A prospective study of clinical, biological and functional aspects of outcome in first episode psychosis

Dissertation presented by

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Declaration

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Summary

Prospective, longitudinal clinical studies in first-episode schizophrenia have become relatively commonplace over the past two decades or more and have provided a wealth of useful information regarding the clinical presentation, treatment, course and outcome of the illness. However, there remain several unanswered questions. The majority of the studies have been conducted in upper income countries using often costly medication with heterogeneous samples. While the overall outcome of patients showed some progress, there is room for improvement yet. The overall aim of the dissertation was to study the clinical, biological and functional aspects of outcome in first episode schizophrenia in a resource constrained setting.

We conducted a prospective, non-comparative, longitudinal study over 12 months assessing the efficacy and tolerability of a cost effective, long-acting injectable antipsychotic (LAI; flupenthixol decanoate) combined with an assertive monitoring program (AMP) among first-episode schizophrenia patients. Efficacy was measured by examining rates of response, remission and relapse, as well as quality of life and social and occupational functioning. Tolerability of our intervention was assessed by measuring extrapyramidal symptoms, and weight and metabolic changes. We also examined the evolution of treatment refractoriness by studying the rates of non-response, and other associated predictor and outcome features.

We found high rates of acceptance and adherence to the LAI and AMP. Seventy percent of our patients completed the 12 months of treatment. Treatment response was achieved by 82% of the participants

and 60% achieved remission. Although 19% of our patients relapsed, the majority of the relapses were mild and did not require hospitalisation. Patients experienced significant quality of life and social and occupational functioning improvements. We found mild rates of extrapyramidal effects, present in only a third of our cohort. The majority of the extrapyramidal effects were treated with anticholinergics or propranolol. Only 3% of our patients developed transient dyskinesia over the duration of the study. However, our cohort gained considerable weight, with statistically significant increases in BMI ($p< .0001$) and waist circumference ($p=0.0006$). Our cohort also experienced significant deleterious changes to their lipid profiles. Of particular concern was the increase in triglycerides ($p=0.03$) and a significant decrease in high density lipoprotein ($p=0.005$) leading to a 91% increase in the triglyceride/high density lipoprotein ratio.

With regards to emerging treatment refractoriness, 12% of our patients met our pre-defined criteria for non-response. Non-responders were younger and at baseline showed more prominent disorganised symptoms, poorer social and occupational functioning, poorer quality of life for psychological, social and environmental domains, more prominent neurological soft signs (NSS), and lower BMI. At endpoint the non-responders were characterised by higher levels of symptomatology in all domains; poorer functional outcome, poorer quality of life and greater cognitive impairments. They also had more prominent NSS and a lower BMI. The strongest predictors of non-response were prominent baseline NSS and poor early (7 weeks) treatment response.

In conclusion, the combination of an LAI with an AMP may be an effective and safe intervention in first-episode schizophrenia, and may be particularly suitable for resource-constrained settings. The risk of weight gain and metabolic syndrome associated with antipsychotic treatment in first-episode

schizophrenia are not restricted to second generation antipsychotics and low-potency first-generation antipsychotics. Ensuring effective treatment for first episode schizophrenia patients is a global problem, and likely to be under-recognised in LMICs.

Opsomming

Oor die afgelope twee dekades het toenemend meer longitudinale kliniese studies, wat eerste episode skisofrenie bestudeer, die lig gesien. Die studies het ‘n magdom van waardevolle inligtng oor die kliniese voorkoms, behandeling, verloop en uitkomste van die siekte opgelewer. Die meerderheid van die studies is egter in hoë inkomste ontwikkelde lande gedoen met pasiënte wat duur medikasie gebruik en hoofsaaklik in heterogene steekproewe. Alhoewel dit blyk uit hierdie studies dat daar oor die algemeen vordering gemaak word ten opsigte van die behandeling van pasiënte is daar steeds ‘n gebrek aan voldoende inligting oor die onderwerp veral in minder gegoede, ontwikkelende lande. Die oorhoofse doel van hierdie proefskrif is om binne ‘n hulpbron beperkte konteks die kliniese, biologiese en funksionele aspekte van pasiënt -uitkomste in eerste episode skisofrenie te ondersoek.

Ons het ‘n longitudinale studie gedoen waarin ons die effektiwiteit en toleransie van ‘n enkele antipsigotiese medikasie vir 12 maande nagevors het. Die medikasie wat ons ondersoek het, is flupenthixol decanoate en word deur ‘n inspuiting gegee en die medikasie word dan geleidelik deur die liggaam geabsorbeer. As deel van die behandeling het ons pasiënte ook streng gemonitor. Ons het die effektiwiteit van die behandeling gemeet nagelang van hoe pasiënte reageer op die behandeling, hoeveel pasiënte in remissie gaan en terugval, en ook pasiënte se kwaliteit van lewe en hulle sosiale en beroepsfunksionering. Ons het toleransie gemeet nagelang van pasiënte se gewig en metaboliese verandering sowel as die voorkoms van medikasie geïnduseerde newe-effekte. Verder het ons pasiënte wat nie op medikasie gereageer het nie ondersoek sowel as die aspekte wat moontlik hiernee verband hou.

Ons het bevind dat die meerderheid van pasiënte hulle medikasie getrou geneem het en ook die streng monitering aanvaar het. Sewentig persent van die pasiënte het hulle 12 maande behandeling voltooi, 82% het op die medikasie gereageer en 60% het in remissie ingegaan. Alhoewel 19% van die pasiënte teruggeval het, was dit nie so ernstig dat ons hulle moes hospitaliseer nie. Pasiënte het beduidende verbetering ten opsigte van hulle kwaliteit van lewe en sosiale en beroepsfunksionering getoon. Ons het slegs ‘n gematigde mate van medikasie geïnduseerde newe-effekte opgemerk en alleenlik by ‘n derde van die kohort. In die meerderheid van gevalle het ons die newe-effekte met anticholinergics of propranolol behandel. Slegs 3% van die pasiënte het gedurende die verloop van 12 maande die kondisie transient dyskinesia ontwikkel. Ongelukkig het ons kohort geweldig baie gewig opgetel en die toename in pasiënte se BMI ($p < .0001$) en middellyf omtrek ($p=0.0006$) was statisties beduidend. Ons het ook bevind dat veranderinge in ons kohort se lipied profiele kommerwekkend is veral as in ag geneem word dat die toename in trigliseriede ($p = 0,03$) en die beduidende afname in die hoë digtheid lipoproteïen ($p = 0,005$) gelei het tot ‘n 91% verhoging in trigliseriede: hoë digtheid lipoproteïen verhouding.

