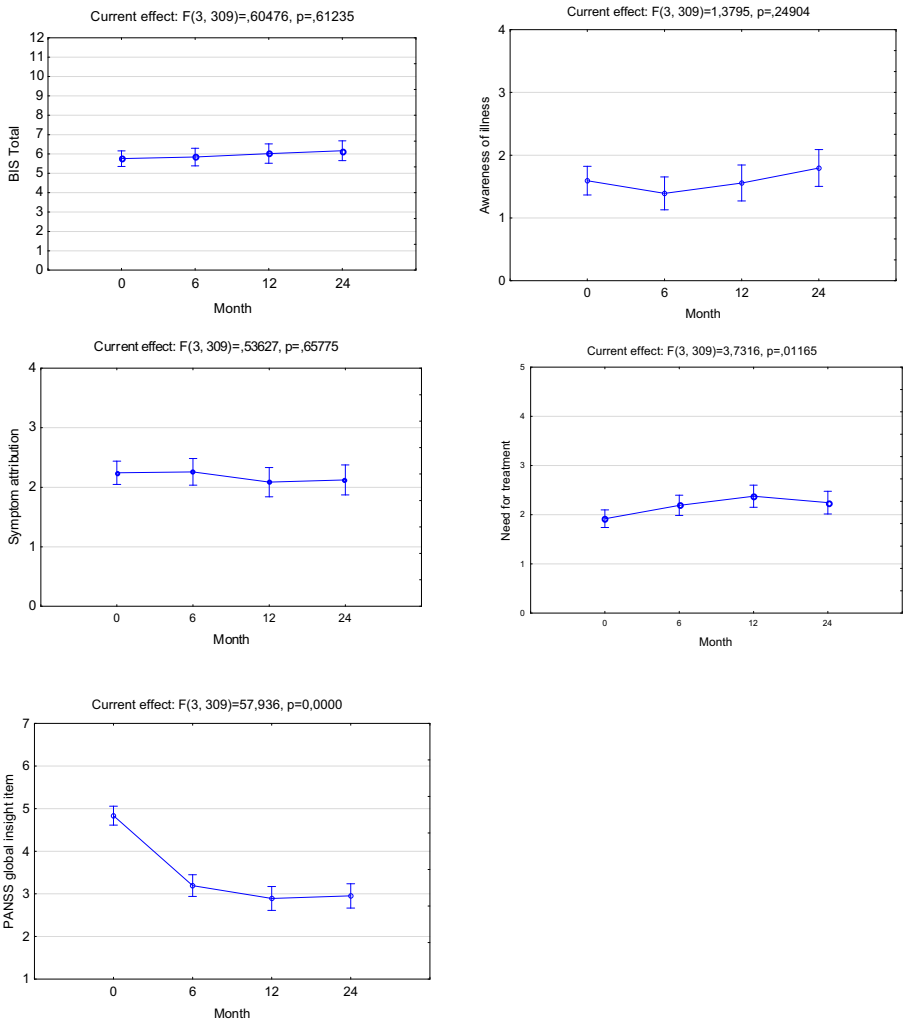

Fig. 1. Linear mixed effects (LS means and 0.95 confidence intervals) for the patient- and clinician-rated insight measures over time.

and this unawareness typically does not improve with treatment (Arango and Amador, 2011).

The failure of patient-rated insight to improve significantly with treatment, and the fact that this occurred despite the generally favourable response in other domains, is consistent with a phenomenologically orientated hypothesis in which insight impairment in schizophrenia is considered a long-standing disorder of the self, from which the psychotic symptoms emerge. While psychotic symptoms respond to treatment, the anomalous self-experiences persist and are considered to be trait-like features (Henriksen and Parnas, 2014). Our findings argue for a large trait-related component to insight in schizophrenia and schizophreniform disorder, perhaps more so than with many of the other clinical manifestations of the illness. Our findings therefore support and extend the proposal that a substantial component of insight impairment is trait-related (Wiffen et al., 2010a, 2010b) and are consistent with reports of specific neurobiological underpinnings of insight impairment (Shad et al., 2007). Indeed, in two neuroimaging studies that we conducted in the present study cohort, we found an association between symptom misattribution and frontal cortical thinning (Asmal et al., 2016) as well as between global insight impairment and white matter connectivity deficits involving a widespread network of tracts with a predilection for cortical midline structures (Asmal et al., 2017).

Our findings are of clinical relevance. They suggest that, even when patients with schizophrenia respond favourably to treatment, fundamental insight impairments persist. This has implications for shared decision making models regarding treatment choice, treatment engagement and medication adherence. Given the high rates of non-adherence in schizophrenia and the risks associated with relapse (Emsley et al., 2013) the most effective psychosocial and pharmacological ways of ensuring continuous treatment in individuals with

Table 2
Pearson correlation coefficients for the insight scores and clinical, functionality and cognitive scores at endpoints.

Variable	BIS Total endpoint		PANSS G12 endpoint	
	r	p-Value	r	p-Value
PANSS	−0.11	0.3	**0.63**	**0.0001**
CDSS	0.09	0.4	−0.05	0.6
SOFAS	0.08	0.5	**−0.40**	**0.0001**
WHOQOL-BREF				
Physical health	0.01	0.9	0.04	0.7
Psychological	−0.17	0.09	**0.23**	**0.02**
Social relationships	0.02	0.8	0.15	0.14
Environment	0.01	0.9	0.18	0.18
MCCB (composite scores)	0.15	0.34	−0.30	0.5
NES	−0.05	0.67	**0.43**	**0.0001**

BIS, Birchwood Insight Scale; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functional Assessment Scale; MCCB, MATRICS Consensus Cognitive Battery; WHOQOL-BREF, World Health Organization Quality of Life Questionnaire-Brief Version; NES, Neurological Evaluation Scale.
Bold values indicates statistically significance at 0.05.

persistent deficits in illness awareness and recognition of the need for treatment should be considered.

In our study, the only predictor of patient-rated overall insight was depression score at baseline. Indeed, depression score also predicted clinician rated insight at baseline. This inverse relationship is in keeping with the well documented "insight paradox", which defines a relationship between better insight and higher depression levels in psychosis (Belvederi et al., 2016). However, the fact that that this was only apparent at baseline suggests that the relationship is only present in the acute psychotic state. Poorer insight according to the clinician global rating was predicted by higher psychopathology levels at baseline and endpoint, consistent with previous studies reporting significant associations between insight and other symptoms. However, similar to our study, effect sizes reported to date were small (Mintz et al., 2003). The association between insight impairment and poorer quality of life on some domains, is consistent with some previous reports (Wiffen et al., 2010a, 2010b; Dickerson et al., 1997; Lysaker et al., 1998; Roseman et al., 2008; Schwartz, 1998) although others found no association (Gharabawi et al., 2006) and others still reported an inverse relationship, i.e. between better insight and poorer quality of life. The relationship between insight impairment and more prominent neurological signs has been previously reported (Hill et al., 2012). The lack of an association between cognition and insight deserves consideration. A systematic review and meta-analysis including data from 72 studies and a total population of 5429 patients reported a small but significant relationship between clinical insight and cognition (Nair et al., 2014). However, evidence remains conflicting, likely due to methodological differences such as different patient samples (e.g. broadly or narrowly defined psychotic disorders, acute or chronic, symptomatic or clinically stable patients and the use of different instruments to assess both insight and cognitive functioning). Our findings are consistent with several longitudinal studies that did not find an association between insight and cognition (David et al., 1995; McEvoy et al., 1993; Kemp and David, 1996; Cuesta et al., 2006). The small effect sizes of the associations that were found with clinician rated global insight measures and other domains, together with the absence of associations with functionality and cognition, are consistent with other studies suggesting that insight is relatively independent of these other domains (Wiffen et al., 2010a, 2010b; Parellada et al., 2011). This appears to be particularly true for patient-rated insight, suggesting that this would be the best measure of trait-related insight.

4.1. Strengths and limitations

This study addressed several important methodological shortcomings of previous studies. First, by including minimally treated, first-episode patients we avoided effects of previous antipsychotic treatment and illness chronicity. Second, standardisation of treatment avoided possible differential effects of various antipsychotics, and use of a depot formulation removed the confounding effect of non- and partial adherence. While the association between poor insight and poor outcome could be explained by more severe symptoms causing poorer insight, it is equally possible that impaired insight causes non-adherence which in turn results in poorer treatment outcome (Lysaker et al., 2018). Third, the longitudinal nature of the study and relatively long follow-up period over 24 months, together with multiple assessment points, allowed us to track changes in insight over time. Finally, using the BIS allowed assessment of different components insight and together with the PANSS global insight item allowed comparison of both patient-rated and clinician-rated assessments of insight.

There are also limitations to consider. First, a possible explanation for the lack of improvement in patient-rated insight in our study is that cross-cultural factors may play a role. The clinical assessment of insight focuses largely on the biomedical model and may underestimate the role that cultural and social-environmental factors play in explanatory models that may fundamentally shape insight (Belvederi and Amore, 2018; Jacob, 2014). This means patients who may offer a culturally appropriate explanation for symptoms of illness may be scored lower than those who offer a biomedical explanation. Second, it is also possible that the limited educational status of our participants restricted their capacity to comprehend the statements in the BIS, and that consequently the clinician-rated assessment may more accurately reflect their true levels of insight. We consider this unlikely however, as our two study nurses took care to explain the meaning of each of the BIS questions and assisted participants in completing the scales, and in any event educational status did not correlate significantly with insight scores. Third, an alternative explanation is that patient-rated and clinician-rated instruments may not be measuring the same aspects of insight. While the clinician-rated PANSS insight item has been reported to strongly correlate with other, more comprehensive insight scale (Sanz et al., 1998) it not only rates insight but also "judgement" and is mono-dimensional. As such, it is subject to inter-rater bias and fails to capture the multidimensional nature of insight. Most importantly, it is possible that clinician assessments of insight may be influenced by overall impressions of illness improvement (Marks et al., 2000) and may not represent actual insight levels. This would be consistent with our finding of a significant correlation between patient-rated and clinician-rated insight at baseline but not at endpoint, as well as the significant associations of clinician-rated global insight with psychopathology and quality of life at both baseline and endpoint. Fourth, the narrow diagnostic inclusion criteria, while having the advantage of assessing insight in schizophrenia spectrum disorders specifically, means that results cannot be generalised to other diagnostic groups. Similarly, standardisation of treatment precludes generalisation of our findings to patients treated with other antipsychotics. Finally, our participants did not receive any formal psychological interventions aimed at improving insight. These interventions may improve insight, although a significant effect has not yet been demonstrated (Pijnenborg et al., 2013).

In conclusion, our findings suggest that insight as rated by patients is not responsive to antipsychotic treatment, and should be considered a trait feature of the illness. Future studies should take care to differentiate between patient and clinician rated assessments of insight.

Authors' contribution

Robin Emsley, Lebogang Phahladira, Laila Asmal and Bonginkosi Chiliza were responsible for the study conception and design. Sanja Killian, Freda Scheffler, Stefan Du Plessis and Hilmar Luckhoff were responsible for collection, extraction and coding of data included in the study. Robin Emsley provided the analysis and interpretation. Lebogang Phahladira and Robin Emsley drafted the manuscript, and all other authors provided critical comments.

All authors provided intellectual contribution and approved the final manuscript.

Declaration of interest

Bonga Chiliza has received speakers fees from Cipla, Lundbeck, and Sanofi. Robin Emsley has received speakers fees and participated in advisory boards from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck.

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CHAPTER 3

Early recovery in the first 24 months of treatment in first-episode schizophrenia-spectrum disorders. *This first-author manuscript was published in NPJ Schizophrenia.*

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ARTICLE OPEN

Early recovery in the first 24 months of treatment in first-episode schizophrenia-spectrum disorders

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Studies assessing the treatment outcomes in first-episode schizophrenia have reported mixed results. While symptom improvement is frequently robust, when other domains are considered outcomes are generally poorer. We explored response trajectories, rates and predictors of recovery in the domains of core psychopathology, clinician-rated social and occupational functioning and patient-rated quality of life over 24 months of treatment in 98 patients with first-episode schizophrenia spectrum disorders who were treated with a long-acting antipsychotic medication. There was robust improvement in core psychopathology (effect size $d = 3.36$) and functionality ($d = 1.78$), with most improvement occurring within the first six months of treatment. In contrast, improvement in subjective quality of life was less marked ($d = 0.37$) and slower, only reaching significance after 12 months of treatment. Symptom remission was achieved by 70% of patients and over half met our criteria for functional remission and good quality of life. However, only 29% met the full criteria for recovery. Patients who met the recovery criteria had better premorbid adjustment, were less likely to be of mixed ethnicity and substance use emerged as the only modifiable predictor of recovery. Only 9% of our sample achieved both functional remission and good quality of life despite not being in symptom remission. We found high rates of symptom remission, functional remission and good quality of life in patients, although relatively few achieved recovery by meeting all three of the outcome criteria. Symptom remission is not a necessary prerequisite for functional remission and good quality of life, although few non-remitters achieve other recovery criteria.

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INTRODUCTION

While the clinical course of schizophrenia is characterised by marked variability between individuals and over time, the overall outcome is poor for many patients.[1,2] Schizophrenia was long considered a lifelong illness with little or no hope of recovery.[3] Following the introduction of antipsychotics more than sixty years ago, treatment prospects were initially modest, with clinicians settling for outcomes such as 'behavioural control', 'symptom control', or 'stability'.[4] However, advances in pharmacological treatment and psychosocial interventions have heightened expectations for outcomes.[5] Indeed, there has been a progression of treatment goals from containment, through response, to remission, and more recently, to recovery.[6] Recovery became a focus of attention when it was recognised that symptom reduction alone was not sufficient, and that functionality and outcomes that are most meaningful to patients and families need to be considered.[3] Outcome measures that mainly focus on symptom remission should ideally be extended to include other components of recovery, as this would better fit the needs of patients.[7] There is growing acknowledgement that people with schizophrenia do not inevitably experience deterioration over time, and most have the potential to experience considerable symptomatic improvement and achieve a substantial degree of recovery.[8]

The lack of a widely accepted and validated definition of recovery has been an obstacle for clinicians and researchers. Recovery is a complex construct. It is multifaceted and difficult to assess, particularly across communities where psychosocial and cultural factors may influence aspects such as independent living, daily activities, education and vocational status.[4,9] Most of the instruments developed to measure recovery were designed for use in Western cultures, and may not be appropriate for use in other settings. Shrivastava et al. highlighted the lack of consensus for defining recovery. They argue that outcome measures should be multidimensional, since social and functional improvements are not necessarily linked with antipsychotic treatment response. Importantly, they emphasise that psychosocial, vocational and functional parameters differ across communities, and propose that the decision as to which components of recovery are relevant should be taken within the cultural context.[6]

While opinions differ as to what should be included in a definition of recovery, there is general consensus that symptom remission should be one of the components.

The Remission in Schizophrenia Working Group (RSWG)[3] laid a foundation for the measurement of remission by operationally defining a threshold for symptom severity, with no significant interference with behaviour, for a period of at least six months. These criteria are easy to apply in both clinical and research settings, and have been widely adopted. The RSWG considered remission to be a "necessary but not sufficient step toward recovery," although they also recognised that it is not an absolute prerequisite for functional improvement. The RSWG regarded recovery as a more demanding and longer-term state than symptom remission.[3] However, they did not provide criteria for recovery, citing the need for further evidence on the longitudinal course of recovery components. In particular, there is a need to assess relationships between symptom remission and other outcome measures, particularly functional outcome and quality of life (QOL). In the present study, we sought to address this

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knowledge gap by assessing the rates, trajectories, correlations and predictors of recovery across three domains (i.e. core psychopathology, clinician-rated social and occupational functioning and patient-rated QOL) in a cohort of first-episode schizophrenia spectrum disorder patients treated over 24 months. To assure treatment and circumvent nonadherence, assessments were scheduled at regular time point intervals and patients were treated with a long-acting antipsychotic medication.

RESULTS

We screened 234 patients for eligibility, 64 did not meet the inclusion criteria, 19 declined to participate and 18 were excluded for other reasons. Of the133 who entered the study six patients were excluded for no longer meeting the inclusion criteria and 29 were excluded for not completing 6 months of treatment. The sample therefore comprised 98 patients, of whom 72 (73%) were men and 26 (27%) women, aged 24.2 ± 6.4 years, of mixed ($n = 75$, 77%), black ($n = 13$, 13%) and white ($n = 10$, 10%) ethnicity, with a DSM-IV TR diagnosis of schizophrenia ($n = 66$, 67%), schizophreniform ($n = 31$, 32%) and schizoaffective ($n = 1$,1%) disorder. The mean duration of untreated psychosis (DUP) was 34.6 ± 44.8 weeks. The mean modal dose of flupenthixol decanoate was 11.7 ± 3.8 mg 2 weekly. Seventy-two (73%) completed 24 months of treatment. Reasons for study withdrawal were: withdrawal of consent ($n = 10$), lost to follow-up ($n = 6$), relocation ($n = 3$), incarceration ($n = 2$), poor treatment response ($n = 2$), severe side-effects ($n = 1$), general medical condition ($n = 1$), and severe drug abuse ($n = 1$). Regarding substance use, $n = 11$(11%) patients were classified as cannabis use only and n = 37 (38%) as polysubstance (cannabis, alcohol, methamphetamine and methaqualone) use.

Improvement trajectories for the recovery domains

Figure 1 provides a graphical representation of the change in psychopathology (PANSS core item total score), functionality (SOFAS score) and QOL (patient-rated overall WHOQOL-Bref score) over 24 months. There were significant improvements in PANSS core item total scores from baseline to month six, and again from month six to month 12, as shown in Table 1. SOFAS scores improved significantly from baseline to month six, but not after that. Improvement in patient-rated overall QOL was slower and only reached statistical significance at month 12. None of the domains showed further significant improvement after month 12. Effect sizes for improvements from baseline to endpoint were 3.36 for PANSS core item total scores, 1.78 for SOFAS scores and 0.37 for patient-rated overall QOL.

Recovery rates and correlations between recovery domains

In Fig. 2 a Venn diagram depicts the proportion of patients meeting criteria for individual and overlapping components of the recovery criteria at endpoint. While more than half of the patients met criteria for each of the individual components, only 29% met our full criteria for recovery. Endpoint SOFAS scores were negatively correlated with PANSS core item total scores ($r = -0.53$, $p < 0.0001$) and positively correlated with patient rated overall QOL scores ($r = 0.26$, $p = 0.01$). However, the correlation between PANSS core item total scores and patient rated overall QOL scores did not reach statistical significance ($r = -0.17$, $p = 0.1$).

Predictors of recovery

Table 2 and 3 provides a comparison of the demographic and baseline clinical scores for patients meeting recovery criteria and the rest of the sample. Those meeting recovery criteria were older, better educated, had better premorbid adjustment, were less likely to be of mixed ethnicity, less likely to use substances, and had a higher composite MCCB score. In the logistic regression analysis, substance use (OR = 9.3, 95% CI 1.6–53.0, $p = 0.01$), ethnicity, (OR 0.2, 95% CI 0.03–1.6, $p = 0.01$) and premorbid adjustment (OR = 0.003, 95% CI 0.00003–0.5, $p < 0.001$) were significant predictors of overall recovery. We then compared patients meeting criteria for the individual components of

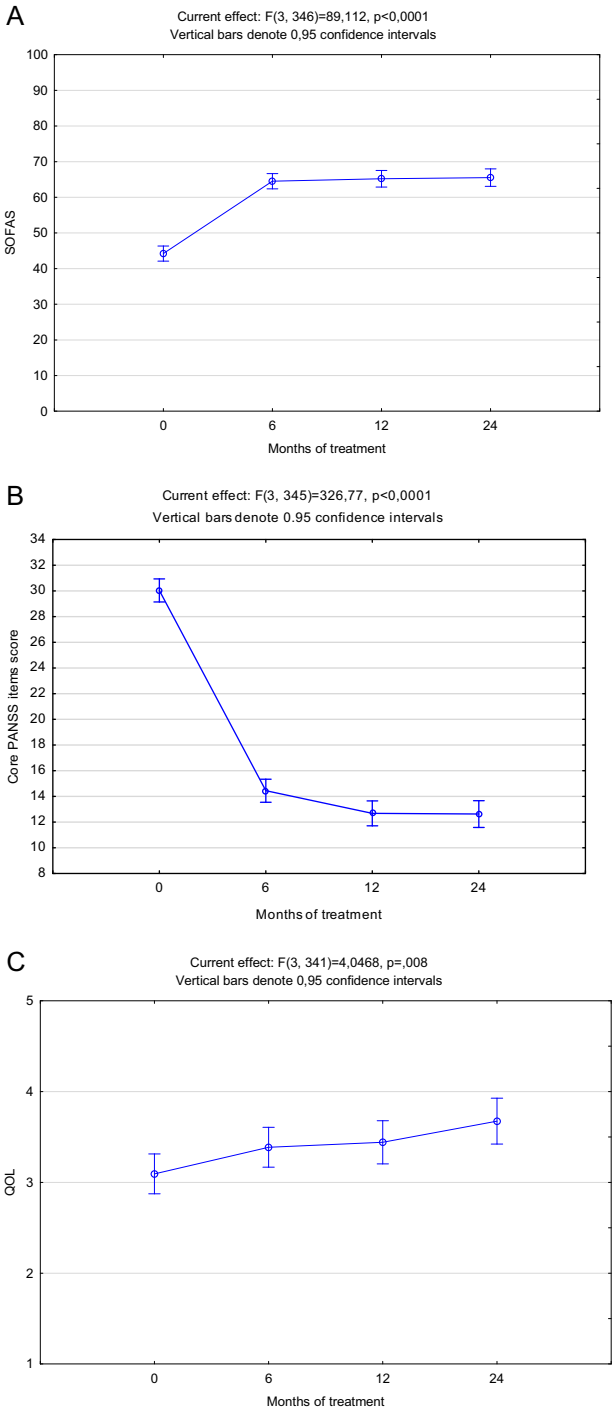

Fig. 1 A graphical representation of the change in psychopathology, functionality and quality of life over 24 months. Mixed model repeated measures for the **a** SOFAS, **b** PANSS core items total, and **c** patient rated overall QOL scores over 24 months. SOFAS = Social and Occupational Functioning Assessment Scale, PANSS = Positive and Negative Syndrome Scale, QOL = Quality of life.

Table 1. The results of the LSD tests showing changes in the three outcome domains over 24 months.

Outcome measure	Mean difference	−95% CI	+95% CI	*p*-value
Core PANSS				
Month 0 to Month 6	15.5918	14.3277	16.856	<0.001[a]
Month 6 to Month 12	1.76073	0.43995	3.08151	0.009[a]
Month 12 to Month 24	0.05210	−1.3731	1.47728	0.9
SOFAS				
Month 0 to Month 6	−20.306	−23.317	−17.295	<0.001[a]
Month 6 to Month 12	−0.693	−3.8399	2.4539	0.7
Month 12 to Month 24	−0.2977	−3.6678	3.0724	0.9
QOL				
Month 0 to Month 6	−0.2936	−0.6041	0.01688	0.06
Month 6 to Month 12	−0.3485	−0.6724	−0.0247	0.04[a]
Month 12 to Month 24	−0.2329	−0.5795	0.11362	0.2

CI confidence interval, *PANSS* Positive and Negative Syndrome Scale, *SOFAS* Social and Occupational Functioning Assessment Scale, *WHOQOL-BREF* World Health Organisation quality of life-BREF scale

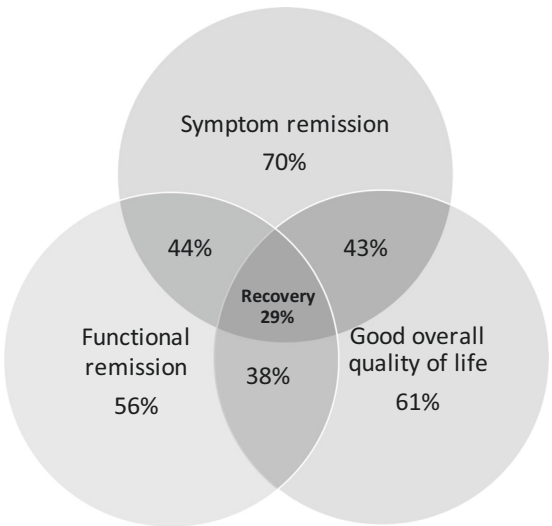

Fig. 2 A Venn diagram illustrating the proportion of patients with individual or overlapping components of the early recovery criteria.

recovery to the rest of the sample. Those achieving symptom remission at endpoint had higher baseline PANSS positive domain scores (17.7 ± 3.1 vs. 16.3 ± 3.8, $t = 2.0$, $p = 0.05$) and better premorbid adjustment during late adolescence (0.3 ± 0.2 vs. 0.4 ± 0.2, $t = -2.5$, $p = 0.02$). In a logistic regression model, both baseline PANSS positive domain scores (OR 1.2, 95% CI 1.0–1.3, $p = 0.04$) and better premorbid adjustment during late adolescence (OR 0.04, 95% CI 0.003–0.5, $p = 0.01$) remained significant predictors of recovery. According to the preliminary univariate analyses patients meeting criteria for functional remission criteria were older (25.9 ± 7.5 vs 22.0 ± 4.2 yrs., $t = 3.0$, $p = 0.004$), more likely to be employed ($n = 14/54$; 26% vs. $n = 4/43$; 9%, $X^2 = 4.4$, $p = 0.04$), less likely to use substances ($n = 17/54$; 31% vs. $n = 30/43$, 70%, $X^2 = 14.0$, $p = 0.0002$), had lower baseline scores for the PANSS excitement/hostility domain (7.5 ± 3.7 vs. 9.1 ± 4.2, $t = -2.1$, $p = 0.006$), better general premorbid adjustment (0.4 ± 0.2 vs. 0.6 ± 0.2, $t = -3.2$, $p = 0.002$), less impairment of motor co-ordination (1.1 ± 1.3 vs. 1.7 ± 1.5, $t = -2.1$, $p = 0.03$) and better performance on the MCCB working memory domain (32.2 ± 11.9 vs. 26.4 ± 11.5, $t = 2.2$, $p = 0.03$). However, none of these variables remained significant predictors of SOFAS remission in the regression model. Finally, in the preliminary analyses patients with good or very good overall QOL at endpoint were less likely to be of mixed ancestry ($n = 40/59$; 68% vs. $n = 34/38$; 89%, $X^2 = 6.4$, $p = 0.04$), less likely to have had a history of substance use ($n = 23/59$; 40% vs. $n = 24/38$; 63%, $X^2 = 5.4$, $p = 0.02$), had lower baseline excitement/hostility scores (7.4 ± 3.9 vs. 9.2 ± 3.6, $t = -2.1$, $p = 0.03$), better baseline overall QOL (3.3 ± 1.1 vs. 2.8 ± 1.1, $t = 2.1$, $p = 0.03$) and better performance on the MCCB speed of processing (29.0 ± 14.0 vs. 22.6 ± 11.2, $t = 2.1$, $p = 0.04$) and reasoning/problem solving domains (39.3 ± 12.1 vs. 33.7 ± 9.6, $t = 2.2$, $p = 0.04$). However, none of these variables remained significant predictors of QOL in the regression model.

Table 2. Comparison of demographic profile for patients meeting recovery criteria vs. the rest of the sample.

Variables	Recovery ($n = 28$, 29%)	Rest of the sample ($n = 70$, 71%)	*t*-value	*p*-value
Age in years, mean (SD)	27.39 (7.93)	22.89 (5.34)	3.26	0.002[a]
Highest school grade passed, mean (SD)	10.67 (1.96)	9.51 (2.13)	2.44	0.017[a]
Sex, *n* (%)				
Male	20 (71%)	52 (74%)		0.80
Female	8 (29%)	18 (26%)		
Ethnicity, *n* (%)				
Africans	7 (25%)	6 (8%)		
Mixed	15 (54%)	60 (86%)		0.003[a]
White	6 (21%)	4 (6%)		
DSM-IV-TR diagnosis *n* (%)				
Schizophreniform disorder	6 (21%)	25 (36%)		0.10
Schizophrenia	21 (75%)	45 (64%)		
Schizoaffective disorder	1 (4%)	0 (0%)		
Substance use *n* (%)	5 (18%)	43 (61%)		<0.001[a]
Employment status *n* (%)				
Unemployed	21 (75%)	59 (84%)		0.20
Informal	0 (0%)	2 (3%)		
Full time	7 (25%)	9 (13%)		

DSM-IV-TR Diagnostic and Statistical Manual of Mental Diseases, 4th edn, Text Revision, *SD* standard deviation, *p* significance value, *T-test* for continuous variables

DISCUSSION

Our patients responded robustly to antipsychotic treatment in terms of psychopathology improvement, with 70% achieving symptom remission. This is consistent with previous reports of a favourable treatment response in first-episode schizophrenia,[10] and suggests that when treatment is assured, the majority of first-episode patients will achieve sustained symptom remission. In

addition to the improvements in psychopathology, over half of our participants achieved functional remission and favourable subjective QOL. Despite this, fewer than 1/3 met our recovery criteria in all three domains. While comparison of our results with those of other longitudinal studies is complicated by methodological differences, our findings are similar to others reporting poorer outcomes when domains beyond just symptom remission are considered as outcome measures.[9–12]

The improvement trajectories for the PANSS core symptom scores and SOFAS scores were similar, indicating a close relationship between these two domains. Robust improvements were observed in both domains, with most improvement occurring during the first six months of treatment and reaching a plateau at 12 months. The highly significant correlation between endpoint psychopathology and functionality provides further evidence of a close relationship between these two domains, consistent with findings reported in previous studies.[13] However, of note is that 26% of patients achieving symptom remission did not achieve functional remission, and 12% of patients who were in functional remission did not achieve symptom remission. These findings confirm that, while symptom remission is closely related to functional remission, it is not a necessary prerequisite for functional remission.[3,6]

An association between QOL and symptom remission has been reported in previous studies.[14–16] Patients who achieved symptom remission reported a better QOL[15] and failure to achieve symptom remission was associated with poorer QOL.[16] Also, a recent meta-analysis found a significant negative correlation between QOL and symptom severity.[17]

However, in our study we found that endpoint symptom remission and subjective QOL were not significantly correlated, and 27% of those achieving symptom remission did not rate their QOL as good or very good. These differences in findings may be explained by our focus on the core positive, negative and disorganised symptoms of schizophrenia, which may not be closely associated with QOL. Indeed, an earlier meta-analysis reported weak associations between psychiatric symptoms and QOL, with general psychopathology showing the strongest associations.[18] Further, a review of studies assessing QOL in schizophrenia reported that affective symptoms were major obstacles to QOL improvement, while positive and negative symptoms were largely independent from subjective QOL.[19] Additionally, in a pooled analysis of eight longitudinal studies, it was found that, while a reduction in psychiatric symptoms was associated with improvements in QOL, only improvements in depression/anxiety and hostility domains remained significant in the multivariate model.[20] Finally, our findings are consistent with those reported in a recent meta-analysis conducted by Van Eck et al., which explored the relationship between clinical recovery and personal recovery, the latter being related to QOL.[7] While the authors found a significant relationship between symptom severity and personal recovery, the association was strongest for affective symptoms and weaker for positive and negative symptoms. In our study, relative independence of QOL was further supported by the observation that the improvement trajectory in this domain was different in that it occurred more gradually, and to a much lesser degree, than symptom and functional improvement. Taken together, these findings suggest that factors other than core symptoms of the illness influence QOL, and that QOL may be less responsive to antipsychotic treatment. Interventions focusing on symptom reduction and functional improvement alone may therefore fail to improve QOL.[19]

Remission has been proposed as a necessary, but not sufficient, step toward recovery.[3] Our results suggest that this is not necessarily the case, although few who failed to achieve symptom remission met the other recovery criteria. In fact, only 9 (9%) of our sample achieved both functional remission and good or very good subjective QOL despite not being in symptom remission.

Post-hoc *t*-test comparison of endpoint PANSS domains of these 9 patients with the rest of the sample suggests that specifically, more prominent negative symptoms account for their failure to achieve symptom remission (score of 13.3 vs 10.3, $t = 2.03$, $p = 0.045$). Although small, this might be an important subgroup to further research. Studies could explore factors other than antipsychotic treatment response contributing to their QOL and functionality. It would also be interesting to investigate the effects of both increasing and decreasing antipsychotic dose in these individuals. It could be that the antipsychotic dose is suboptimal in these patients with persistent symptoms and that increasing the dose may result in further improvements. On the other hand, it may be that these individuals are less responsive to antipsychotics and that dose reductions may benefit the patients by reducing the side-effect burden without worsening the symptoms.

Other studies have identified several significant predictors of recovery, including better educational and occupational status,[21] shorter DUP,[10,21] better premorbid adjustment,[22,23] fewer negative symptoms at baseline,[24] younger age at diagnosis,[11] Caucasian ethnicity,[25]better cognitive functioning at stabilisation[26] and more cerebral asymmetry.[10] In our study, patients meeting recovery criteria were older, better educated, had better premorbid adjustment, were less likely to be of mixed ethnicity, and less likely to use substances. However, in the logistic regression analysis, only substance use, ethnicity and premorbid adjustment emerged as significant predictors of recovery. Substance use is the only modifiable predictor of recovery. Integration of substance use treatment in mental health treatment protocols and services may promote recovery in this population.