Ons het bevind dat 12% van ons pasiënte voldoen het aan ons voorafopgestelde kriteria vir pasiënte wat nie reageer op behandeling nie. Diegene wat nie op behandeling gereageer het nie was jonger by basislyn, het meer prominente ongeorganiseerde simptome, swakker sosiale en beroepsfunksionering, swakker kwaliteit van lewe (op sielkundige, sosiale en omgewingsgebiede), meer prominente neurologiese sagte tekens, en laer BMI gehad. By eindpunt het diegene wat nie gereageer op behandeling nie nie erger simptome, swakker funksionering, swakker kwaliteit van lewe en erger kognitiewe gebrekke getoon. Dit blyk dat die beste aanduiding dat pasiënte nie op behandeling sal reageer nie prominente neurologiese sagte tekens en swak reaksie op vroeë behandeling (gedurende die eerste 7 weke) is.

Ten slotte die kombinasie van medikasie, wat geleidelik deur die liggaam geabsorbeer word, en streng monitering is meer geskik vir lae-inkomste lande met beperkte hulprbronne. Die risiko vir gewigstoename en metaboliese sindroom wat geaasosieer word met antipsigotiese behandeling in eerste episode skisforrenie is nie beperk tot tweede generasie antipsigotiese medikasie en lae dosisse eerste generasie antispsigotiese medikasie nie. Effektiewe behandeling vir eerste episode skisforrenie is ‘n globale probleem en kry nie die nodige aandag in lae-inkomste lande nie.

Dedication

I dedicate this dissertation to my family for their unconditional love and constant support. To God be the honour and glory.

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Chapter 1

Introduction

Introduction

Clinical features of Schizophrenia

Schizophrenia is a complex disorder with heterogeneous outcomes. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in order to make a diagnosis of schizophrenia, patients must have two or more of the following symptoms present for at least one month: delusions, hallucinations, disorganised speech, disorganised behaviour and negative symptoms (APA, 2013). However the majority of patients with schizophrenia have additional symptoms including depression, anxiety, cognitive, and motor symptoms.

In contrast to the DSM-5 categorical approach, a dimensional approach hypothesizes that the symptoms of schizophrenia cluster together to form dimensions. These dimensions co-exist in patients with schizophrenia and are more likely to be correlated to aetiological, biological, and other clinical factors than the DSM-5 diagnosis (Andreasen et al., 2005). The majority of studies that used factor analysis to examine symptoms of schizophrenia using data obtained from the Positive and Negative Syndrome Scale (Kay et al., 1987) found that the symptoms of schizophrenia can be clustered into five dimensions (Potuzak et al., 2012; Wallwork et al., 2012). These dimensions are called positive, disorganised, negative, excitement and depression factors.

The positive dimension consists of delusions and hallucinations, which have long been regarded as characteristic of schizophrenia. Delusions and hallucinations are easily identifiable and are most commonly associated with schizophrenia although they are not diagnostic, as they can be observed in other disorders. There is increasing evidence that positive symptoms may exist on a continuum with other experiences that are considered normal, such as odd or strange beliefs and occasional

auditory hallucinations. The latter experiences are quite common in the general population; in fact they are substantially more common than the positive psychotic symptoms in people with schizophrenia (van Os et al., 2009). There is no consistent evidence of an association between the positive dimension and functional outcome in people with schizophrenia. It has been suggested that the other symptom clusters have more influence on outcome than positive symptoms (Rabinowitz et al., 2012).

The disorganised dimension is made up of disorganised speech and behaviour, conceptual disorganisation, difficulty in abstracting, and poor attention. Disorganised speech and behaviour have been traditionally regarded as positive symptoms; however they have been shown to form a separate cluster in factor analysis and are associated with different clinical and neurobiological features (Wallwork et al., 2012). Disorganised symptoms are associated with poor outcome in patients with schizophrenia in areas such as social functioning, work performance and social skills (Roche et al., 2014). This dimension has also been strongly associated with cognitive dysfunction, which may partially explain its ability to predict poor functional outcome (Ventura et al., 2009).

The negative dimension includes affective flattening, alogia, asociality, avolition, and anhedonia. These symptoms have been labelled ‘negative’ symptoms due to the perceived loss of behaviours, interests, motivation and desires. Negative symptoms are a core feature of schizophrenia but they need to be differentiated from secondary negative symptoms. The latter may be as a result of comorbid depression, extra-pyramidal effects of antipsychotics, social exclusion, or a lack of environmental stimulation (Kirkpatrick et al., 2006). Recent studies have found that negative symptoms can be broadly divided into two clusters of symptoms: avolition and decreased emotional expression (APA, 2013; Millan et al., 2014). Avolition includes decreased motivation, asociality and

anticipatory anhedonia. Decreased emotional expression consists of diminished verbal and non-verbal expression (facial expression, gestures and vocal intonations). Negative symptoms have been associated with poor functional outcomes and are not readily responsive to treatment however the association may also be mediated by other symptom clusters including social cognition (Millan et al., 2014).

The excitement dimension is made up of impulsivity, hostility, excitement and uncooperativeness. These symptoms represent an activation syndrome or behavioural disinhibition. They are particularly prominent during the active phase of the illness and they represent significant clinical challenges (Lindenmayer et al., 2004). They have also been associated with aggressive behaviour during hospitalisations (Colasanti et al., 2010). The depression dimension consists of anxiety, tension, depression, guilt feelings and somatic concerns. Depressive symptoms commonly occur not only as part of the so-called post-psychotic depression, but also during the acute phase of illness (Buckely et al., 2009; El Yajazi et al., 2002). The depressive and anxiety symptoms that are part of the acute phase are associated with good outcomes (Emsley et al., 1999), whilst persistent symptoms of depression have been associated with poor outcome and require more specific clinical investigation and treatment (Oosthuizen et al., 2006).

Therefore it is evident that schizophrenia has enormous clinical variability in terms of symptom expression, which makes it a complex clinical disorder. It is also unknown to what degree the symptom domains influence outcome and whether this may be mediated by additional clinical features including social cognition (Millan et al., 2014).

First-episode schizophrenia

The diagnosis of schizophrenia is most commonly made in young adults following their first episode of psychosis. The median age at onset of schizophrenia is between 25 and 35 years, with men having their onset in the mid-twenties and women in the mid-thirties (McGorry et al., 2011). Prospective, longitudinal clinical studies in first-episode schizophrenia have become relatively commonplace over the past two decades, and have provided a good deal of useful information regarding the clinical presentation, course and treatment of the illness.

Studies that have used factor analysis to study symptom dimensions in first-episode schizophrenia have found interesting results. It appears that symptom expression during the first episode may be more complex than observed in chronic multi-episode schizophrenia patients. Three studies that used exploratory factor analyses found that symptoms were explained better by a seven factor, rather than five factor solution, with the separation of depression and anxiety dimensions and a new motor dimension (Emsley et al., 2003; Rapado-Castro et al., 2010; Wolthaus et al., 2000). Interestingly, the motor dimension was found at study entry in antipsychotic-naïve patients and consisted of mannerisms and posturing as well as motor retardation. These motor symptoms are part of the catatonic group of symptoms which were common prior to the antipsychotic treatment era. Catatonic symptoms have been found in up to 25% of antipsychotic-naïve patients and are associated with poor outcome (Cortese et al., 2005). Drake et al. (2003) followed up early psychosis patients for 18 months and found that the symptom dimensions at 18 months were similar to the symptom dimensions described in patients with chronic schizophrenia compared to the baseline data. In addition, models derived from 18 month data did not fit well with the baseline data. The emerging evidence therefore suggests that symptom dimensions may change with time making first-episode schizophrenia patients more clinically heterogeneous than multiple episode patients.

Long-term course and outcome of schizophrenia

The long-term course of schizophrenia is heterogeneous with patterns ranging from patients having a single episode to patients with a continuous unremitting course. Most patients with schizophrenia have a course that falls between the above extremes, with relapses and remissions. According to the DSM-5, the course of schizophrenia is described after examining both the cross-sectional as well as longitudinal features of the illness (APA, 2013). The cross-sectional 'specifiers' address the issue of whether a patient meets the criteria of being in the active phase and whether they are in partial or full remission. The longitudinal pattern of the illness describes how the illness has progressed over the period of at least one year. The DSM-5 describes the course of schizophrenia in the following way:

- First episode, currently in acute episode
- First episode, currently in partial remission
- First episode, currently in full remission
- Multiple episodes, currently in acute episode
- Multiple episodes, currently in partial remission
- Multiple episodes, currently in full remission
- Continuous
- Unspecified

Historically the course of schizophrenia has been described as the longitudinal pattern of the illness, whilst the outcome has been described as a cross-sectional measure. Therefore the outcome of patients with schizophrenia can be described at a single time point (e.g. at 5 years) (Gaebel and Frommann, 2000). One of the seminal studies on the long-term course of schizophrenia, the International Study of Schizophrenia, was conducted by the World Health Organization (WHO)

(Harrison et al., 2001). The study followed more than 1600 subjects with schizophrenia from 14 culturally diverse treatment incident cohorts and four prevalence cohorts for up to 25 years. A Life Chart Schedule was used to assess the course of illness, including symptoms, treatment utilisation, residential status and work functioning. They found almost 30% of the patients had an acute onset of illness with multiple episodes of relapses and a good outcome, while 22% had an insidious onset of illness with multiple episodes of relapses and a good outcome. More than two-thirds (68%) of the patients with episodic illness had two or more episodes. Patients with an insidious onset of illness with continuous symptoms and poor outcome accounted for almost 15% of the sample. Interestingly, almost 15% of the patients that had initially been classified as having a continuous trajectory improved later and were reclassified as having a good outcome at the 15 year follow-up assessment.

Various other studies on the long-term course of schizophrenia have been conducted however since they used inconsistent case definitions, different sampling methods and outcome measures comparison was difficult (Menezes et al., 2006). Jobe and Harrow (2005) reviewed studies that examined the long-term outcome of schizophrenia in North America including studies that were at least 10 years in duration. Their results were similar to the WHO study, that there was heterogeneity in the course and outcome of patients with schizophrenia. Approximately 20% of the patients with schizophrenia had a single episode of illness with good outcome, and a further 20 – 30% of patients had multiple episodes with remissions and good outcome (Jobe and Harrow, 2005). The view that schizophrenia is a progressive illness with an invariably poor outcome has thus been challenged by well-designed long-term studies that show that patients with schizophrenia can experience periods of recovery and may even function well at work and socially.

Treatment of first-episode schizophrenia

In the last two decades, there have been a large number of studies reporting on how best to treat first-episode schizophrenia patients. The prevailing approach is to treat with comprehensive multi-element biopsychosocial treatment that is available in many early intervention centres around the world (McGorry, 2015). The guiding principle in the treatment of first-episode schizophrenia patients is that of the 'critical period hypothesis' (Birchwood et al., 1998). This hypothesis identified the first five years of illness as an important determinant on the trajectory of illness and intervention during this period is likely to have maximum impact on the future course. The three principles of treatment adopted by Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia and subsequently followed by many other early intervention services include: (i) early detection, (ii) comprehensive acute phase care, and (iii) recovery-focused continued care (McGorry, 2015).

Early detection and treatment is the first component of early intervention services. This is aimed at reducing the time between the onset of psychotic symptoms and initiation of successful treatment, or duration of untreated psychosis (DUP). It is important to aim at reducing DUP as prolonged DUP has been shown to be an independent predictor of poor outcome in patients with first-episode schizophrenia (Marshal et al., 2005; Perkins et al., 2005). Interventions are aimed at increasing the awareness of mental illness in the general population and reducing treatment delays that are due to blockages in the pathways to care (Iyer et al., 2015).

Comprehensive acute phase care often includes individual case management, family education and support, individual or group cognitive behavioural psychotherapy, and educational or vocational rehabilitation (Hughes et al., 2014; Iyer et al., 2015). A number of controlled trials have shown that

intensive early treatment of first-episode schizophrenia is more effective than standard care. For example, the large OPUS trial in Denmark showed that intensive treatment consisting of assertive community treatment, family intervention and social skills training had significant positive effects on psychotic symptoms, negative symptoms, secondary substance abuse, lower doses of antipsychotics, and higher satisfaction with treatment at the end of the two years (Petersen et al., 2005). However these positive outcomes were not observed at the five year follow up, except for fewer days in hospital and fewer patients in supported employment (Bertelsen et al., 2008). A recent Cochrane systematic review that examined the effects of early detection, phase specific treatments and specialized early intervention teams found some support for early intervention, but further trials are desirable, as there is uncertainty in whether the treatment gains can be maintained beyond the early intervention treatment period (Marshall and Rathbone, 2011).