Detailed comparisons of recovery rates and predictors across studies are difficult and of limited value, given the methodological differences. Most importantly, the lack of consensus in defining and measuring recovery is problematic. Mausbach et al.[27] reviewed eight measures of functional ability and concluded that no “gold standard” measure exists. The authors noted that most studies utilising these scales were cross-sectional, with little being known about their validity in predicting real-world health outcomes.

Similarly, a review of measures assessing QOL in schizophrenia identified 35 different scales and highlighted the lack of consensus on their clinical value.[19] The lack of uniformly accepted criteria and assessment instruments, together with wide variation in patient populations and methodology, markedly limits generalisability of studies conducted to date. Of the recovery domains, psychopathology improvement is likely to be less influenced by environmental factors than functionality and QOL, although even expression of psychopathology may differ across cultures. For example, it has been proposed that “social kindling” could account for observed differences in auditory hallucinations across distinct cultural groups.[28] Nevertheless, the relative stability of symptoms across populations likely contributed to the success and widespread adoption of the RSWG remission criteria,[3] as they only consider improvements in core psychopathology. In contrast, the substantial impact of sociocultural and other environmental factors on functionality and QOL[6] are barriers to developing broader criteria for recovery in schizophrenia. One way of minimising the impact of sociocultural differences is to use global scores for assessing functionality and QOL, which was the rationale adopted in the present study.

The strength of our study lies in the addressing of several important methodological shortcomings which defined previous studies. Using first-episode, minimally treated patients reduced the possible confounding effects of disease chronicity and previous treatment. Using standardised treatment addressed the possible confounding effects of antipsychotic heterogeneity, and

Table 3. Comparison of baseline clinical scores for patients meeting recovery vs. the rest of the sample.

Variables	Recovery ($n = 28$, 29%)	Rest of the sample ($n = 70$, 71%)	*t*-value	*p*-value
DUP weeks, mean (SD)	44.59 (46.55)	30.64 (43.72)	1.40	0.17
PANSS total change at 7 weeks, mean (SD)	0.52 (0.18)	0.57 (1.93)	−0.13	0.89
PANSS, total score, mean (SD)	91.68 (18.45)	95.70 (15.05)	−1.12	0.27
PANSS, positive, mean (SD)	17.75 (3.48)	17.14 (3.32)	0.81	0.42
PANSS, negative, mean (SD)	18.79 (5.72)	20.61 (5.23)	−1.52	0.13
PANSS disorganised, mean (SD)	11.29 (2.97)	12.33 (2.72)	−1.67	0.09
PANSS excitement/hostility, mean (SD)	7.07 (3.97)	8.64 (3.76)	−1.84	0.07
CDSS total score, mean (SD)	3.75 (4.13)	3.33 (4.23)	0.45	0.66
SOFAS, mean (SD)	47.75 (14.95)	42.70 (10.43)	1.90	0.06
WHOQOL-BREF, mean (SD)				
Psychological	13.19 (2.64)	12.83 (2.53)	0.62	0.54
WHOQOL-BREF Social	13.19 (4.30)	11.43 (3.85)	1.95	0.05
WHOQOL-BREF Environment	12.15 (3.22)	11.48 (3.02)	0.96	0.34
PAS total childhood, mean (SD)	0.24 (0.17)	0.23 (0.15)	0.04	0.97
PAS total early adolescence,	0.23 (0.14)	0.32 (0.16)	−2.59	0.011[a]
PAS total late adolescence	0.27 (0.14)	0.42 (0.19)	−3.63	<0.001[a]
PAS total adult	0.35 (0.24)	0.39 (0.23)	−0.81	0.42
PAS total general	0.36 (0.14)	0.53 (0.20)	−4.15	<0.001[a]
PAS overall	0.29 (0.13)	0.38 (0.14)	−2.96	0.004[a]
NES sensory integration, mean (SD)	2.50 (2.66)	2.61 (2.09)	−0.23	0.82
NES motor coordination, mean (SD)	1.25 (1.40)	1.34 (1.46)	−0.29	0.78
NES sequencing of motor acts, mean (SD)	2.64 (2.61)	2.94 (2.35)	−0.55	0.58
NES total, mean (SD)	13.93 (8.39)	14.73 (6.84)	−0.49	0.63
BIS subscale 1, mean (SD)	1.92 (0.97)	2.40 (1.06)	−1.91	0.06
BIS subscale 2, mean (SD)	1.54 (1.28)	1.60 (1.28)	−0.20	0.84
BIS subscale 3, mean (SD)	2.36 (1.06)	2.08 (0.98)	1.15	0.25
BIS total, mean (SD)	5.82 (2.33)	6.08 (1.81)	−0.54	0.59
MCCB SoP mean, (SD)	30.88 (12.42)	24.49 (13.21)	2.00	0.049[a]
MCCB AV, mean (SD)	33.65 (11.43)	30.08 (9.75)	1.39	0.17
MCCB WM, mean (SD)	32.33 (12.48)	28.80 (11.65)	1.21	0.23
MCCB Vrbl Lrng, mean (SD)	38.38 (9.57)	34.18 (9.52)	1.80	0.08
MCCB Vis Lrng, mean (SD)	37.46 (13.80)	31.59 (13.32)	1.78	0.08
MCCB RPS, mean (SD)	41.67 (11.83)	35.09 (10.83)	2.41	0.018[a]
MCCB SC, mean (SD)	44.27 (20.55)	44.85 (20.28)	−0.11	0.91
MCCB Composite score, mean (SD)	29.17 (13.29)	22.42 (12.75)	2.06	0.043[a]

SD standard deviation, *MATRICS* Measurement and treatment research to improve cognition in schizophrenia, *MCCB* MATRICS consensus cognitive battery, *SOP* speed of processing, *AV* attention/vigilance, *WM* working memory, *Vrbl Lrng* verbal learning, *Vis Lrng* visual learning, *RPS* reasoning and problem solving, *SC* social cognition, *PANSS* positive and negative syndrome scale, *SOFAS* social and occupational functioning assessment scale, *CDSS* Calgary depression scale for schizophrenia, *BIS* Birchwood insight scale, *PAS* premorbid adjustment scale, *EAdol* early adolescence, *LAdol* late adolescence, *NES* neurological evaluation scale, *WHOQOL-BREF* World Health Organisation quality of life-BREF scale, *p* significance value, *T-test* for continuous variables

treatment with a long-acting formulation removed the effect of covert non-adherence, which may be substantial in outcome studies. Finally, comprehensive characterisation of the cohort with regular assessment points allowed us to investigate changes over time in multiple outcome domains. However, there are also several important limitations that need to be considered when interpreting our findings. First, the study duration of two years, while longer than most longitudinal studies conducted in a controlled setting, does not provide an indication of the longer-term outcomes in our sample. A longer follow-up duration is particularly important when considering recovery as an outcome measure, given that the improvements should be sustained over a protracted period.

Second, our use of global measures of functionality and QOL, while helpful in circumventing the influence of environmental disparities, was not able to assess different aspects of functionality and QOL. Third, since the majority of our subjects were drawn from a socio-economically deprived community, our findings may not be generalisable to other populations. Fourth, this was a convenience sample of patients who presented to health care services and may not be representative of the larger population. Fifth, because of the small numbers of black and white participants, our findings regarding ethnicity should be treated with caution. Finally, the use of a single antipsychotic, while removing the effects of treatment heterogeneity, precludes the generalisation of our findings to patients treated with other antipsychotics.

In summary, we found high rates of symptom remission, functional remission and favourable subjective QOL in patients with a first episode of schizophrenia spectrum disorder treated

over 24 months, although fewer than a third managed to achieve recovery by meeting all three of the outcome criteria. Given the need to assess treatment outcome in schizophrenia in domains beyond just symptom improvement, the development of valid, culture-free measures of components of recovery should enjoy priority amongst the research community.

METHODS

Ethics approval

Approval to conduct the study was obtained from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences. Written, informed consent was obtained from the patients and/or their legal guardians. The study registered at the South African National Clinical Trials Register (DOH-27-0710-1957; http://www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx).

Selection of study participants

This was a longitudinal single-site cohort study which included 98 first-episode schizophrenia spectrum disorder patients treated according to a standardised protocol over 24 months. Patients were recruited during their first hospital admission and at community clinics situated in a well demarcated catchment area of the eastern and northern districts of the Greater Cape Town municipality. These are multicultural areas with an estimated official unemployment rate of 23.9% and many barriers of access to mental health services. Inclusion criteria were: men and women, inpatients and outpatients, aged 16–45 years, experiencing a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria were a lifetime exposure to more than 4 weeks of antipsychotic medication, previous treatment with a long-acting depot antipsychotic, serious or unstable general medical condition and intellectual disability.

Substance use

We included patients with substance use but excluded those who met the DSM-IV-TR criteria for substance abuse or dependence disorder. Urine toxicology screening for cannabis, methaqualone and methamphetamine was conducted at baseline and at three-monthly intervals over the 24 months of treatment.

Alcohol use was assessed using a self-report questionnaire based on the CAGE criteria.[29]

Antipsychotic treatment

There was a one week lead-in period of oral flupenthixol 1–3 mg per day followed by long-acting flupenthixol decanoate injections every two weeks for the duration of the study. The starting dose of flupenthixol decanoate was 10 mg two-weekly intramuscular injection (IMI), with six weekly increments of 10 mg two weekly IMI permitted, to a maximum of 30 mg two-weekly IMI. A starting dose of 5 mg 2-weekly was allowed for patients aged 18 years or younger. Additional oral flupenthixol tablets were prescribed at the discretion of the investigator for acute exacerbation of psychotic symptoms between visits. Investigators were encouraged not to increase the dose of flupenthixol decanoate too rapidly, but rather prescribe lorazepam up to 12 mg during the acute phase and thereafter up to 4 mg per day, for agitation. Prohibited medications included other antipsychotics, mood stabilisers and psychostimulants. No additional structured psychosocial interventions were routinely provided.

Clinical assessments

Patients were assessed and diagnosis confirmed using the Structured Clinical Interview for DSM-IV (SCID).[30]

Assessment of psychopathology, functioning and quality of life

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS).[31] using the eight previously defined "core symptom" items[3] to assess psychopathology changes over time and to define remission.

We also used factor-analysis derived domains for positive, negative, disorganised and excitement/hostility symptoms at endpoint.[32] Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS).[33] Functionality was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS)[34] derived from the Global Assessment of Functioning Scale.[35] SOFAS estimates the overall level of social and occupational functioning at the time of assessment, and rates social and occupational functioning on a continuum from grossly impaired functioning (1–10) to superior functioning (91–100). The impairment must be a direct consequence of mental and physical health problems, but is not directly influenced by the overall severity of the individual's symptoms. The validity and reliability of this scale have been verified.[36,37] Patient rated QOL was assessed with the World Health Organization Quality of Life-Bref (WHOQoL-Bref) questionnaire, which comprises 24 items grouped into four domains, namely physical, psychological, social and environmental, and two individual items for overall perception of QOL and satisfaction with general health. The WHOQoL-Bref is the most frequently used QoL-instrument in studies investigating patients with schizophrenia[19] and good to excellent reliability and validity has been reported.[38]

Recovery criteria

We defined recovery according to symptom remission, clinician rated social and occupational functioning and patient-rated overall QOL. Symptom remission was defined according to the RSWG criteria, comprising a score of mild at most on each of 8 PANSS items considered to represent core features of schizophrenia, in the positive, negative and disorganised domains. Additional requirements for symptom remission are that symptoms do not interfere significantly with functioning and are present for at least 6 months.[3] Functional remission was defined as a SOFAS score of 61 or higher (some difficulty in social, occupational, or school functioning, but generally functioning well, has some meaningful interpersonal relationships) as previously described.[39,40] For QOL, we used the item rating an individual's overall perception of QOL and selected a score of 4 (good) or 5 (very good) to qualify for recovery.[7] We chose a single item global rating for QOL to reduce effects of sociocultural factors, as well as to reduce the number of variables.

Additional assessments

We assessed neurological soft signs with the Neurological Evaluation Scale (NES),[41] insight with the Birchwood Insight Scale (BIS),[42] premorbid functioning with the Premorbid Adjustment Scale (PAS),[43] and cognitive performance with the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery (MCCB).[26]

Rater training and reliability

Psychiatrists rated the PANSS, CDSS, ESRS and SOFAS. A comprehensive rater training by a series of videotaped and live clinical interviews was conducted prior to rating patients in the study and each rater was required to reach a score of 0.75 for the inter-rater correlation coefficient. The MCCB was carried out by research psychologists with a masters degree minimum level of qualification.

Statistical analyses

For changes in the recovery domains over time: linear mixed-effect models for continuous repeated measures (MMRM) were constructed to assess the changes in PANSS core items total,[3] SOFAS and WHOQOL-BREF patient-rated overall QOL scores over time, with age and sex as covariates. Within analyses, Fisher's Least Significant Difference (LSD) post-hoc tests were used to compare the means between visits.

For endpoint analyses. Endpoint scores were calculated by last observation carried forward (LOCF). We only included patients who had completed at least six months of treatment, as our longitudinal evaluations indicated that the bulk of the improvements occurred during this period. Cohen's d effect sizes were calculated for score changes from baseline to endpoint from the means and standard deviations. Pearson correlation coefficients were calculated to assess the linear relationship between the PANSS core items total, SOFAS and WHOQOL-BREF patient-rated overall QOL scores at end-point.

For predictor analyses. To select variables for our regression models we used T-tests for continuous variables and Chi-squared tests for categorical variables to compare those meeting recovery criteria with the rest of the

group. Differences at the $p = 0.1$ significance level were used to select predictor variables for logistic regression with recovery (yes/no) as the dependent variable.

We constructed similar logistic regression models for dependent variables of PANSS remission status, SOFAS remission status and WHOQOL-BREF patient-rated QOL.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

R.E., L.P., L.A. and B.C. were responsible for the study conception and design. S.K., F.S., S.D.P. and H.L. were responsible for collection, extraction and coding of data included in the study. Robin Emsley provided the analysis and interpretation. Lebogang

Phahladira and Robin Emsley drafted the manuscript, and all other authors provided critical comments. All authors provided intellectual contribution and approved the final manuscript.

COMPETING INTERESTS

R.E. has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka. B.C. has received speakers fees from Cipla, Lundbeck, and Sanofi. L.P., H.L., F.S., S.D.P., L.A. and S.K. declare that they have no conflicts of interest.

ADDITIONAL INFORMATION

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CHAPTER 4

The course and concomitants of depression in first-episode schizophrenia spectrum disorders: A 24-months longitudinal study. *This first-author manuscript was published in Psychiatry Research*

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The course and concomitants of depression in first-episode schizophrenia spectrum disorders: A 24-month longitudinal study

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ABSTRACT

Depressive symptoms are common in schizophrenia and have been associated with both favourable and unfavourable outcomes. We studied the longitudinal course of depressive symptoms and explored their temporal relationships with other manifestations of the illness and its treatment. This longitudinal cohort study included 126 antipsychotic naïve or only briefly treated patients with first-episode schizophrenia spectrum disorders treated with a long-acting antipsychotic over 24 months. Depressive symptoms were assessed at three monthly intervals using the Calgary Depression Scale for Schizophrenia and changes over time were assessed using linear mixed-effect models for continuous repeated measures. Depressive symptoms were most prominent at baseline with highly significant reductions during the first three months of treatment and maintenance of improvement thereafter. Most improvement occurred with antipsychotic treatment alone, with few patients requiring additional antidepressants. We also found that depressive symptoms were associated with positive symptoms, better insight and poorer quality of life, but not with negative symptoms, extrapyramidal symptoms, substance use or cumulative antipsychotic dose.There were few differences between patients who met criteria for depression during the acute phase of treatment and those in the post-acute phase.

1. Introduction

Depressive symptoms are recognized as a discrete symptom domain in schizophrenia (Siris et al., 2001; Chiappelli et al., 2014), and their importance is underlined by the fact that they are rated by patients as the major determinant of illness severity (Fervaha et al., 2015) Depressive symptoms are described on average in about 25% of patients with schizophrenia and may occur at any phase of the illness (Siris, 2000; Buckley et al., 2009). First-episode psychosis studies report prevalence rates ranging between 14% and 45% at baseline (Upthegrove et al., 2017; Coentre et al., 2017) and upwards of 22% of patients are still depressed in follow-up studies (Upthegrove et al., 2010, Cotton et al., 2012; Sonmez et al., 2016). Depressive symptoms may accompany an acute psychotic episode, persist following resolution of psychosis or may emerge without concomitant psychotic symptoms (post-psychotic depression) (Cotton et al., 2012; Chiappelli et al., 2014; Kjelby et al., 2018).