Efficacy of antipsychotic treatment

Although comprehensive, multiple psychosocial interventions are essential ingredients in early intervention services, antipsychotic treatment remains the cornerstone of the management of first-episode schizophrenia. The majority of patients with first-episode schizophrenia have a robust response to antipsychotic treatment, unlike multi-episode patients (Robinson et al., 1999). Two recent meta-analyses studied the efficacy and side effects of antipsychotics in first-episode schizophrenia (Crossley et al., 2010; Zhang et al., 2012). The first study compared the efficacy of atypical versus typical antipsychotics in the treatment of early psychosis (Crossley et al., 2010). They included 15 randomised controlled trials that included a total of 2522 patients. They found no significant difference between atypical and typical antipsychotics in acute symptom response (at 3 months) as the majority of patients with first-episode schizophrenia showed a good response to treatment. The second meta-analysis compared the efficacy and tolerability of individual second generation antipsychotics compared with first generation antipsychotics (Zhang et al., 2012). They

found that only olanzapine and amisulpride were superior to haloperidol in terms of short term symptom reduction and response to treatment. They also found that pooled second generation antipsychotics were similar to first generation antipsychotics in terms of treatment response. These two meta-analyses lend further weight to the principle that patients with first-episode schizophrenia respond robustly to most antipsychotics, irrespective of the drug class.

Furthermore patients with first-episode schizophrenia require lower doses of antipsychotics for treatment of their symptoms and are more sensitive to the extrapyramidal effects of antipsychotics compared to chronic schizophrenia patients (Kapur et al., 1996; Oosthuizen et al., 2001). A seminal double-blind, randomised controlled study showed that low doses of haloperidol are as effective as higher doses in reducing psychotic symptoms in patients with first-episode schizophrenia (Oosthuizen et al., 2004). Low doses were better tolerated, with significantly fewer extrapyramidal symptoms, less utilisation of anticholinergic medication and lower levels of prolactin.

Although short term response to antipsychotics is robust in patients with schizophrenia, longer term outcome of treatment is more important with regards to schizophrenia – a potentially life-long illness. Therefore studying remission in the treatment of patients with first-episode schizophrenia may be more meaningful. Remission is defined as the presence of mild, or no, 'core' psychotic symptoms for a period of six months (Andreasen et al., 2005). The core psychotic symptoms include delusions; unusual thought content; hallucinatory behaviour; conceptual disorganization; mannerisms/ posturing; blunted affect; passive/ apathetic social withdrawal; lack of spontaneity and flow of conversation. Five large studies have since been published that examined remission and its correlation in first-episode schizophrenia (see table 1 below).

The first study examined remission using data from a large multinational, randomized controlled trial comparing haloperidol with risperidone in early psychosis (Emsley et al. 2007). Four hundred and sixty two participants with schizophrenia, schizoaffective disorder, or schizophreniform disorder were treated with low doses of either haloperidol (mean modal dose of 2.9mg) or risperidone (mean modal dose of 3.3mg) for two to four years. Assessments were made using the Positive and Negative Symptom Scale (PANSS), Extrapyramidal Symptom Rating Scale (ESRS), and the Wisconsin Quality of Life Index. The authors found that 70% (n=323) of the patients met the cross-sectional remission criteria at some point during the trial. However, only 23.6% (n=109) were able maintain the low severity of symptoms for six months in order to achieve the remission criteria. Patients who achieved remission had greater overall symptom improvement, greater improvement in subjective quality of life, fewer relapses, and had a more favourable attitude towards their medication. The remitted patients also required lower doses of antipsychotic medication and had fewer extrapyramidal side effects. However, there was no difference in suicidality, cognition, body mass index, and whether patients were on risperidone or haloperidol. The authors noted that despite the good rate of initial response seen in first episode psychosis, the majority of patients failed to maintain the low severity of symptoms in order to achieve remission status (Emsley et al., 2007).

The second study assessed the predictive validity of the remission criteria in first episode psychosis patients who had shown initial response to antipsychotics (Wunderink et al., 2007). The participants were enrolled into the study if they had positive psychotic symptom remission within their first year of treatment. They were then followed up for 18 months with symptoms measured using the PANSS, functioning measured using the Groningen Social Disabilities Schedule (GSDS), and quality of life measured by the World Health Organization Quality of Life Scale (WHOQOL-Bref). Of the 125 patients included in the study, 60 (48%) patients achieved remission, whilst 65 (52%) failed to achieve remission. Patients who achieved remission had lower positive, negative, and

disorganization symptoms and better social functioning. However remission did not associate with a better quality of life.

Addington and Addington (2008) examined the remission criteria in a secondary analysis of a first episode psychosis cohort from the Calgary Early Psychosis Program in Canada. They included data from 240 individuals with schizophrenia spectrum disorder or other psychotic disorder. Participants were given comprehensive treatment for three years. Assessments were made using the PANSS, CDSS, the Quality of Life Scale (QLS), the Cannon-Spoor Premorbid Functioning Scale, and the Case Manager Rating Scale for Substance Use Disorder. The authors found that 36.7% (n=88) met the remission criteria; 19.6% (n=47) met the cross-sectional criteria at the last assessment; 20.4% (n=49) met the cross-sectional criteria at some time point but not at the last assessment (fluctuating group); and 23.3% (n=56) did not meet the criteria at any stage. The participants who achieved remission had lower levels of overall symptoms and a higher level of functioning at baseline and at the last assessment. They also had improved premorbid functioning and shorter DUP. They found no difference in the groups that achieved remission or the cross-sectional criteria only. The authors postulated that the latter group may well have met the remission criteria had the study continued for a longer period of time. The group that met the cross-sectional criteria at some time points (fluctuating group) had more severe positive psychotic symptoms at baseline and at end point. This group had higher levels of cannabis use at endpoint, possibly accounting for more severe positive psychotic symptoms at baseline (Addington and Addington, 2008).

A secondary analysis from the European First-Episode Schizophrenia Trial, an open-treatment randomized trial compared the effectiveness of antipsychotics, and examined rates of remission (Boter et al., 2009). The primary aim of the trial was to compare the effectiveness of haloperidol

versus second generation antipsychotics in first episode psychosis patients. The investigators recruited 498 patients with schizophrenia, schizophreniform disorder or schizoaffective disorder. Patients were treated with low doses of haloperidol, amisulpride, olanzapine, quetiapine or ziprasidone in an open label randomized design for 12 months. Outcome assessments were made using the PANSS. Remission was achieved by 17% (n=18) of patients on haloperidol, 40% (n=42) on amisulpride, 41% (n=43) on olanzapine, 24% (n=25) on quetiapine, and 28% (n=23) on ziprasidone at 12 months. Patients on amisulpride, olanzapine and ziprasidone had statistically significantly higher remission rates than patients on haloperidol. The study thus found that fewer patients on haloperidol achieved remission than some of the second generation antipsychotics (Boter et al., 2009).

The last study examined the longer-term outcome of first episode psychosis patients followed up in a specialized early psychosis program EPPIC in Melbourne, Australia (Henry et al. 2010). 723 patients were treated in the program for at least two years. Study participants had been diagnosed with either non-affective psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychosis, and psychosis not otherwise specified) or affective psychosis (bipolar disorder and major depressive disorder with psychotic features) and were an epidemiologically representative cohort of first episode psychosis. Psychopathology was measured using the Brief Psychiatric Rating Scale, the Scale for Assessment of Negative Symptoms, and the Beck Depression Inventory. Quality of life was measured using the QLS, and functioning using the SOFAS and GAF scales. The follow up data was collected at approximately seven years after presentation. The investigators found that 36.8% (n=156) of the entire first episode psychosis patients met the cross-sectional remission criteria, whilst only 28.9% (n=72) of the patients with schizophrenia spectrum disorders met remission. The majority of the patients in remission (76.5%) had affective psychosis. Patients in remission also had higher mean scores for functioning and

quality of life (Henry et al. 2010). Although the five studies used different methodologies and followed participants up for varying lengths of time, it is clear that the majority of patients with first-episode schizophrenia did not reach remission when followed up for at least one year.

Table 1: Remission in first-episode schizophrenia studies

Study	N	Duration	Treatment	Remission
Emsley et al., 2007	462	2-4 years	Haloperidol or Risperidone	23.6%
Wunderink et al., 2007	125	1.5 years	Risperidone, Olanzapine, Quetiapine, or Clozapine	48%
Addington and Addington, 2008	240	3 years	Specialised early psychosis program	36.7%
Boter et al., 2009	498	1 year	Haloperidol, Amisulpride, Olanzapine, Quetiapine, or Ziprasidone	Haloperidol = 17%; Amisulpride = 40%; Olanzapine = 41%; Quetiapine = 24%; Ziprasidone = 28%
Henry et al., 2010	723	7 years	Specialised early psychosis program	36.8%

Tolerability of antipsychotic treatment

The first experience of antipsychotics may have a lasting influence on subsequent engagement and adherence to antipsychotic medications therefore the choice of antipsychotic treatment in first-episode schizophrenia patients is particularly important. Since there is little difference in the long-term efficacy of antipsychotics, the choice of antipsychotic may be dependent on its adverse effect profile. Yet first-episode schizophrenia patients are more likely to experience adverse effects from antipsychotic treatment compared to multi-episode patients (McEvoy et al. 1999). This increased

sensitivity has traditionally been observed with first generation antipsychotics and their propensity to cause extrapyramidal side effects (EPS). Haddad et al. (2012) conducted a systematic review of randomised controlled trials in first-episode schizophrenia to examine the risk of extrapyramidal side effects of different antipsychotics. They found that second generation antipsychotics were less likely than first generation antipsychotics to cause EPS. However the majority of the studies used haloperidol as the comparator drug which is a high potency antipsychotic with leads to significantly higher rates of parkinsonism and akathisia. Patients treated with haloperidol had greater use of anticholinergic drugs as well as beta-blockers. They found very little difference in EPS rates between the second generation antipsychotics, which was possibly explained by the low doses used in the studies.

With the increasing use of second generation antipsychotics, greater attention has shifted to the weight and metabolic adverse effects of antipsychotic. This is particularly important as patients with schizophrenia experience disproportionate rates of medical morbidity and mortality compared to the general population. Among causes of death, cardiovascular disease is responsible for as much as 50% of the excess mortality associated with the diagnosis of schizophrenia. The suggested causes of cardiovascular disease within the schizophrenia population include lifestyle choices (i.e., smoking, inactivity, poor diet); substandard medical care; and iatrogenic contributions (e.g. antipsychotic-induced weight gain) (Fan et al., 2013).

Three systematic reviews have examined weight gain due to antipsychotics in first-episode schizophrenia patients. A systematic review of antipsychotic-induced weight gain in patients with schizophrenia treated by commonly prescribed antipsychotics (risperidone, olanzapine or haloperidol) found that patients with first-episode schizophrenia are at particularly high risk of

weight gain (Alverez-Jimenez et al., 2008). In fact, first-episode schizophrenia patients gained three to four times the amount of weight gained by multi-episode schizophrenia patients in both short term and long term studies. They concluded that young patients who had limited exposure to antipsychotics are particularly vulnerable to rapid and substantial weight gain.

The second systematic review and meta-analysis that examined weight gain in antipsychotic-naïve patients found that weight gain and an increase in body mass index (BMI) were highly significant within the first few weeks of treatment (Tarricone et al., 2010). They found that patients gained on average 3.8 kg or their BMI increased by 1.2 points within 12 weeks of treatment. They also found that weight gain continues and does not plateau the longer patients are on treatment, although there were few studies that looked at long term treatment.

Lastly, a recently published systematic review and meta-analysis examined the differential effects of antipsychotics on weight gain in first-episode psychosis patients (Tek et al., 2015). The authors conducted a meta-analysis of short and long term weight gain between placebo and antipsychotics. They found the overall mean weight gain difference between placebo and antipsychotics to be 3.22 kg or 1.46 BMI points at or before 12 weeks. The only antipsychotic that did not cause significant weight gain in the short term was ziprasidone. The long term studies showed a mean weight gain of 5.3 kg or 1.86 BMI points at 12 months. Interestingly, haloperidol and aripiprazole which are noted as weight neutral in chronic multi-episode studies were associated with significant weight gain in first-episode psychosis patients.

Very few studies have examined other cardiometabolic effects of antipsychotics in first-episode schizophrenia (de Hert et al., 2011; Foley and Morley, 2011). Antipsychotic-induced weight gain is

associated with increases in blood glucose, fasting triglycerides and total cholesterol. Young patients are at particular risk of these cardiometabolic effects particularly from second generation antipsychotics (de Hert et al., 2011). A systematic review of cardiometabolic changes in first-episode schizophrenia patients found an increased risk of cardiovascular disease due to antipsychotics (Foley and Morley, 2011). Although there was limited data, the authors were able to separate individual antipsychotics' cardiometabolic profiles but found no evidence for any class differences. And finally, a recent comprehensive meta-analysis of head-to-head trials that compared second generation to first generation antipsychotics in first-episode schizophrenia patients found that weight gain and glucose and lipid metabolism changes were not always consistent (Zhang et al., 2012). The antipsychotics that were associated with the most weight gain were not necessarily associated with greater increases in glucose and lipid parameters.

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Chapter 2

Early intervention in schizophrenia in developing countries: Focus on duration of untreated psychosis and remission as a treatment goal

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Early intervention in schizophrenia in developing countries: Focus on duration of untreated psychosis and remission as a treatment goal

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Abstract

Early intervention services are based on the premise that untreated psychosis may have a deleterious effect on outcome, particularly in the early years of illness. The majority of the studies on duration of untreated psychosis have been conducted in developed countries; therefore this review focuses on publications from developing countries. We also review studies from developing countries that have been published following the Remission in Schizophrenia Working Group criteria.