Previous studies reported that during acute episodes, depressive symptoms correlated positively with psychotic symptoms (Emsley et al., 1999; Kjelby et al., 2018) and resolved with antipsychotic treatment (Koreen et al., 1993; Iqbal et al., 2000; Oosthuizen et al., 2006). However, for stable patients, depressive symptoms are often independent of other symptom domains (Baynes et al., 2000; Krynicki et al., 2018) and may represent trait features of the illness (Chiappelli et al., 2014), requiring additional therapeutic interventions. Historically, mood symptoms in schizophrenia were regarded as a favourable prognostic indicator; however, recent studies suggest that depressive symptoms may be associated with a poorer quality of life (Gardsjord et al., 2018), poor treatment response, suicide, substance abuse (Conley et al., 2007) and more frequent hospital admissions (Buckley et al., 2009).

Depression in schizophrenia has been associated with an older age at onset of illness, unemployment, being single (Bottlender et al., 2000), female sex, persistent alcohol use, poor social functioning in childhood (Romm et al., 2010) and a longer duration of untreated psychosis (DUP)

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(Sonmez et al., 2016). The negative association of depression and quality of life is well described (Rocca et al., 2009; Gardsjord et al., 2018; Watson et al., 2018), although studies focusing primarily on this relationship are sparse (van Rooijen et al., 2019).

Another fairly consistently reported finding is that better of levels of insight are associated with depressive symptoms in schizophrenia (Misdrahi et al., 2014; Belvederi Murri et al., 2015). Identifying depressive symptoms may be difficult. Clinicians need to differentiate them from the negative symptoms of schizophrenia and from antipsychotic induced extrapyramidal symptoms (Tollefson et al., 1998; Oosthuizen et al., 2006). There are multiple possible causes of depression in schizophrenia, including a psychological reaction to the illness and its implications (Birchwood et al., 1993), secondary to substance abuse (Tollefson et al., 1998), a direct effect of antipsychotics - so-called neuroleptic dysphoria, possibly linked to their D2 blocking effects on frontal reward pathways (Voruganti and Awad, 2004a) or an independent comorbid major depressive disorder (Harrow et al., 1994). Also, it has been proposed that, rather than a separate entity, depressive symptoms represent a core component of the symptom expression of schizophrenia (Johnson, 1981; Koreen et al., 1993).

In summary, previous fairly extensively reported research, including longitudinal studies of depressive symptoms in first episode psychosis, (Koreen et al., 1993; Sands and Harrow, 1999; van der Heiden et al., 2005; Sonmez et al., 2013; Sonmez et al., 2016), reported varied findings in respect of baseline predictor variables, prevalence, trajectory of symptoms and relationship with other outcome measures. Interpreting these findings and those of prior studies investigating depression in schizophrenia and related psychotic disorders is complicated by various methodological limitations, including a lack of appropriate instruments to assess depression and other outcome domains, inclusion of patients at varying phases of illness and different degrees of prior antipsychotic exposure, non- standardized treatments, varying follow up periods and reliance on retrospective information. Other important possible confounding factors including substance abuse and treatment adherence were often not considered.

To address these limitations, we conducted a study in previously antipsychotic naïve or only briefly treated patients with a first episode of schizophrenia spectrum disorders (FES) who were treated with a long-acting antipsychotic according to a set protocol over 24 months, and were repeatedly assessed at regular timepoints with reliable and validated measures of depression and other clinical outcome domains. Our overall aim was to assess the prevalence, trajectory, clinical concomitants and predictors of depressive symptoms in FES.

2. Methods

2.1. Study design

Patients were recruited from a well demarcated catchment area in the Greater Cape Town Municipality, including district hospitals and community clinics. We included males and females, aged 16 to 45, in- or outpatients who met the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (Association, 1994) diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder. We excluded those individuals who met DSM-IV-TR criteria for substance abuse or dependence disorder, had a lifetime exposure to more than four weeks of antipsychotic medication, were previously treated with a long-acting antipsychotic, were known to have a serious or unstable general medical condition, or were intellectually disabled. Approval to conduct the study was obtained from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences. Written informed consent was obtained from all patients or their legal guardians. Patients assented in cases where we obtained legal guardian consent.

2.2. Treatment protocol

The 24-month open label treatment period was preceded by a washout phase of up to seven days during which all psychotropic medications were discontinued, and 1-week lead-in period of oral flupentixol at 0.5 - 4 mg per day as a test dose for hypersensitivity. During the treatment phase, patients were commenced on 5 - 10 mg two weekly flupentixol decanoate intramuscular injection (IMI), with six weekly increments of 10 mg two weekly increments permitted, to a maximum of 30 mg two weekly IMI. Dosing was flexible throughout the treatment period and adjusted according to patient response and adverse effects. The lowest effective dose was prescribed throughout. Concomitant use of other antipsychotic medication, mood stabilizers, psychostimulants and long-acting benzodiazepines was not permitted. Anticholinergic medication was allowed to treat extrapyramidal symptoms, only if reduction in trial medication was not effective. Low dose lorazepam was permitted to treat agitation provided it was used for a short duration.

We calculated the cumulative antipsychotic dose, expressed as flupenthixol milligram equivalents, according to consensus-derived guidelines for dose equivalencies (Gardner et al., 2010)

2.3. Assessments

Participants were assessed with the Structured Clinical Interview for DSM-IV (SCID) (First, 1994) and diagnosis was made by consensus by the study clinicians. Diagnoses were reviewed and revised by the investigators throughout the study. Sociodemographic variables were collected during the interviews with patients, relatives and caregivers. The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) was used to assess depressive symptoms. It was designed to evaluate depression in patients with schizophrenia and is reported to differentiate between depressive, negative and extrapyramidal symptoms (Addington et al., 1994). It is reliable and valid when compared to other instruments measuring depression in schizophrenia (Lako et al., 2012). Depression was assessed at baseline, week 2,4, 6, month 3, 6, 9, 12, 15, 18, 21 and 24. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). We used factor-analysis derived domains to assess the positive, negative, disorganized and excitement/hostility symptoms (Emsley et al., 2003). Insight was measured using the Birchwood Insight Scale (BIS), (Birchwood et al., 1994) with three subscales, i.e. symptom attribution, illness awareness, and recognition of the need for treatment, in addition to a total score. Premorbid functioning was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). Functionality was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS) (Association, 1994). Patient-rated quality of life was evaluated using the World Health Organization Quality of Life-Bref (WHOQoL-Bref) (Mas-Exposito et al., 2011). DUP was estimated as the time from the first onset of continuous psychotic symptoms to the initiation of treatment.

2.4. Statistical analysis

All participants who underwent full evaluation at baseline and received at least one dose of study medication were included in the analyses which were conducted using Statistica version 13 software (*Dell*). We assessed the distribution of the data by inspecting histograms and normal probability plots. Normally distributed data are report as the mean and standard deviation (SD) and skewed data are reported as the median and interquartile range (IQR).

Change in depression scores over time: A linear mixed-effect model for continuous repeated measures (MMRM) was constructed to assess the changes in CDSS Total score at baseline and three-monthly intervals (13 timepoints), with age and sex as covariates. We used restricted maximum likelihood estimation for fitting the linear mixed models. All of the variables were entered as fixed effects, except participant number,

which was entered as a random effect. CDSS Total score was the dependent variable, modelled together with time as a repeated measure, and both were entered as grouping variables. Within analyses Fisher's Least Significant Difference (LSD) tests were used for post-hoc comparisons of scores between visits.

Relationships between depression and other outcome measures over time: In a further MMRM we investigated the relationships over time (five timepoints, at months 0, 6, 12, 18, 24) between depressive symptoms and changes in psychopathology, insight, functionality, quality of life and extrapyramidal side-effects. CDSS Total score was the dependent variable and time was entered as a grouping variable. PANSS Total score, BIS Total score, SOFAS score, WHOQoL-Bref patient-rated overall QoL (item 25) and ESRS Total score were entered as time-dependent fixed effects, age and sex as time-invariant covariates and participant number as a random effect. Bonferroni correction was applied for the multiple comparisons for the fixed effects and the corrected significance level was $p=0.01$

Comparing those with depression versus those without a depressive disorder: In accordance with previous studies (Maggini and Raballo, 2006; Schennach-Wolff et al., 2011) we used a cut off score of ≥ 6 on the CDSS scale to define depression in our patients. We grouped patients into those who experienced depression at any time during the 24-month treatment period, and those who did not. As a first step we used *t*-tests and Chi-squared tests to compare the groups for demographic and baseline clinical features.

We selected variables that were significantly different ($p<0.05$) and entered them into a logistic regression model, with group status (depressive disorder yes/no) as the dependent variable.

Acute vs. post-acute depression: To assess whether the patients with depression only in the acute treatment phase differed from those with depression in the post-acute phase, we divided the patients with depression into those in whom it occurred at any time during the first 12 weeks (acute) and those in whom depression emerged or persisted beyond 12 weeks (post-acute). We compared demographic details and baseline and endpoint clinical features with *t*-tests and Chi-squared tests. We then entered the variables that were significantly different ($p<0.05$) into a logistic regression model, with group status (acute vs. post-acute depressive disorder) as the dependent variable.

3. Results

3.1. Patient characteristics

The study flow diagram is provided in Fig. 1. Ninety-four (74%) of the 126 participants were male. Their mean±SD age at study entry was 24.1±6.6 years, while the highest school grade was 9.7± 2.2 years. The patients were from a diverse ethnic background (Mixed ancestry: 98 [78%]; Black: 18 [14%]; white: 10 [8%]). Eighty-four patients (66%) met the DSM-IV TR diagnosis criteria for schizophrenia and forty (32%) were diagnosed with schizophreniform disorder. Only two (2%) met the DSM-IV-TR diagnostic criteria for schizoaffective disorder. The median (IQR) DUP was 22 (7.5–39.4) weeks and the mean baseline PANSS total score was 94.8 ± 16.5. Fifty (40%) patients had a history of substance use and fifty-six (44%) had previous exposure to antipsychotic medication, for a mean duration of 9.4 ± 7.0 days. For the study medication, the mean modal antipsychotic dose was 11.7 ± 3.8 milligrams of flupenthixol decanoate 2 weekly, with a mean duration of treatment of 68.7 ± 41.3 weeks. Seven patients were prescribed antidepressant medication and the mean time to initiation was 18.5 ± 9.9 weeks. Sixty-six patients (52%) completed the 24 months of treatment.

3.2. Changes in CDSS scores over 24 months

The MMRM analysis revealed highest CDSS scores at baseline, with time effects characterised by reductions that persisted over the course of the study (Fig. 2). Pronounced reductions occurred from baseline to

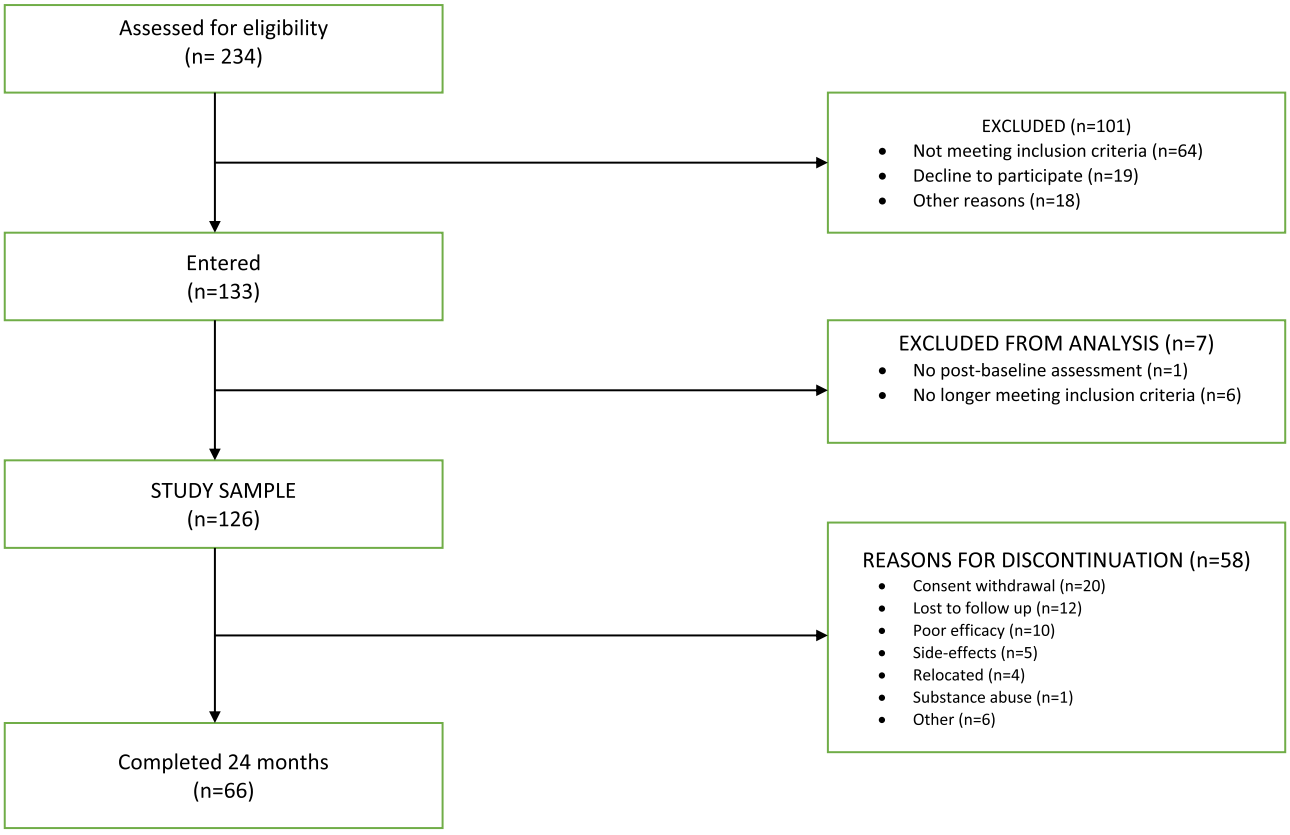

Fig. 1. Study flow diagram.

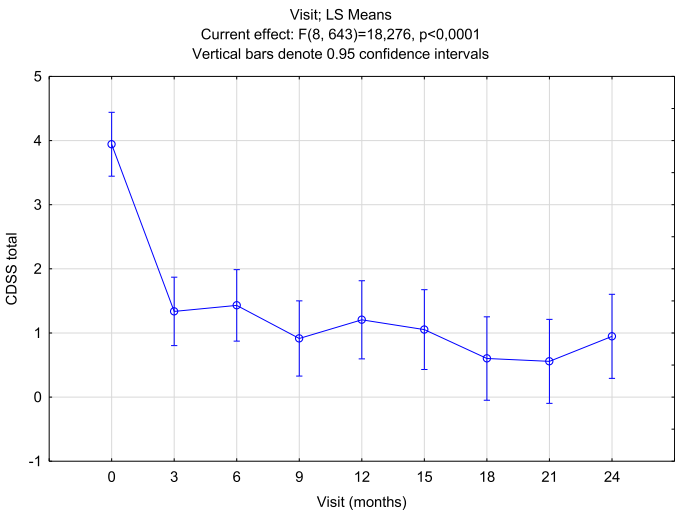

Fig. 2. MMRM least square means for CDSS total scores at 3 monthly intervals over the 24 months of treatment.

month 3 (-2.61, 95% CI = -3.24 to -1.97, $p<0.0001$), with no further improvements after that ($p>0.05$) Results of the post-hoc LSD tests are provided in Supplementary Table 1. There were significant fixed effects for time ($F = 17.63$, $p < 0.0001$) and gender ($F = 7.05$, $p = 0.008$), but not for age ($F = 1.57$, $p = 0.21$).

3.3. Relationships between depression and other outcome measures over time

There were significant time-dependent fixed effects on CDSS Total change scores for PANSS Total ($F = 58.46$, $p < 0.0001$) and BIS Total ($F = 7.88$, $p = 0.006$), but not for SOFAS ($F = 0.81$, $p= 0.3681$), WHOQoL-Bref overall QoL ($F = 1.76$, $p = 0.1865$) or ESRS Total ($F = 1.43$, $p = 0.2325$) scores. To further interrogate which components of these outcome variables were associated with CDSS Total score changes over time we conducted an additional post-hoc MMRM analysis, applying a similar model to those described above.