The duration of untreated psychosis is longer in developing countries, and is also associated with poor outcome, whereas remission rates following treatment of first-episode schizophrenia in developing countries appear to be higher than in developed countries. These two findings strongly argue for the establishment of early intervention services for schizophrenia in developing countries.

Introduction

Although there is a large body of research to understand the causes and to improve the treatment of schizophrenia, it remains one of the most complex, burdensome and costly illnesses to date (Rossler et al., 2005). In fact, schizophrenia is considered to be one of the most costly illnesses that psychiatrists treat (Rice, 1999). This has important implications for developing countries where most healthcare budgets are under resourced. Yet there is now increasing evidence that early intervention services are cost-effective. Resources diverted to early intervention programmes can have positive long-term effects on the outcome of schizophrenia (Chen et al., 2008). There are hundreds of early intervention programmes being implemented around the world; however, the majority of these programmes are in developed countries. Developing countries in Africa, where the majority of the population is under the age of 25 years, have progressed slowly in bringing early intervention services to the continent (Ndetei, 2008). Developing countries in Latin America have made more progress than Africa. There are now at least seven sites in Latin America where there is on-going research and services provided to people with the first episode of psychosis; however, the majority of these services are in Brazil (Brietzke et al., 2011). Recently Latin American researchers have called for more collaboration and increased efforts in expanding their services. Developing countries in Asia have perhaps made the most progress in developing early intervention services, with some services mirroring the best models from developed countries (Iyer et al., 2010). However, there is also a call to expand these services to benefit more people and to examine the best models to implement in resource-limited settings (Keshavan et al., 2010).

Early intervention services are based on the premise that untreated psychosis may have a deleterious effect on outcome, particularly in the early years of illness, and optimal intervention during the so called 'critical period' will improve long-term outcome in schizophrenia (Birchwood et al., 1998). We have thus focused this review on recent publications from developing countries examining duration of untreated psychosis and remission following treatment of the first episode of psychosis.

Duration of untreated psychosis

The duration of untreated psychosis (DUP) is defined as the time from manifestation of the first psychotic symptom to initiation of adequate antipsychotic treatment (Marshall et al., 2005). The study of DUP and outcome has received increasing attention over the last two decades. This is largely due to the

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establishment of early intervention services designed to shorten the delay in seeking treatment in people with early psychosis (McGorry et al., 2008). The study of DUP has thus important implications as this may lead to improved understanding of the pathophysiology of schizophrenia. Furthermore, DUP is seen as a potentially modifiable predictor of outcome with important clinical implications, as outcome could theoretically be improved by reducing DUP (Perkins et al., 2005). There are, however, some authors who question the direction of the correlation between DUP and outcome; advancing that DUP may just be a marker of poor prognosis (Bosanac et al., 2010; McGlashan, 1999).

Two influential systematic reviews published at approximately the same time concluded that DUP is an independent predictor of outcome in first-episode psychosis (Marshall et al., 2005; Perkins et al., 2005). Marshall et al. (2005) reviewed prospective studies of first-episode psychosis cohorts that examined DUP and outcome. The authors included studies that restricted participants to schizophrenia-related disorders, assessed outcome blind to DUP status, achieved a follow-up rate of >50%, and used a standardized method to assess DUP. They found small or non-significant correlations between DUP and outcome at baseline, but the correlations became significant for most outcomes studied at 6- and 12-month follow-up. At baseline there were correlations between DUP and depression and anxiety symptoms, as well as quality of life. At six months there were significant correlations between DUP and all symptom measures and overall functioning but not for quality of life. At twelve months there were significant correlations between DUP and all symptom measures, overall functioning and quality of life. At the two-year time point data was only available from two studies but also showed significant correlations between DUP and positive symptoms, overall functioning, and quality of life but not for negative symptoms or social functioning. The authors then examined the effect of premorbid adjustment on the relationship between DUP and outcome. They found that the association between DUP and particularly positive symptoms was robust even after adjusting for premorbid adjustment. Marshall et al. (2005) concluded that there was convincing evidence of an association between DUP and outcome.

The second meta-analysis reviewed the relationship between DUP and relapse risk, neurocognitive function, and brain morphology in first-episode schizophrenia (Perkins et al., 2005). They included 43 studies that used quantitative measures of DUP; cross-sectional analyses of DUP and baseline symptoms, brain morphology, cognition, or functional measures or prospective analyses of symptom change; clinician rated instruments to measure psychopathology; and most of the subjects had a diagnosis of non-affective psychotic disorder. The authors found that shorter DUP was significantly associated with greater response to antipsychotic treatment as measured by global psychopathology, positive symptoms and negative symptom severity, and global functional outcome. There was, however, no association between DUP and baseline cognition. DUP was associated with severity of negative symptoms at baseline, but not with positive symptoms and general psychopathology. There was no association between DUP and abnormalities in brain morphology at baseline. And lastly, there was not enough evidence supporting the association between DUP and risk of relapse. The authors concluded that DUP was an independent predictor of treatment response and the extent of recovery from a first-episode of schizophrenia (Perkins et al., 2005).

The majority of the studies included in the above two systematic reviews were studies conducted in developed countries; however, a recent systematic review examined DUP and outcome in low and middle income (LAMI) countries (Farooq et al., 2009). The review included studies that examined an association between DUP and improvement in symptoms, disability, or mortality, studies that used clinician rated instruments, and studies that met the criteria for a psychotic diagnosis according to DSM or ICD classification systems. However, in an effort to include as many studies as possible, they did not exclude any studies on the basis of the quality of the measurement of DUP. They included 11 studies that were conducted in eight LAMI countries (Poland, Mexico, Turkey, Brazil, India, South Africa, China and Indonesia), out of a possible 152 countries. The authors found that longer DUP was negatively associated with the degree of reduction of symptoms following treatment. There was a negative association between DUP and positive symptoms but DUP was not associated with negative symptoms at baseline. Longer DUP was associated with greater disability, but definite association between DUP and mortality could not be inferred from the available data. The authors concluded that although there were a small number of studies from LAMI countries, longer DUP was also associated with poorer response in LAMI countries.

In a related study, the same group then compared the findings from above systematic review of DUP and outcome from LAMI countries to studies from high income countries and examined a possible association with gross domestic product (GDP) (Large et al., 2008). The authors found the average mean DUP was significantly longer in studies from LAMI countries compared to studies from high income countries (125.0 versus 63.4 weeks; $p = 0.012$). Interestingly, however, studies from upper middle

income countries had a shorter DUP than studies from high income countries. In a subset of studies that examined DUP in patients with non-affective disorders who had received some treatment, the mean DUP from studies from the LAMI countries was also longer than similar studies from high income countries. The authors then examined the relationship between DUP and GDP purchasing power in the studies from LAMI countries. They found a linear relationship between DUP and GDP, where DUP was reduced by 6 weeks for each increase of US$1,000 GDP purchasing power. However, this relationship did not hold true for data from high income countries. Nevertheless they concluded that long DUP in LAMI countries may be associated with low income rather than previously identified factors such as lack of insight and insidious onset of illness, and family's lack of understanding of need for treatment. Long DUP in LAMI countries may be due to low income as well as the cost of treatment.