We entered the domain/subscale scores for PANSS, BIS and WHOQoL-Bref as time-dependent fixed effects. Bonferroni corrected significance level was set at p=0.0045. For the PANSS factor-analysis derived domains we found a significant effect for the positive ($F = 54.36$, $p < 0.0001$), but not for the negative ($F = 0.45$, p = 0.5032), disorganised ($F = 2.84$, $p = 0.0937$) or excitement/hostility ($F = 2.02$, $p = 0.1571$) domains. For the BIS there was a significant effect for Subscale 2 (Awareness of illness) ($F =20.08$, $p < 0.0001$) but not for Subscales 1 (Awareness of symptoms) ($F = 0.03$, $p = 0.8529$) or Subscale 3 (Recognition of the need for treatment) ($F = 1.26$, $p = 0.2631$). For the WHOQoL-Bref there were significant effects for the physical ($F = 12.50$, $p = 0.0005$) and psychological ($F = 14.38$, $p = 0.0002$) domains, but not the social ($F = 0.85$, $p = 0.3568$) and environment ($F = 0.51$, $p = 0.4781$) domains.

3.4. Prevalence and predictors of depressive disorder in first-episode schizophrenia spectrum disorders

Of the 126 participants, 49 (39%) met criteria for depression at some stage during the 24 months of treatment. Table 1 provides the demographic, baseline clinical and antipsychotic exposure details and the univariate comparisons of those who experienced depression (n=49) versus those who did not (n=77). Compared to the rest of the sample, those who experienced depression had higher baseline scores on BIS subscale 2 (awareness of illness), subscale 3 (recognition of the need for treatment) and total score. They also had poorer quality of life in the WHOQoL-Bref psychological and social relationship domains, and

Table 1
Demographic, baseline clinical and antipsychotic exposure details for the 49 patients who experienced an episode of depression* at any stage compared to the 77 who did not.

	Depression (n=49, 39%)	No depression (n=77, 61%)	Test value**	*p*-value
Age in years, mean (SD)	24.31(6.83)	23.92 (6.49)	0.32	0.7514
Sex, n (%)				
Male	32 (65%)	61 (78%)	2.99	0.0858
Female	17(35%)	16 (22%)		
Ethnicity, n (%)			4.63	0.0980
Mixed	43(88%)	55 (71%)		
Black	4(8%)	14 (18%)		
White	2 (4%)	8 (11%)		
Highest school grade passed, mean (SD)	9.77 (2.02)	9.68 (2.19)	0.23	0.8185
DSM-IV-TR diagnosis, n (%)			4.44	0.1083
Schizophrenia	29 (59%)	55 (71%)		
Schizophreniform	18 (37%)	22 (29%)		
Schizoaffective	2(4%)	0		
DUP weeks, median (IQR)	20 (6.0-38.58)	21.58 (7.58-40.58)	1879	0.9868
Patients on any prior antipsychotic medication, n (%)	20 (41%)	36 (47%)	0.43	0.5132
Duration of treatment days, mean (SD)	5.42 (6.55)	6.20 (7.40)	-0.50	0.6159
Cumulative antipsychotic dose received over the study, flupenthixol mg equivalents, mean (SD)	1428.25 (932.45)	1526.58 (1005.01)	-0.55	0.5830
History of substance abuse, n (%)	17 (35%)	33 (43%)	0.68	0.4089
PANSS, mean (SD) Total score	96.49 (18.20)	93.69 (15.31)	0.93	0.3543
Positive	17.67 (3.41)	17.30 (3.26)	0.62	0.5382
Negative	19.73 (6.62)	19.95 (4.96)	-0.21	0.8369
Disorganised	11.88 (3.14)	12.06 (3.00)	-0.34	0.7376
Excitement/hostility	7.94 (3.83)	7.30 (3.81)	-1.49	0.1401
SOFAS, mean (SD)	42.00 (11.64)	45.34 (11.38)	-1.59	0.1141
WHOQOL-BREF, mean (SD) Physical,	11.82 (2.40)	12.03 (2.37)	-0.48	0.6319
	12.01 (2.71)			
	10.81 (3.58)			
	11.10 (2.94)			
Psychological		13.47 (2.62)	-2.97	0.0036
Social		12.50 (4.42)	-2.22	0.0285
Environment		12.04 (3.54)	-1.53	0.1285
PAS, mean (SD) Total childhood	0.24 (0.15)	0.23 (0.16)	0.19	0.8467
	0.28 (0.15)	0.30 (0.16)		
	0.32 (0.18)	0.39 (0.19)		
	0.33 (0.22)	0.40 (0.24)		
	0.43 (0.18)	0.50 (0.20)		
	0.32 (0.13)	0.37 (0.15)		
Total early adolescence			-0.75	0.4537
Total late adolescence			-1.89	0.0607
Total adult			-1.42	0.1594
General			-1.96	0.0529
Overall			-1.72	0.08828
BIS, mean (SD)	2.36 (0.99)	2.13 (1.03)	1.19	0.2352
Symptom attribution	2.25 (1.18)	1.25 (1.26)		
	2.18 (0.94)	1.85 (0.85)		
	6.80 (2.04)	5.23 (2.00)		
Illness awareness			4.25	0.0001
Need for treatment			2.00	0.0483
Total			4.09	0.0001

SD, standard deviation; IQR, interquartile range; PANSS, positive and negative syndrome scale PAS, premorbid adjustment scale WHOQOL-BREF, World Health Organisation quality of life-BREF scale; SOFAS, social and occupational functioning assessment scale; BIS, Birchwood Insight Scale; p, significance value; T-test, for continuous variables

*Depression defined as a CDSS total score of ≥6

**test value: t, Chi square or U score for t-test, Chi square test and Mann-Whitney U test, respectively

poorer premorbid adjustment in late adolescence. For the logistic regression analysis we entered the scores for WHOQoL-Bref domains 2 (psychological) and 3 (social), BIS subscales 2 (awareness of illness) and 3 (need for treatment), PAS late adolescence score and gender. The only significant independent predictor of depression in a model that explained 30% of the variance (Nagalkirke R^2) was BIS subscale 2 (awareness of illness) (beta = 0.32, 95% CI 0.11to 0.54, $p = 0.0035$).

3.5. Acute vs. post-acute depression

Of the 49 patients with depression, 29 (59%) had an episode that occurred in the first 12 weeks of the study only, while 20 (41%) had an episode that persisted or emerged after 12 weeks of treatment. Demographic, baseline and endpoint clinical and treatment details and univariate comparisons of the two groups are provided in Table 2. The only significant differences were that those with post-acute depression had poorer quality of life in the WHOQoL-Bref Environment domain and poorer General premorbid adjustment. In the logistic regression model with acute vs. post-acute depressive disorder as the dependent variable only WHOQoL-Bref domain 4 (environment) remained as a significant predictor (beta = -1.43, 95% CI -2.68 to -0.18, $p = 0.0251$), in a model that accounted for only 8% of the variance (Nagalkerke R^2).

4. Discussion

This study is the first to prospectively assess the longitudinal course of depressive symptoms in patients with FES who received standardised treatment and in which adherence was assured with a long-acting formulation of antipsychotic medication. As such, we were able to address the potential confounding effects of illness chronicity, prior treatment exposure, and non-adherence to treatment. The latter may be particularly important, given the very high rates of non-adherence reported in FES (Coldham et al., 2002). The study provides new findings on the trajectory of depressive symptoms in FES over the first two years of treatment, and on their dynamic link with other outcome domains. We found that depressive symptoms were most prominent at baseline, with highly significant reductions during the first three months of treatment, and maintenance of improvements over the course of the study. The trajectory was similar to the improvements in core psychopathology that we observed in the same cohort and reported separately (Phahladira et al., 2020). This, together with our finding that the time-dependent PANSS Total scores, and specifically those of the positive domain, significantly predicted depression scores over time, suggests that depression in the acute phase of FES is intrinsic to psychosis rather than a separate entity.

Our findings are consistent with others reporting a link between depression and positive symptoms specifically (Norman and Malla, 1994; Emsley et al., 1999; Kjelby et al., 2018) and with previous studies (Koreen et al., 1993; Hafner et al., 2005; Oosthuizen et al., 2006; Kjelby et al., 2018) indicating that depressive symptoms at the onset of illness generally respond well to treatment with antipsychotics, without the need for concomitant antidepressant medication. Indeed, antidepressant medication was prescribed in only seven of the patients with comorbid depression. These findings would appear to contradict some previous reports of depression being associated with persistence of symptoms and poorer outcome (Tollefson et al., 1999; Reine et al., 2003; Resnick et al., 2004; Conley et al., 2007). However, this apparent discrepancy might be explained on the basis of illness phase. Our sample included only patients with a first episode of psychosis, while those studies were conducted in individuals with chronic schizophrenia. Thus, depressive symptoms in the early phase may be different to those later in the course of the illness. Indeed, in one study that included patients at different phases of illness it was found that the patients who remained depressed were all multi-episode patients (Schennach-Wolff et al., 2011).

In addition to the temporal relationship with positive symptoms, we observed significant time-dependent effects for insight impairment and quality of life on depressive symptoms. This relationship was also found in our logistic regression models predicting the presence of depression in

Table 2
Demographic and baseline clinical details for the patients with acute vs. post-acute depression*.

	Acute depression n=29 (59%)	Post-acute depression n=20 (41%)	Test value**	p-value
Age in years, mean (SD)	23.34 (7.08)	25.70 (6.36)	-1.19	0.2391
Sex, n (%) male	21 (72%)	11 (55%)	1.58	0.2081
female	8 (28%)	9 (45%)		
Highest school grade passed, mean (SD)	9.61 (1.71)	10.00 (2.45)	-0.65	0.5197
Ethnicity, n (%)			0.50	0.7774
Mixed	25 (86%)	18 (90%)		
Black	3 (10%)	1 (5%)		
White	1 (4%)	1 (5%)		
Substance use ever, n(%)	10 (34%)	7 (35%)	0.01	0.9593
DSM-IV-TR diagnosis, n (%)			2.46	0.2916
Schizophrenia	15(52%)	14(70%)		
Schizophrenifrom	12(41%)	6(30%)		
Schizoaffective	2(7%)	0		
DUP, weeks, median (IQR)	18 (5.72-37.15)	27.29 (10.57-67.22)	571.5	0.1923
Cumulative antipsychotic dose received over the study, flupenthixol mg equivalents, mean (SD)	1266.53 (970.95)	1662.71 (842.30)	-1.48	0.1456
PANSS Total and domain scores, mean (SD) Total	97.97 (18.35)	94.35 (18.22)	0.68	0.5000
Positive	17.76 (3.73)	17.55 (2.98)	0.21	0.8359
Negative	12.52 (2.90)	10.95 (3.32)	0.12	0.9073
Disorganised)	19.83 (7.00)	19.60 (6.19)	1.75	0.0860
Excitement/hostility	8.31 (4.06)	7.40 (3.49)	0.82	0.4188
CDSS total score, mean (SD)	6.52 (3.75)	7.35 (5.37)	-0.64	0.5253
SOFAS, mean (SD)	41.17 (12.29)	43.20 (10.82)	-0.60	0.5544
WHOQOL-BREF, mean (SD)	11.92	11.69	0.32	0.7510
Physical	(2.26)	(2.64)		
Psychological	12.27 (2.86)	11.67 (2.52)	0.75	0.4547
Social	11.11 (3.62)	10.40 (3.58)	0.67	0.5067
Environment	**12.02 (2.73)**	**9.85 (2.82)**	**2.66**	**0.0109**
PAS, mean (SD)				
Childhood	0.23 (0.13)	0.26 (0.16)	-0.58	0.5653
Early adolecence	0.27 (0.17)	0.29 (0.14)	-0.37	0.7100
Late adolescence	0.31 (0.17)	0.35 (0.19)	-0.75	0.4602
Adult	0.30 (0.24)	0.37 (0.19)	-0.98	0.3325
General	**0.38 (0.17)**	**0.49 (0.17)**	**-2.05**	**0.0469**
Overall	0.30 (0.14)	0.35 (0.12)	-1.31	0.1978
BIS, mean (SD)				
Symptom attribution	2.15 (0.93)	2.63 (1.09)	-1.41	0.1676
Illness awareness	2.30 (1.22)	2.06 (1.18)	0.59	0.5598
Need for treatment	2.27 (0.93)	2.46 (1.03)	-0.59	0.5597
Total	6.72 (1.64)	7.15 (2.39)	-0.64	0.5278

SD, standard deviation; IQR, interquartile range; DUP, Duration of Untreated Psychosis; PANSS, Positive and negative syndrome scale; CDSS, Calgary depression scale for schizophrenia; SOFAS, Social and occupational functioning assessment scale; WHOQOL-BREF, World Health Organisation quality of life-BREF scale; PAS, Premorbid adjustment scale; BIS, Birchwood insight scale.
*Depression defined as a CDSS total score of ≥6
**test value: t, Chi square or U score for t-test, Chi square test and Mann-Whitney U test, respectively

our sample. These results are consistent with the so-called "insight paradox" (Lysaker et al., 2007), i.e. that better insight in schizophrenia is associated with depression and poorer quality of life, although not all studies have found this association (Belvederi Murri et al., 2015), including a recent meta-analysis (Subotnik et al., 2020). Various psychological explanations have been proposed for the inverse relationship between insight and depression. For example, patients with better insight may have less denial of their illness and be more aware of the implications and consequences of the illness (McGlashan and Carpenter, 1976). The effect size of the association is reported to be stronger in longitudinal studies, and when potentially confounding and moderating factors are taken into account (Belvederi Murri et al., 2016) which is borne out by our findings of a strong association even after considering multiple other factors.

Studies have reported a negative association between QoL and depression in schizophrenia (Reine et al., 2003; Resnick et al., 2004; Conley et al., 2007), although the nature of the association was not previously explored. Two recent studies used structural equation modelling in longitudinal samples to investigate this relationship, but reported different findings. In the first study, van Rooijen et al (2019) reported that depression had a direct negative impact on QoL. They also found that social functioning was directly associated with QoL, and other symptoms influenced QoL indirectly, via social functioning. In the second study, Ehrminger et al (2019) investigated the relationships between insight, QoL, depression and suicidality. They found that the best fitting model for the temporal sequence was a unidirectional relationship, with better insight predicting poorer QoL, which in turn predicted increased depression, followed by increased suicidality. Our study was not designed to establish directionality of the association between depression and QoL. However, we found that in addition to poorer baseline QoL predicting depressive symptoms over time, there was also a time-dependent effect for QoL on depressive symptoms. Also, our results suggest that this effect is restricted to the physical and psychological QoL domains, and not the social and environmental domains. However, the pathways to subjective QoL in schizophrenia are not clear cut because of the complex interplay between clinical, social and environmental variables (Ehrminger et al., 2020).

Some of the diversity in reported rates and associations of depression in schizophrenia might be ascribed to difficulty in differentiating it from other symptoms. This is particularly the case for negative symptoms, where so-called secondary negative symptoms may be a consequence of depression (Barnes et al., 1989). Some of the inconsistencies may be related to the instruments used to assess negative and depressive symptoms. For example, using the original PANSS negative subscale to assess negative symptoms may not be optimal. Numerous factor analyses have confirmed a five-factor model as the best fit for the PANSS, with the negative factor differing on several items from the negative subscale (Emsley et al., 2003). Also, our use of the CDSS to assess depressive symptoms enhanced our ability to distinguish between depressive and negative symptoms. The CDSS was developed specifically to assess depression in schizophrenia, and to distinguish between secondary negative symptoms as a result of depression and primary negative symptoms (Addington et al., 1996). Similarly, it may be difficult to distinguish depression from extrapyramidal symptoms related to antipsychotic treatment. Antipsychotic induced akinesia or akathisia (Van Putten and May, 1978) may mimic depression (Van Putten, 1975). We were able to address this, and we did not find a significant effect for ESRS scores over time, suggesting that in our sample the depressive symptoms could not be accounted for by extrapyramidal symptoms. Furthermore, we did not find that substance use was a confounder in our sample (Tollefson et al., 1998)

Finally, we did not find evidence for a direct depressogenic effect of antipsychotic treatment. Using a long-acting injectable formulation of antipsychotic enabled us to quantify the cumulative antipsychotic dose received by each of our participants with some precision. The absence of a significant association in our sample should not however be generalised to other populations. Neuroleptic dysphoria is underrecognised in clinical settings, and in addition to inducing an unpleasant dysphoric mood is characterised by cognitive blunting and a loss of motivation (Voruganti and Awad, 2004b). It is associated particularly with first-generation antipsychotics, and has been linked to their high striatal D2 binding capacity (Bressan et al., 2002) and to their blocking of D2 frontal reward pathways (Tollefson et al., 1998). While flupenthixol is a first generation antipsychotic, it has a receptor binding profile that is similar to several newer generation antipsychotics (de Wit, 2010), and in any event, was used in very low dosage in our study. Thus, neuroleptic dysphoria may be more apparent in settings where patients receive other first generation antipsychotics, and where higher doses are prescribed.

We did not find strong evidence to suggest that depression in the acute phase of illness only is different to that occurring outside of the acute psychotic episodes. Once again, this may be due to the fact that our study was limited to the first two years of treatment. We found few differences between those who met criteria for depression during the acute phase of treatment and those in the post-acute phase. In our univariate analysis, the patients with acute depression had a shorter duration of illness, better premorbid level of functioning and better baseline quality of life related to the environment, but the only independent predictor of acute depression that retained significance in the regression model was the baseline WHOQoL-Bref environment domain, which is consistent with findings reported in a previous cross-sectional study (Sim et al., 2004).

Given the considerable evidence that depression in chronic schizophrenia predicts poorer outcomes (Tollefson et al., 1999; Reine et al., 2003; Resnick et al., 2004; Conley et al., 2007), it is plausible that a more persistent depressive syndrome that negatively impacts upon outcome emerges at a later stage, and is associated with illness chronicity, relapse and emergent refractoriness. Contributions of factors such as adherence, substance abuse and antipsychotic medication effects could be explored in this population in future studies. Also, the role of psychosocial stressors should be considered, particularly in relation to the more prominent depressive symptoms in acute illness. Experiencing psychotic symptoms for the first time may be distressing and early psychosis can be accompanied by disruptions in work, school and relationships. Furthermore, hospitalization can be disruptive and stressful.

The design of our study allowed us to address several important methodological shortcomings which defined previous studies. By restricting the study to first-episode patients who were treated for less than four weeks, we minimised confounding effects of disease chronicity and previous treatment. The standardised treatment protocol addressed confounding effects of antipsychotic heterogeneity, and treatment with a long-acting formulation allowed accurate assessment of adherence and antipsychotic load. Further, comprehensive, repeated assessments allowed us to investigate changes over time in depression and other outcome domains. Several important considerations limit the generalisation of our findings. First, the study duration of two years does not provide an indication of the longer-term outcomes. Second, as with other longitudinal clinical studies in schizophrenia, participant attrition was considerable. Third, most of our subjects were recruited from a socio-economically deprived community. Fourth, this convenience sample of patients who presented to health care services may not be representative of the larger population. Fifth, the use of a single antipsychotic, while removing the effects of treatment heterogeneity, means that our findings may not be applicable to patients treated with other antipsychotics. Last, an additional clinician rated insight scale may have added value, as patients may have interpreted the self-rating BIS as referring to depressive rather than psychotic symptoms.

In conclusion, depressive symptoms were common at the onset of treatment but appear state-related insofar as they resolved with antipsychotic treatment.

Author statement

Robin Emsley, Lebogang Phahladira, Laila Asmal and Bonginkosi Chiliza were responsible for the study conception and design. Sanja Killian, Freda Scheffler, Stefan Du Plessis and Hilmar Luckhoff, Retha Smit and Chanelle Buckle were responsible for collection, extraction and coding of data included in the study. Robin Emsley provided the analysis and interpretation. Lebogang Phahladira and Robin Emsley drafted the manuscript, and all other authors provided critical comments.

All authors provided intellectual contribution and approved the final manuscript

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request

Declaration of Competing Interest

Robin Emsley has received speakers fees and participated in advisory boards from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck. Bonga Chiliza has received speakers fees from Cipla, Lundbeck, and Sanofi. Lebogang Phahladira, Laila Asmal, Hilmar Lückhoff, Stefan du Plessis, Freda Scheffler, Retha Smit, Chanelle Buckle and Sanja Kilian declare that they have no conflicts of interest

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.113767.

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CHAPTER 5

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The trajectories and correlates of two negative symptom subdomains in first-episode schizophrenia

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ABSTRACT

Background: Recent studies suggest a two-factor structure for negative symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS) in schizophrenia, namely experiential and expressive subdomains. Little is known about their clinical correlates and treatment trajectories.
Objectives: We sought to replicate the two factor-analysis derived subdomains for PANSS negative symptoms in schizophrenia and to assess their independent demographic, premorbid and treatment-related characteristics.
Methods: This was a longitudinal study of 106 minimally treated participants with a first episode of a schizophrenia spectrum disorder who received treatment with flupenthixol decanoate 2-weekly injections over two years. Factor analysis was used to characterize the PANSS negative symptom subdomains and linear mixed-effect models for continuous repeated measures were constructed to assess the temporal relations between the negative symptom subdomains and premorbid and treatment related variables.
Results: Factor analysis confirmed a two-factor solution for experiential and expressive subdomains of negative symptoms, although they were strongly correlated. The treatment response trajectories for the two subdomains did not differ significantly, and neither subdomain was significantly associated with our premorbid variables. We found significant main effects for disorganised symptoms and extrapyramidal symptoms on the expressive subdomain, and for disorganised symptoms and depressive symptoms on the experiential subdomain. Post-hoc testing indicated that reductions in HDL-cholesterol levels were associated with less improvement in both expressive and experiential subdomain scores.
Conclusion: The two negative symptom subdomains are closely related, have similar premorbid correlates and respond similarly to antipsychotic treatment. Depression affects the experiential subdomain, whereas extrapyramidal symptoms affect the expressive subdomain.

1. Introduction

Negative symptoms are a core feature of schizophrenia (Carpenter et al., 1988) and may represent a separate disease entity within the syndrome (Kirkpatrick et al., 2001). There is growing research interest in negative symptoms owing to their association with markers of poor outcome (Albert et al., 2011; Chang et al., 2019; Buchanan, 2007; Katschnig, 2000) and a dearth of effective therapeutic interventions (Bucci et al., 2020; Fusar-Poli et al., 2015). Studies aimed at improving assessment of the symptom expression of schizophrenia have explored the factor structure of negative symptoms and the focus has shifted from a unitary to a two-factor model as the best fit. The model comprises an experiential subdomain consisting of avolition, asociality and anhedonia, and an expressive subdomain, consisting of blunted affect and alogia (Kirkpatrick, 2014; Liemburg et al., 2013; Messinger et al., 2011). Strauss et al. (2013) suggested that the two subdomains follow distinct trajectories over the course of illness and are associated with different premorbid and clinical variables, and as such may represent separate therapeutic targets. Research comparing the treatment response and longitudinal trajectories of each of the subdomains is sparse. Previous findings suggest that the experiential deficits are more prevalent during the early phase of illness (Lyne et al., 2015), and are significantly related to a longer duration of untreated psychosis (DUP) (Malla et al., 2002) as well as poorer functional outcome (Strauss et al., 2013) while

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expressivity symptoms persist over time (Kelley et al., 2008; Malla et al., 2004).

The overall aim of the present study was to replicate the two-factor model for negative symptoms in schizophrenia, and to explore the associations of the two subdomains with demographic, premorbid and treatment related variables. We hypothesised that the subdomains would have different demographic, premorbid and treatment related correlates. Specifically, we hypothesised that experiential deficits would show closer associations with state-related features of the illness such as depressive and positive symptoms, whereas expressive deficits would have stronger associations with trait-related features of the illness, such as poorer premorbid adjustment (Bucci et al., 2016) and more prominent neurological abnormalities (Peralta et al., 2014).

2. Material and methods

2.1. Study design and participants

This prospective, two-year longitudinal study included 126 patients with first-episode schizophrenia spectrum disorders who were recruited from first admissions to hospitals and community clinics in the metro and rural areas of North-Eastern Cape Town, the Winelands, and West Coast. Inclusion criteria were: (1) males and females aged 16 to 45, (2) meeting the Diagnostic and Statistical Manual for Mental Disease, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association, 1994) diagnostic criteria for schizophrenia, schizophreniform and schizoaffective disorder based on the Structural Clinical Interview for DSM-IV (SCID)-Patient Edition. We excluded participants who 1) met the DSM-IV TR criteria for substance abuse or dependence disorder, 2) had a lifetime exposure to more than four weeks of antipsychotic medication, 3) were previously treated with a long-acting antipsychotic, 3) were known to have a serious or unstable general medical condition, or 5) were intellectually disabled. Participants provided written, informed consent and we obtained ethics approval from the Human Research Ethics Committee of Stellenbosch University.

2.2. Clinical evaluations

At baseline, a comprehensive psychiatric and medical evaluation was performed. Psychopathology was evaluated by administering the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). We used previously described factor-analysis derived domains for positive and disorganised symptoms (Emsley et al., 2003). Premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS). The PAS assesses the degree of achievement of developmental goals across four age periods, namely childhood, early adolescence, late adolescence and adulthood, and a general score to estimate the highest level of functioning before illness onset. An overall score can be calculated by averaging the subscale scores (Cannon-Spoor et al., 1982). Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) and neurological soft sings were assessed with the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989). Patient-rated quality of life was evaluated using the World Health Organization Quality of Life-Bref (WHOQoL-Bref) (Mas-Exposito et al., 2011). Functionality was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994) following interviewing patients and informants. Duration of untreated psychosis (DUP) was estimated as the time from the onset of continuous psychotic symptoms to the initiation of treatment. Body weight was measured at baseline, months 3, 6, 9, 12, 15, 18, 21 and 24 using an electronic scale that was calibrated regularly during the study. Height was measured with a pre-fixed wall-mounted measuring tape to the nearest centimeter (cm). Body mass index (BMI) was calculated as the patient's body weight in kilograms (kg) divided by their height in meters squared (m^2). A peripheral venous blood sample was collected following an eight-hour or overnight fasting period for biochemical determination of glucose levels and lipid profiles, i.e. triglycerides, total, low-density (LDL) and high-density lipoprotein (HDL) cholesterol levels. Urine toxicology for cannabis, methaqualone and methamphetamine was performed at baseline, and again at three-monthly intervals.

2.3. Antipsychotic treatment

All participants were treated according to a standard protocol. After a week of oral flupenthixol, participants were treated with a flupenthixol decanoate injections 2-weekly for the duration of the study. The initiation dose was 10 mg 2-weekly, with 6-weekly increments of 10 mg 2-weekly intramuscular injection (IMI) as necessary, up to a maximum dose of 30 mg 2-weekly IMI. Psychiatrists prescribed oral flupenthixol, lorazepam, anticholinergics, propranolol, and antidepressants at their discretion. No benzodiazepines, propranolol or anticholinergics were permitted within the 12 h prior to assessment.

2.4. Statistical analyses

Demographic, premorbid and treatment-related variables were measured using descriptive statistics and are described as means (SD) and numbers (percentages). To explore the latent structure of the PANSS negative symptoms we conducted two factor analyses. The first was a confirmatory five-factor analysis with varimax rotation on the PANSS individual item scores. We excluded the following items that were previously identified as loading inconsistently: P6, N7, G1, G4, G5, G13 and G15 (Emsley et al., 2003). We then performed a second factor analysis, using only the items loading >0.5 on the Negative factor in the initial factor analysis. In this model we selected the factors with Eigenvalues greater than one.

A linear mixed effects model for repeated measures (MMRM) was constructed to compare the visit-wise changes from baseline for the expressive and experiential subdomain scores at 5 timepoints (months 0, 6, 12, 18 and 24) over the 24 months of treatment. The subdomains had unequal numbers of items. Therefore, to compare their relative changes over time, we calculated percentage change scores from baseline at each timepoint. Percentage change score was the dependent variable, group, visit and group*visit were main effects and patient number was entered as a random effect. Post-hoc Fisher's least significant difference tests were used to compare the two subdomain change scores at each of the timepoints. We then constructed three MMRM models to assess the fixed effects of selected demographic, premorbid and treatment-related variables on these subdomain change scores: 1) For demographics we entered age, sex, ethnicity and educational level as time-invariant predictors and adjusted for baseline subdomain scores; 2) for premorbid factors we entered family history of psychosis, obstetric complications, PAS General and Overall scores, history of recent (past 3 months) illicit substance use and DUP as time-invariant predictors. We covaried for baseline subdomain scores and ethnicity, as the latter was a significant independent predictor in the first model; 3) for Treatment-related factors we entered the total cumulative antipsychotic dose (calculated as flupenthixol mg equivalents) as a time-invariant variable, and scores at each timepoint for the PANSS positive and disorganised domains, CDSS Total score, SOFAS, WHOQoL-Bref Overall score, NES Total, ESRS Total score and BMI, all as time-dependent variables and again covarying for baseline subdomain scores and ethnicity. Finally, to explore the premorbid and treatment-related effects on the two negative symptom subdomains in more detail we conducted a secondary MMRM analysis, entering the following subscale scores as predictors: PAS childhood, early adolescence, late adolescence and adulthood, WHOQOL-Bref Physical, Psychological, Social and Environmental domains, NES sensory integration, motor coordination and motor sequencing subscales, ESRS Parkinsonism and Dyskinesia subscales and fasting blood glucose, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol. We again covaried for ethnicity and baseline scores for the dependent

variables. For the fixed effects tests, we used Benjamini-Hochberg False Discovery Rate (Benjamini and Hochberg, 1995) to correct for multiple testing. The adjusted significance level was 0.0159. For the secondary MMRM analyses the adjusted significance level was 0.0272.

3. Results

3.1. Description of the sample

Table 1 provides details of the demographic, premorbid, baseline clinical and laboratory and antipsychotic treatment exposure variables. Of the 126 participants entered, 66 completed 24 months of treatment. Reasons for dropout were: consent withdrawal (n = 20), loss to follow up (n = 12), poor efficacy (n = 10), side-effects (n = 5), relocated (n = 4), substance abuse (n = 1) and other (n = 6).

3.2. Negative symptom subdomains

The forced 5-factor solution for the PANSS items explained 61.5% of the variance. The Negative factor was the first principal component, with an Eigenvalue of 5.99, and explained 26% of the total variance. Items loading >0.5 in the Negative factor were N1, N2, N3, N4, N6, G7 and G16. The second factor analysis including only these items confirmed the two-factor model for experiential and expressive subdomains of negative symptoms (Table 2). Item N3 (poor rapport) loaded >0.5 on both factors but with a stronger loading on the expressive subdomain. Pearson correlation coefficients indicated that the two subdomains were strongly correlated (r = 0.6, p < 0.0001).

Table 1
Demographic, premorbid, baseline clinical and laboratory, and antipsychotic exposure variables for the 126 patients.

Age in years, mean (SD)	24.1 (6.6)
Highest grade passed, mean (SD)	9.8 (2.1)
Modal antipsychotic dose, mean (SD)	11.7 (3.8)
Treatment duration weeks, mean (SD)	68.7 (41.3)
Total antipsychotic dose flupentixol mg equivalents, mean (SD)	1455.8 (986.5)
Sex, male, n (%)	93 (74%)
Family history of psychosis, n (%)	47 (37%)
Obstetric complications, n (%)	17 (13%)
No previous antipsychotic exposure, n (%)	70 (56%)
Substance use in the past 3 months, n (%)	49 (39%)
DUP in weeks, mean (SD)	34.4 (43.2)
PANSS Positive domain, mean (SD)	17.4 (3.3)
PANSS Disorganized domain, mean (SD)	12.0 (3.0)
PANSS Negative domain, mean (SD)	22.9 (6.2)
Expressive subdomain, mean (SD)	12.5 (4.2)
Experiential subdomain, mean (SD)	10.4 (2.7)
CDSS, total score, mean (SD)	3.4 (4.1)
SOFAS, mean (SD)	44.0 (11.5)
WHOQOL-BREF, physical, mean (SD)	11.9 (2.4)
WHOQOL-BREF, psychological, mean (SD)	12.9 (2.7)
WHOQOL-BREF, social, mean (SD)	11.9 (4.2)
WHOQOL-BREF, environmental, mean (SD)	11.7 (3.3)
PAS, total childhood, mean (SD)	0.2 (0.2)
PAS, total early adolescence, mean (SD)	0.3 (0.2)
PAS, total late adolescence, mean (SD)	0.4 (0.2)
PAS, total adult, mean (SD)	0.4 (0.2)
PAS, total general, mean (SD)	0.5 (0.2)
PAS, overall, mean (SD)	0.4 (0.1)
NES, sensory integration, mean (SD)	2.8 (2.5)
NES, motor coordination, mean (SD)	1.4 (1.6)
NES, sequencing of motor acts, mean (SD)	2.9 (2.5)
NES, total, mean (SD)	15.0 (8.0)
ESRS, parkinsonism subscale, mean (SD)	1.8 (3.7)
ESRS, dyskinesia subscale, mean (SD)	0.0 (0.3)
ESRS, total, mean (SD)	2.7 (5.5)
BMI, kg/m^2, mean (SD)	21.6 (3.8)
Fasting glucose, mmol/L, mean (SD)	4.8 (0.7)
HDL cholesterol, mmol/L, mean (SD)	1.2 (0.6)
LDL cholesterol, mmol/L, mean (SD)	2.7 (0.9)
Triglycerides, mmol/L, mean (SD)	0.9 (0.5)

SD, standard deviation; PANSS, positive and negative syndrome scale; PAS, premorbid adjustment scale; WHOQOL-BREF, World Health Organization Quality of Life-Brief Scale; SOFAS, social and occupational functioning assessment scale; DUP = duration of untreated psychosis; NES = Neurological Evaluation Scale; CDSS = Calgary Depression Scale for Schizophrenia; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ESRS = Extrapyramidal Symptoms Rating Scale.