A number of studies conducted in LAMI countries have been published since the above systematic review. A recently published study from Iran examined DUP and pathways to care in a group of patients with first-episode psychosis admitted to a psychiatric hospital (Sharifi et al., 2009). Their sample (n = 91) included patients diagnosed with both affective and non-affective psychosis, and the majority of patients had bipolar disorder (40.6%). The mean DUP was found to be 52.0 weeks. The median DUP in patients with schizophrenia was much longer, though, close to two years. Interestingly they found that acute onset of illness and living in rural areas were predictive of a shorter DUP. Another study examined DUP and pathways to care in patients with schizophrenia who presented for treatment in Karachi, Pakistan (Naqvi et al., 2009). DUP was measured using the Interview for Retrospective Assessment of the Onset of Schizophrenia. They included 93 patients with schizophrenia. The mean DUP was 64 weeks. The DUP was not correlated with any demographic variables. Interestingly, the majority of patients presented to psychiatrists first as the primary healthcare services were not well developed. A recently published large epidemiological study of patients with first-episode psychosis in Sao Paulo, Brazil, found remarkable results (Oliveira et al., 2010). The investigators included 200 patients from a defined area of Sao Paulo who had made their first contact with the mental health services, with most patients accessing the emergency psychiatric services. The majority of the participants included in the study had non-affective psychosis (61%) and were living with their families (81%). The median DUP for their sample was surprisingly short at 4.1 weeks. Following multivariate analyses, participants living alone were three times more likely to have a long DUP than those living with their families. The study concluded that the context in which patients live influences the DUP and its correlates.

Another recently published study examined clinical features in a sample of first-episode psychosis patients admitted to a psychiatric hospital in South Africa (Burns et al., 2010). The investigators included 54 patients with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. DUP was defined as the duration from onset of first positive psychotic symptoms to hospitalization. The mean DUP was 35.08 weeks, with a median of 6 weeks. Patients who attributed their illness to a spiritual or traditional cause had a significantly longer DUP. Patients who visited a traditional healer prior to being hospitalized also had a longer DUP. The study was limited, however, by the small sample size which precluded multivariate analyses. Lastly, Thirthalli et al. (2011) prospectively studied DUP and outcome in a cohort of antipsychotic naïve schizophrenia patients in the south of India. The authors included patients with schizophrenia or schizophreniform disorder diagnosed using a computerized diagnostic interview schedule for DSM-IV. DUP was measured using the Interview for Retrospective Assessment of Onset of Schizophrenia. Symptom scores were measured using the Positive and Negative Symptom Scale (PANSS) and functioning using the Social and Occupational Functioning Scale. Of the 119 patients included in the study, they were able to assess 93 patients at 1-year follow-up. The mean DUP was 90.2 weeks and was positively correlated to baseline total PANSS scores, total PANSS scores at 1-year follow-up and level of functioning.

There is considerable evidence that longer delays in initial treatment of schizophrenia is associated with a poorer outcome. However, what delays treatment in LAMI countries is not well understood. Future research directions in the area of DUP should involve establishing methodologically sound studies in geographically diverse LAMI countries that explore cultural, economic, biological and demographic factors as well as health system barriers that may contribute to DUP.

Symptomatic remission as a measure of outcome

In an attempt to improve the study of outcome in schizophrenia, the Remission in Schizophrenia Working Group (RSWG) proposed a consensus definition of remission in schizophrenia (Andreasen et al., 2005). The RSWG published an operational set of criteria that defined remission as the presence of mild, or absence of, eight 'core' psychotic symptoms

for a minimum period of 6 months. The 'core' symptoms include delusions; unusual thought content; hallucinatory behaviour; conceptual disorganization; mannerisms/posturing; blunted affect; passive/apathetic social withdrawal; lack of spontaneity and flow of conversation. The criteria can be assessed using the PANSS, the Brief Psychiatric Rating Scale (BPRS), and the Scale for Positive Symptoms/Scale for Negative Symptoms (SAPS/SANS). The threshold of mild severity of symptoms means that the symptoms, if present, do not interfere with daily activities. The eight symptoms are considered to be the most diagnostically specific for schizophrenia and are most often utilized for hospitalization of patients with schizophrenia (van Os et al., 2006). The time criteria of 6 months is an arbitrary cut-off; however, it is long enough to ensure that the improvement of symptoms is sustained and stable (van Os et al., 2006).

Prior to the publication of the RSWG criteria, studies that examined remission in first-episode psychosis cohorts used different remission definitions which led to a diverse variation of remission rates. Lieberman et al. (2003) defined remission as 50% reduction in total BPRS scores from baseline with no more than a score of 3 on five BPRS psychosis items and Clinical Global Impression Scale (CGI) of mild or less. However, there was no duration criterion as part of their remission criteria. Remission was the primary outcome in their double-blind randomized trial comparing chlorpromazine to clozapine in first-episode psychosis patients that were antipsychotic-naïve. They found remission rates of approximately 80% for both antipsychotics at the 1-year follow-up, whereas another double-blind randomized controlled trial of olanzapine versus haloperidol found remission rates of only 57.25% for olanzapine and 43.94% for haloperidol after 2 years (Green et al., 2006). Their definition of remission was mild or less positive psychotic symptoms (P1, 2, 3, 5 and 6 on the PANSS) and a CGI of 3 or less for 4 weeks consecutively. A 1-year follow-up of an epidemiological cohort of first-episode psychosis in India found 50% remission rates (Saravanan et al., 2010). The authors used a broad definition of remission that were no positive or negative psychotic symptoms for a period of 1 month. A different epidemiological cohort study from Canada found higher remission rates (70%) at the end of 1-year follow-up (Malla et al., 2002). Their definition of remission was absence of psychotic symptoms (1 or 0 on all global items of the SAPS) for a period of 1 month.