3.3. Treatment response trajectories for the experiential vs expressive negative symptom subdomains

Fig. 1 illustrates the least square means and 95% confidence intervals for the percentage change scores from baseline at each timepoint for the experiential vs expressive negative symptom subdomains. The main effect for time (F = 282.84, p < 0.0001) indicated highly significant reductions over the treatment period. However, the group * time interaction effect (F = 1.23, p = 0.2689) indicated that the symptom improvement trajectories for the two subdomains did not differ significantly. Table 3 provides the two subdomain percentage change scores at each of the timepoints. While the experiential subdomain scores showed a significantly greater reduction at 6 months, there were no significant differences between the subdomains at 12, 18 and 24 months.

3.4. Effects of demographic, premorbid and treatment related variables on the two subdomain scores over the 24-month treatment period

In Table 4 we provide the results of the fixed effects tests derived from the MMRMs. Ethnicity was the only demographic variable that had a significant effect (at unadjusted significance level) and was included in the subsequent MMRM models as a covariate, together with the baseline subdomain scores. For the premorbid variables of interest, only the PAS General score showed a significant (unadjusted) effect, and only for the expressive subdomain. For the treatment-related variables of interest we found significant main effects for the PANSS disorganised domain (p < 0.0001) and ESRS Total score (p = 0.012) on the expressive subdomain, and for the visit-wise CDSS Total score (p = 0.0057) and the visit-wise PANSS disorganised domain (p < 0.0001) on the experiential subdomain. Mean (95% CI) CDSS Total scores at each timepoint were: M0 = 3.7 (3.1–4.2); M6 = 1.6 (1.0–2.2); M12 = 1.3 (0.6–1.9); M18 = 0.9 (0.2–1.5); and M24 = 1.0 (0.4–1.7). Mean (95% CI) PANSS disorganised domain scores at each timepoint were: M0 = 12.0 (11.5–12.5); M6 = 6.7 (6.2–7.2); M12 = 6.1 (5.6–6.6); M18 = 5.8 (5.3–6.4); and M24 = 5.8 (5.2–6.3). An unadjusted significant effect was found for the total cumulative antipsychotic dose (p = 0.0466) and the SOFAS score (p = 0.0177) on the experiential subdomain. Given a previously reported association between the experiential negative subdomain specifically and functional outcome (Harvey et al., 2017), we conducted a further MMRM analysis in which the experiential and expressive domain scores were entered as independent time-dependent predictors and visit-wise SOFAS as the dependent variable. The experiential subdomain (F = 14.72, p = 0.0002), but not the expressive subdomain (F = 4.0, p = 0.05)

Table 2
Results of the second factor analysis including only the selected PANSS negative symptom items.

PANSS item	Factor 1 "Expressive deficit"	Factor 2 "Experiential deficit"
N1 Blunted affect	**0,75**	0,28
N2 Emotional withdrawal	0,45	**0,74**
N3 Poor rapport	**0,71**	**0,52**
N4 Passive social withdrawal	0,37	**0,76**
N6 Lack of spontaneity	**0,83**	0,28
G7 Motor retardation	**0,85**	0,04
G16 Active social avoidance	0,01	**0,85**
Explained variance	2,82	2,27
Proportion of total variance	0,40	0,32

Items loading >0.5 are highlighted in bold.

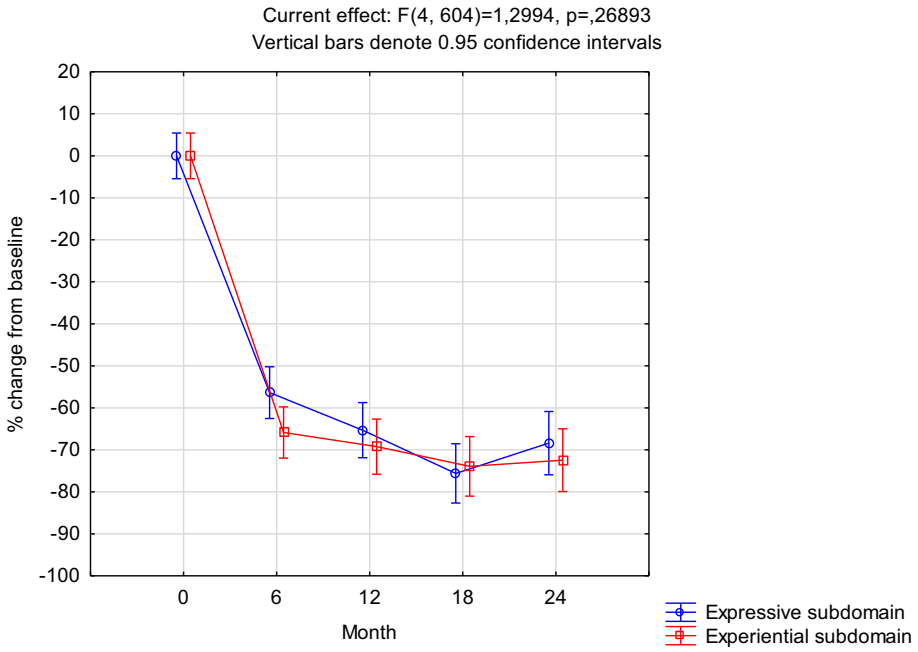

Fig. 1. MMRM least square means and 95% confidence intervals for the negative symptom subdomain percentage change scores from baseline at each of the timepoints.

Table 3
Percentage (95% CI) change from baseline at each timepoint for the expressive and experiential negative symptom subdomain scores, derived from the MMRM model.

Month	Expressive subdomain	Experiential subdomain	p[a]
	% (95% CI) change from baseline	% (95% CI) change from baseline	
6	−56 (−50 to −63)	−66 (−60 to −72)	0.0166
12	−65 (−59 to −72)	−69 (−63 to −76)	0.3573
18	−76 (−69 to −83)	−74 (−67 to −81)	0.7168
24	−68 (−61 to −76)	−72 (−65 to −80)	0.4149

[a] Post-hoc Fisher's least significant difference pairwise comparison of the subdomain percentage change scores at each timepoint.

scores, significantly predicted the SOFAS scores over time.

Finally, in the post-hoc analysis exploring the effects of the individual subscale scores of the assessment instruments and blood glucose and lipid values, significant main effects were found for HDL-cholesterol levels on the expressive subdomain ($p = 0.0061$) and the experiential subdomain ($p = 0.0003$). At unadjusted significance levels we found effects for the ESRS parkinsonism subscale scores ($p = 0.0193$) and LDL-cholesterol levels ($p = 0.0197$) on the expressive subdomain and for triglycerides and on the experiential subdomain ($p = 0.0488$) (Supplementary Table 1).

The partial correlational analyses to assess directionality of the significant associations indicated that higher expressive subdomain scores were predicted by higher PANSS disorganised domain scores and higher ESRS Total scores; higher experiential subdomain scores were predicted by higher visit-wise CDSS Total scores, and higher visit-wise PANSS disorganised domain scores. In the post -hoc analysis, higher expressive subdomain scores were associated with higher ESRS parkinsonism scores and lower HDL-cholesterol levels; and higher experiential subdomain scores were associated with lower HDL-cholesterol levels.

4. Discussion

Consistent with other factor analyses of the PANSS (Emsley et al.,

Table 4
Fixed effects for the selected demographic, premorbid and treatment related variables, on the expressive and experiential negative symptom subdomain scores over 24 months of treatment.

Effect	Expressive subdomain		Experiential subdomain	
	F	p	F	p
Demographic				
Age, years	0.0025	0.9606	0.0005	0.9816
Highest level of education	0.2395	0.6249	0.2227	0.6373
Gender	0.3260	0.5684	0.3267	0.5681
Ethnic group	3.6031	0.0284	3.4034	0.0345
Premorbid				
DUP, weeks	0.1782	0.6732	0.1733	0.6775
PAS General	5.4081	0.0207	0.8004	0.3717
PAS Overall	1.4673	0.2268	0.2134	0.6444
Family history of psychosis	0.3451	0.5573	1.3083	0.2536
Obstetric complications	0.3829	0.5365	0.3325	0.5647
Recent substance use	0.0.9957	0.4099	0.2168	0.9290
Treatment-related				
Total AP dose flupenthixol mg equiv.	0.0047	0.9455	4.0024	0.0466
CDSS	0.1445	0.7042	7.7747	**0.0057***
PANSS Positive factor	0.3466	0.5566	0.3233	0.5702
PANSS Disorganised factor	56.9583	**<0.0001***	25.1871	**<0.0001***
SOFAS	0.0805	0.7769	5.7066	0.0177
QoL overall	3.3680	0.0678	0.3949	0.5304
NES Total	0.8023	0.3713	0.1298	0.7189
ESRS Total	6.4128	**0.0120***	0.6588	0.4178
BMI	0.3626	0.5476	0.2309	0.6313

PAS = Premorbid Adjustment Scale; DUP = duration of untreated psychosis; NES = Neurological Evaluation Scale; ESRS = Extrapyramidal Symptoms Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; PANSS = Positive and Negative Syndrome Scale; BMI = body mass index; SOFAS = Social and Occupational Functioning Assessment Scale; QoL = quality of life.
Bold data indicates significance $p < 0.05$.

2003) we found the negative factor to be the dominant component, accounting for the highest proportion of variance (19.5%). This may appear surprising, given that negative symptoms have long been considered to be less prominent in first-episode schizophrenia than in chronic schizophrenia (Mayerhoff et al., 1994). However, this finding may be artefactual and can be explained by the fact that there are more PANSS items in the negative factor than in the other domains. Nevertheless, negative symptoms are prominent during the early stages of illness and it has been noted that 50–90% of subjects with schizophrenia-spectrum disorders show negative symptoms during their first episode of psychosis (Galderisi et al., 2021).

We also replicated the existence of two negative symptom subdomains, namely the expressive and experiential subdomains. This is consistent with several other studies reporting a two-subfactor structure for PANSS negative symptoms, although item loadings were not always the same (Fervaha et al., 2014; Harvey et al., 2017; Jang et al., 2016; Khan et al., 2017; Sevy et al., 2020; Stiekema et al., 2016). However, the strong correlation that we found between the two subdomains suggests a large overlap rather than them being independent constructs. In this respect our findings are similar to those of Jang et al. (Jang et al., 2016), who conducted a factor analysis of the PANSS in 220 patients with schizophrenia spectrum disorders and found that a two-factor model for negative symptoms was a better fit than a one factor model although the two factors were strongly correlated. These authors suggested that the two factors are non-independent, though potentially dissociable.

The response trajectories of the two subdomains to antipsychotic treatment over two years were similar. This finding again argues against their validity as independent constructs, at least in terms of antipsychotic treatment response, and does not support the proposal that the two subdomains follow distinct trajectories over the course of illness (Strauss et al., 2013). However, it should be noted that another study reported differential responses to a psychotherapeutic intervention. That study, examining the effects of cognitive remediation therapy in 78 low functioning individuals with schizophrenia, reported significant improvement in the experiential, but not in the expressive subdomain (Sevy et al., 2020). It could be therefore that the experiential subdomain responds preferentially to psychotherapeutic interventions, while both subdomains respond similarly to pharmacological interventions. In our study, both subdomains showed highly significant reductions, particularly during the first six months of treatment. The overall reductions of 68% and 72% for the expressive and experiential subdomains respectively indicate that, contrary to some reports of negative symptoms responding poorly to treatment (Fusar-Poli et al., 2015), when treatment is assured in early illness, considerable improvements can be anticipated. This could suggest that the evolution of persistent negative symptoms over the course of illness in real world settings may be linked to periods of non-adherence and consequent illness recurrence. While most patients respond well to treatment for their first psychotic episode, the majority sustain multiple relapses leading to progressive and persistent morbidity and disability (Lieberman, 1999). The single most important contributor to relapse is nonadherence to treatment (Robinson et al., 1999). Longitudinal studies have reported the deleterious effects of relapses, which may be a critical factor in the emergence of treatment failure (Emsley et al., 2013). Indeed, in a naturalistic study conducted over 15 years it was found that the probability of poor outcome increased with each relapse episode, not because of continuing psychotic symptoms but because of the appearance of negative symptoms. Persistent negative symptoms gradually increased from 27% after the first episode to 47% after the fourth episode (Wiersma et al., 1998).

Consistent with the findings of Pelizza et al. (2021), we found that improvements in both negative symptom subdomains over the treatment period had the strongest associations with improvement in the PANSS disorganised domain. This suggests that disorganised and negative symptoms are closely related and may share similar neurobiological substrates. On the other hand, the lack of a significant association between the PANSS positive symptom domain and the negative symptom subdomains is well recognised (Drake et al., 2003; Emsley et al., 2003), and consistent with the long-standing concept of positive and negative symptoms representing two syndromes with distinct underlying pathological processes (Crow, 1980).

The importance of distinguishing between primary and secondary negative symptoms has been emphasised (Galderisi et al., 2021). While primary negative symptoms are thought to stem from the pathophysiological substrate underlying schizophrenia, secondary negative symptoms might be caused by identifiable factors such as positive symptoms, depression, medication side-effects and substance use (Marder and Galderisi, 2017). In our cohort we did not find significant effects for positive symptoms or recent substance use on the negative symptom subdomains. However, we did find that depressive symptoms may have contributed to secondary negative symptoms, and that they appear to have a greater impact on the experiential subdomain. This finding is supported by the results of a systematic review by Krynicki et al. (2018) in which it was found that symptoms corresponding to the experiential subdomain overlap with both depressive and negative symptom domains, whereas symptoms that form the expressive deficit subdomain appear to be specific to negative symptoms. Furthermore, our results suggest that treatment emergent extrapyramidal symptoms, particularly parkinsonism, contributed to secondary negative symptoms, specifically on the expressive subdomain, although another study found that extrapyramidal symptoms had a significant impact on both subdomains (Farreny et al., 2018). These discrepancies may be accounted for by the differences in the scales used for rating extrapyramidal symptoms, and that the participants in their study were significantly older, and had a longer duration of illness.

The near-significant effect that we found for social and occupational functioning on the experiential subdomain warrants mention particularly as our follow-up analysis indicated that when controlling for the expressive subdomain scores the experiential domain scores significantly predicted the SOFAS scores over time. This is consistent with a previously reported cross-sectional study of 630 patients with schizophrenia Harvey et al. (Harvey et al., 2017) where it was found that the experiential factor accounted for 21% of the variance in social functioning (although not in work or everyday activities), whereas the expressive factor accounted for, at most, 1% of the variance in functional outcomes. These authors pointed out that the experiential factor, comprising only three PANSS items, was at least as efficient as the total negative symptom score in predicting social outcomes and showed clear separation from the expressive factor in this regard.

Finally, while we did not find an association between body mass changes and negative symptom improvements, the observed association between higher HDL-cholesterol levels and improvements in both negative symptom subdomains is of considerable interest. Weight gain and dyslipidaemia are important adverse effects of antipsychotic treatment, and paradoxically, an association between antipsychotic-associated weight gain and therapeutic benefit is well recognised (Raben et al., 2017). Similarly, deteriorating lipid profiles have been associated with a favourable treatment response. Most such studies focussed on triglycerides, with elevations being associated with overall symptom improvements, and some with negative symptom improvements (Chen et al., 2014; Lally et al., 2013; Procyshyn et al., 2007). Of direct relevance to our findings is a study by Gjerde et al. (Gjerde et al., 2018) in patients with a first episode of a non-affective psychosis. They reported a negative association between HDL levels and negative symptom scores at baseline and a significant reduction in HDL levels at group level over 12 months of treatment. At the same time though, almost half of their patients experienced an increase in HDL levels and their most notable finding was an association between increased HDL levels and negative symptom improvement. They proposed that serum HDL is a peripheral proxy for brain cholesterol, and that their findings might reflect improvements in myelination related to antipsychotic treatment. Consistent with this proposal is the hypothesis that frontal lobe myelination is dysregulated in schizophrenia, and that

antipsychotics stabilise white matter via a promyelination effect, particularly in the early stages of illness (Tishler et al., 2018). An alternative explanation however, is that improvements in negative symptoms may lead to changes in lifestyle and diet with resultant improvement in nutrition and HDL levels (Gjerde et al., 2018). Our replication of the Gjerde et al. (2018) findings certainly suggests a link between blood HDL levels and treatment response in terms of negative symptoms specifically. Our findings also suggest that whatever the cause of the association, it is not specific to either of the negative symptom subdomains.

Several methodological limitations should be considered when interpreting our findings. First, the PANSS does not comprehensively assess negative symptoms. Poor assessment of avolition-apathy and the lack of assessment for anhedonia have been highlighted (Galderisi et al., 2021). Similarly, it has been argued that the two-factor model for PANSS rated negative symptoms may be an artifact attributable to the different rating methods between the two factors. The rating of expressive negative symptoms is based on direct observation during the interview, while the rating of the experiential negative symptoms is based in part on reports of social activities outside of the interview (Liemburg et al., 2013; Sevy et al., 2020). More recent scales designed specifically to assess negative symptoms provide more detailed assessment and have described five factors (Galderisi et al., 2021). On the other hand, the PANSS has been extensively used in clinical and research settings, and the negative symptom factor is clearly defined and is one of its major strengths (Shafer and Dazzi, 2019). The PANSS has also demonstrated long-term stability of the negative symptom factor (Lim et al., 2021). Second, the first post-baseline assessment was at 6 months – after most of the treatment related changes in psychopathology have occurred. The reason for us only including PANSS data after 6 months is because we were primarily interested in changes over time in relation to other outcomes measures, and data for SOFAS, quality of life, neurological soft signs, BMI, glucose and lipids were only collected at the 6-monthly visits. Third, as with most non-naturalistic longitudinal studies in psychosis, was the considerable attrition rate. Although the MMRM models that we used provide a powerful approach to dealing with missing values, the possibility of measurement error should be kept in mind. Fourth, the high attrition rate is that the retained patients may not be representative of the entire sample. Also, the study duration of two years does not address the course of negative symptoms and their relationship to antipsychotic treatment in the longer term. Fifth, the SOFAS is unidimensional, and the use of a global score makes it difficult to delineate between which particular areas of social or occupational functionality are impaired. The specific areas of functioning may respond differently to therapeutic interventions and relate distinctively to factors influencing long-term outcome. Finally, while the use of a single antipsychotic provided treatment homogeneity, it also limits the generalizability of findings to patients treated with other antipsychotics. Strengths of our study include the longitudinal design over a relatively long period of follow up of a treatment naïve or minimally treated first-episode psychosis cohort using a standardised treatment protocol with a single long-acting injectable (LAI) antipsychotic. LAI treatment provided assured antipsychotic delivery and an opportunity to precisely determine the cumulative antipsychotic dose. Our sample was well characterised and allowed assessment of premorbid factors, and at multiple timepoints of the effects of treatment-related factors.

Our findings suggest that the two PANSS-derived negative symptom subdomains are closely related, have similar premorbid correlates and respond similarly to antipsychotic treatment. Regarding secondary negative symptoms, depression appears to affect the experiential subdomain specifically, whereas extrapyramidal symptoms affect the expressive subdomain.

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Credit authorship contribution statement

Robin Emsley, Lebogang Phahladira, Laila Asmal and Bonginkosi Chiliza were responsible for the study conception and design. Freda Scheffler, Stefan Du Plessis, Retha Smit and Hilmar Lückhoff were responsible for collection, extraction and coding of data included in the study. Robin Emsley provided the analysis and interpretation. Lebogang Phahladira and Robin Emsley drafted the manuscript, and all other authors provided critical comments.

All authors provided intellectual contribution and approved the final manuscript.

Declaration of competing interest

Robin Emsley has received speakers fees and participated in advisory boards from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck. Bonga Chiliza has received speakers fees from Cipla, Lundbeck, and Sanofi. Lebogang Phahladira, Laila Asmal, Hilmar Lückhoff, Stefan du Plessis, Freda Scheffler and Retha Smit declare that they have no conflicts of interest.

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CHAPTER 6

CONCLUSIONS AND FUTURE RESEARCH PROSPECTS

6.1. INTRODUCTION

This chapter provides a synthesis of the main findings of the doctoral research presented in this dissertation, which aimed to examine multi-dimensional aspects of outcome over 24 months of assured treatment in first-episode schizophrenia spectrum disorders. Further avenues for future research are discussed, and an overall conclusion provided.

6.2. Changes in insight over 24 months

In sub-study I (Chapter 2), we assessed changes in patient- and clinician-rated insight over 24 months. At baseline, patients displayed significant impairments in awareness of illness, attribution of symptoms and recognition of the need for treatment. In contrast to clinician-rated insight, significant impairments in patient-rated insight persisted over the course of the illness. This was despite the fact that our patients generally responded very well to treatment. The poor response of insight to treatment was an unanticipated finding. Similar to our findings, some previous studies (Cuesta et al., 2000; Pijnenborg et al., 2015; Wiffen et al., 2010) reported only modest improvements in insight impairment, and those significant deficits persisted during the stable phase of the illness. Taken together, these findings support the notion that a substantial component of insight impairment in schizophrenia spectrum disorders is trait-related (Wiffen et al., 2010). Another interesting finding was that better insight was associated with higher levels of depression, in keeping with the well-established “insight paradox” described for schizophrenia (Belvederi Murri et al., 2016). There are several reasons that could explain this paradox. For example, patients with better insight have higher levels of self-reflection (Palmer et al., 2015) and self-stigma (Lysaker et al., 2007), factors which are are associtated with depression. The relationship between depression and insight may be moderated by cannabis; with a three-way interaction between insight, cannabis use and depression (Elowe et al., 2020). Better insight predicts poorer quality of life which in turn predict depression and suicide (Ehrminger et al., 2020). Given that poor insight is associated with non-adherence, poor clinical outcomes and worse psychosocial functioning, clinicians should be aware of the persistence of poor insight and

that this has important implications in shared decision making and choice of antipsychotic formulation.

6.3. Improvement in clinical and functional outcomes over 24 months

In sub-study two (Chapter III), we explored rates and predictors of recovery by examining the trajectories of psychopathology, functional outcomes, and quality of life. The study indicated that when antipsychotic treatment is assured via long-acting formulation, the overall outcome in first-episode schizophrenia is generally favourable. The benefits of long-acting antipsychotics may be most apparent in the early stages of illness when the illness is at its most aggressive, where relapse is most likely to occur and when illness progression is most apparent (Birchwood et al., 1998). It is also the period when patients respond best to antipsychotic medication (Jager et al., 2007). Indeed, our patients did very well in terms of attaining the individual criteria for recovery. Thus, 70% achieved symptom remission, 56% functional remission and 61% rated their quality of life as good or excellent. However, there is a note of caution. Only twenty-nine percent (29%) of patients met all three of our criteria for recovery simultaneously. This highlights the enduring deficits characteristic of the illness even when treatment is optimal and emphasises the need for improved pharmacological and psychosocial interventions in treating schizophrenia. Symptomatic improvement is not sufficient to measure outcome of schizophrenia. However, the fact that only 9% of patients in our sample who did not achieve symptom remission achieved functional remission and good subjective quality of life, suggests that improvements in psychopathology may be a key building construct of recovery in schizophrenia (Liberman & Kopelowicz, 2005). In other words, symptom remission may be a necessary but not sufficient component of recovery. It should be noted that quality of life is a complex construct that is influenced by individual, social, environmental and clinical factors (Becker et al., 2005). Further, there are discrepancies between self-rated and clinician-rated instruments (Jung et al., 2010).

6.4. Improvement in depressive symptoms over 24 months

In sub-study III (Chapter 4), we examined the prevalence, correlates, and trajectories of depression in patients examined at regular 3-monthly intervals using the Calgary Depression Scale for Schizophrenia (CDSS). Furthermore, we explored whether patients with depressive disorder limited to the acute phase of illness differed from those with a depressive disorder in the post-acute phase. At the time of publication, this was the first study to prospectively assess the longitudinal course of depressive symptoms in first-episode schizophrenia spectrum disorders treated with a long-acting injectable antipsychotic. Our finding that depressive symptoms at onset of illness are intrinsic to psychosis and respond well to antipsychotic treatment is consistent with those reported in previous studies (Emsley et al., 1999; Kjelby et al., 2018; Oosthuizen et al., 2006). We found little evidence to suggest that depression in the acute phase of illness differs from that in the post-acute phase. Indeed, few patients exhibited persistent or emergent post-acute depressive symptoms. This contradicts the argument that depressive symptoms in schizophrenia are a marker of poor long-term outcome (Reine et al., 2003; Resnick et al., 2004) that may be related to illness chronicity. We found that poorer quality of life was a significant predictor of depressive symptoms during the post-acute phase. Whilst the relationship between quality of life and depression is not straightforward, lifestyle factors may also have a strong impact on depressive symptoms in schizophrenia (Etchecopar-Etchart et al., 2021). It may be that depressive symptoms during the later course of illness are different to those during the early phase.

6.5. Improvement in Negative Symptoms over 24 Months

In sub-study IV (Chapter 5), we examined improvement in negative symptoms over the first 24 months of treatment. We confirmed the existence of the two negative symptom subdomains, namely, the expressive and experiential subdomains, using factor analysis. Our findings are consistent with previous studies employing the PANSS to assess negative symptoms which demonstrated the two-factor structure (Liemburg et al., 2013; Stiekema et

al., 2016). However, found only limited support for the hypothesis that these two subdomains are independent constructs. Indeed, our finding that the two subdomains are strongly correlated counts against them being independent entities, and rather is in keeping with results of a factor analysis of the PANSS suggesting that they are semi-independent constructs (Jang et al., 2016). The limitation of the PANSS rating scale is that it includes items that are not considered negative symptoms (Jang et al., 2016). However, results of studies using newer rating scales such as the Clinical Assessment Interview for Negative Symptoms (CAINS) and the Brief Negative Symptoms Scale (BNSS) support the two-factor structure of negative symptoms (Rekhi et al., 2019; Strauss et al., 2012). Whilst the two-factor structure appears to be more robust when items unrelated to the negative symptoms are excluded (Galderisi et al., 2021), their existence may be artefactual insofar as expressive deficit items may load together in view of the fact that they are observed and rated during an interview, whereas experiential deficit items are based on patients' self-report (Azorin et al., 2014). We further demonstrated similar antipsychotic treatment response trajectories for both sub-domains, with overall significant reductions at endpoint. It is possible that negative symptoms which respond poorly to treatment are related to illness chronicity and biological factors associated with relapse (Fusar-Poli et al., 2015).

6.6. Limitations and Research Strengths

The doctoral research described in this dissertation had several limitations that need to be kept in mind when interpreting our findings. 1) Although the sample size was relatively large for a single site study, it may not have provided us with sufficient power to detect more subtle effects related to treatment outcomes. 2) As with other longitudinal studies in psychosis, attrition rates were considerable. While our use of mixed model repeated measures provided a powerful approach to analysing the data, the assumption of missingness at random could result in measurement errors. Another limitation of the high attrition rate is that the included patients may not be representative of the entire sample. Several participants directly and indirectly withdrew for treatment-related reasons. 3) While

the standard treatment protocol with flupenthixol decanoate eliminated potential confounds associated with different antipsychotics that are received in real-world settings, it limits comparisons with patients treated with other antipsychotic medication. 4) While all patients received psychoeducation and some received family interventions, they did not receive formal psychotherapeutic interventions that may improve insight (Pijnenborg et al., 2013), negative symptoms (Gaynor et al., 2011), and depression (Upthegrove, 2009). 5) We did not examine the relationship between cognition and the negative symptoms. This may be important, as cognitive impairment is a core feature of schizophrenia (Gold & Harvey, 1993) and the deficits are present through the course of illness (Bora & Murray, 2014) and may influence outcome. The decision not to consider cognition was because a substantial number of participants did not undergo these assessments. This would have resulted in a smaller sample size with reduced statistical power. 6) The study period of 2 years does not permit inferences of outcome trajectories over a longer period. 7) All of the assessment instruments were available in English only. While most of our patients were bilingual, for the majority English was not their first language. To minimise the risk of participants not fully understanding the questions or instructions, care was taken by the investigators and study co-ordinators to explain the meaning in their first language.

However, there were also important strengths. Our study design was able to address limitations highlighted in previous longitudinal studies of first-episode psychosis such as treatment adherence, prior exposure to antipsychotics, appropriate rating instruments and duration of follow-up. By using a long-acting injectable antipsychotic, we were able to calculate the exact dose equivalent for each participant. The standardized treatment protocol using long acting-injectable antipsychotic medication, the regular intervals of assessment and the real-world setting of our study design allowed us to make several new contributions to the academic literature.

6.7. Future Research Considerations

The studies described in this dissertation led to the identification of several avenues for future research.

6.7.1 Studies on insight

Our finding that impaired insight does not improve with antipsychotic treatment was unanticipated and suggests that it is a trait related phenomenon. This is consistent with phenomenological theories conceptualising schizophrenia as a long-standing disorder of the self, from which the psychosis emerges (Henriksen & Parnas, 2014). Further study of this concept may advance our understanding of this complex disorder and provide new treatment targets.

6.7.2 Studies on depressive symptoms

While there is now a considerable literature on depressive symptoms in schizophrenia there remain several uncertainties. The link between depression and better insight is intriguing, and warrants further investigation from both biological and psychological perspectives. Persitent depressive symptoms are likely to be more prevalent in chronic samples and in those with degrees of treatment refractoriness. Studies in these populations are indicated, and importantly, treatment interventions should be prospectively evaluated. We also propose that future studies should evaluate the impact of psychosocial and environmental variables such as stigma, physical activity, diet and smoking on depressive symptoms. In addition, studies exploring the association between cognition, functioning and depressive symptoms are necessary (Etchecopar-Etchart et al., 2021).

6.7.3 Studies on recovery

While recovery is more difficult to define than remission, it's importance as an outcome measure is enormous. It is recognised that patients and their families consider outcomes such as autonomy, independent living, and social interaction to be more important than

symptom remission (Andreasen et al., 2005). Clinical trials and other studies assessing outcome would do well to include these domains in future. Standardised, operationally defined criteria for recovery would be very useful in clinical practice, although developing them would be challenging. While symptom expression is fairly consistent across different populations, psychosocial, educational and social circumstances affecting functionality and quality of life differ within and across communities. As such, there is a need for outcome measures to be multidimensional and to be relevant in different cultural settings (Shrivastava et al., 2010). This is an aspect of particular interest and importance in our own populations.

6.7.4 Studies on negative symptoms

Contrary to commonly held opinion that negative symptoms respond poorly to treatment (Fusar-Poli et al., 2015) , our study indicated that when treatment is assured in first-episode psychosis, highly significant improvements can be anticipated. Therefore, novel interventions targeting negative symptoms in early illness should be a focus of future clinical trials. Our study, and others to date, provide only limited evidence that the experiential and expressive subdomains respond differentially to treatment. Nevertheless, future studies should explore this avenue further, and utilize recently developed scales to evaluate negative symptoms and their subdomains more comprehensively.

Given that inflammatory markers are associated with dyslipidaemia in patients with first-episode psychosis (Russell et al., 2015), and that an abnormal immune-inflammatory response is implicated in psychosis (Noto et al., 2021), the association between HDL-cholesterol and the negative symptom subdomains in our study highlighted the importance of further exploring the association between inflammation and negative symptoms in future studies.

The Social and Occupational Functioning Assessment Scale (SOFAS) is unidimensional and does not delineate between psychopathology and psychosocial facts. Future studies should consider employing the Personal and Social Performance (PSP) scale which is a more reliable instrument for assessing psychosocial functioning during the course of treatment and in the acute phases of illness (Juckel et al., 2008). A longer duration of follow-up may provide an opportunity to study factors related to relapse other than non-adherence.

6.8. Conclusion

In summary, the doctoral research described in this dissertation highlights the complex nature of symptom expression over the course of initial treatment in first-episode schizophrenia spectrum disorders. Our findings challenge earlier work in several important respects. In particular when antipsychotic treatment is assured in early illness, outcomes are generally favourable in terms of improvements in psychopathology (i.e. symptom remission), social and occupational functionality and quality of life. At the same time, highly significant reductions in depressive and negative symptoms can be anticipated. On the other hand, despite a favourable clinical response to treatment, insight remained impaired. Taken together, our findings support the use of long-acting injectable antipsychotics as a first line treatment in schizophrenia spectrum disorders, perhaps particularly in resource constrained settings such as our own. The challenge now is to translate these findings into changes in clinical practice.

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