The large variations in remission definitions made it difficult to compare findings across studies, thus publication of the RSWG criteria has attracted considerable attention. Following the publication of the RSWG criteria, the first published study to examine remission in first-episode psychosis evaluated symptom improvement patterns and variables that predicted remission (Emsley et al., 2006). The authors followed up 57 participants with schizophrenia, schizoaffective disorder, or schizophreniform disorder who were treated with low doses of haloperidol over 2 years in South Africa. Psychopathology was measured using the PANSS and Calgary Depression Scale for Schizophrenia (CDSS). The results showed that 70% (n = 40) of the participants were able to meet the cross-sectional remission criteria at some point during the study. However, only 40% (n = 23) were able to maintain the low levels of symptoms for 6 months in order to achieve the RSWG criteria. Only 19 patients maintained their remission status throughout the study. The mean remission time was 10 months. When studying the symptom improvement patterns, both remitted and non-remitted patients had significant early improvement (6 weeks) of symptoms, including the 'core' psychotic symptoms, but only the remitted patients continued to have symptom improvement until the end of the study. The authors noted that although there were significant differences in the overall level of symptoms between the remitted and non-remitted groups at end point, there was also considerable overlap, particularly with depressive symptoms (Emsley et al., 2006).

A prospective study in first-episode psychosis patients treated with a long-acting injectable antipsychotic showed remarkable rates of remission (Emsley et al., 2008a). The investigators followed up 50 patients with schizophrenia or schizophreniform disorder for two years. The participants were treated with risperidone long-acting injection. Assessments were made using the PANSS, CDSS, ESRS, the Social and Occupational Functioning Scale (SOFAS), and the Drug Attitude Inventory (DAI). The authors found that 64% (n = 32) achieved remission at some point during the study, and interestingly the majority of the patients (n = 31) maintained their remission status throughout the study. Patients in remission showed more improvement in overall symptoms, excitement/hostility factor, depression/anxiety factor and insight scores. They also showed greater improvement in functioning, needed lower doses of risperidone long-acting injection with improvement in extrapyramidal symptoms. Patients in remission also remained longer in the study. The authors concluded that although first-episode psychosis patients respond well to treatment they do not maintain their response into remission. However, in this study the majority of the patients maintained their remission status and this was postulated to be due to the assured antipsychotic delivery with a long-acting injectable antipsychotic (Emsley et al., 2008a).

Later Emsley et al. (2008b) published a post hoc comparison of data drawn from two similar studies conducted at their centre. They used their site's data from a large multinational, randomized controlled trial of first-episode psychosis patients treated with oral haloperidol or risperidone (Schooler et al., 2005) and data from the above-mentioned study where first-episode psychosis patients were treated with risperidone long-acting injection (Emsley et al. 2008a). The two studies had similar methodologies, and patients came from the same catchment area and were treated by the same investigators, albeit a few years apart. The post hoc analysis included 47 patients from the first study (oral group) and 50 patients in the injectable antipsychotic group. The demographics and baseline clinical features were similar between the groups, except the PANSS positive subscale was higher in the injectable antipsychotic group. Both groups showed good early (12 weeks) treatment response but patients in the injectable antipsychotic group continued to show symptomatic improvement until the study end point. The injectable antipsychotic group had fewer discontinuations, more symptomatic improvement, lower relapse rates amongst responders, and a higher remission rate (64% versus 40.4%). The authors concluded that the study added to the evidence that assured antipsychotic delivery with a long-acting injectable antipsychotic leads to improved outcome in first-episode psychosis patients (Emsley et al., 2008b).

A recently published study from Turkey followed up first-episode schizophrenia patients in a naturalistic setting for a mean duration of 5 years (Uçok et al., 2011). The study reported on 93 patients who were followed up and assessed monthly for at least 1 year. Psychopathology was measured using the BPRS, the SAPS and the SANS. Premorbid functioning was assessed by the Premorbid Assessment Scale (PAS). During the first 24 months follow-up, 59.5% (n = 56) met the RSWG criteria for remission. However, only 28% (n = 16) of the patients in remission were able to maintain remission throughout the study. Furthermore, another 16 patients who initially could not maintain remission were able to attain remission during the follow-up period (5 years). The mean time to remission was 8.8 months. Patients in remission had a lower number of hospitalizations, shorter duration of hospitalizations and were more likely to be employed prior to baseline and during the follow-up period. Therefore, remission following first-episode schizophrenia is achievable even with long follow-up periods and is an important indicator of functioning (Uçok et al., 2011). A 6-year follow-up study of patients with schizophrenia living in the rural areas of Bali, Indonesia, was recently published (Kurihara et al., 2011a). The authors assessed patients who had been previously identified in the community as having schizophreniform disorder or schizophrenia at 5.5 years and 6 years later. Of the 37 patients at the 6-year follow-up, only 10 (27%) met the RSWG criteria for remission. Interestingly all 10 patients in remission also met their criteria for functional remission. Low negative symptoms scores at baseline and receipt of psychiatric treatment for more than half the follow-up period were significant independent predictors of remission. The same group then published a long-term follow-up of a group of hospitalized first-episode schizophrenia patients in Bali, Indonesia (Kurihara et al., 2011b). At the 17-year follow-up they were able to assess 43 out of the original 59 patients. Fifteen patients (25.4%) had died and one patient refused to be assessed. Nineteen patients (32.2%) met the RSWG criteria for remission. Interestingly the only predictor of remission was short DUP (less than 12 months) at the baseline assessment.

Conclusions

The well replicated finding of an association between longer DUP and poorer long-term outcome in developed countries also appears to holds true for LAMI countries despite the relatively small number and considerable heterogeneity of LAMI studies. Although DUP may depend on a number of factors, it is cause for concern that the average mean DUP in studies from LAMI countries is significantly longer compared to studies from high income countries. The recently published studies also show that local context, particularly how the health services have been organized, influence access to healthcare and the DUP. It is also interesting that a number of studies found correlations between a shorter DUP and living with family members. Further, studies of outcome in early psychosis in LAMI countries indicate high rates of remission following treatment. However there have been very few studies from developing countries that have measured outcome using the RSWG criteria.

These two observations argue strongly for the establishment of early intervention services for schizophrenia in these countries. While such services would require additional costs, improved outcomes may lessen the overall burden imposed by this illness on healthcare resources. In any event, apart from financial considerations, there is the ethical obligation to provide the best possible care for our patients.

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Chapter 3

Combining depot antipsychotic with an assertive monitoring programme for treating first-episode schizophrenia in a resource-constraint setting

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Original Article

Combining depot antipsychotic with an assertive monitoring programme for treating first-episode schizophrenia in a resource-constrained setting

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Conflicts of interest
Professor Piet Oosthuizen has received honoraria from Pfizer, Lundbeck, Astra-Zeneca and Cipla for speaking at educational meetings. Dr Bonginkosi Chiliza has received honoraria from Sandoz and Janssen for speaking at educational meetings. Professor Robin Emsley has received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Organon, Pfizer, Servier, Otsuka and Wyeth for participating in advisory boards and speaking at educational meetings, and has received research funding from Janssen, Lundbeck and AstraZeneca.

Lundbeck was not involved in any aspect of the conceptualization, design, conductance, analysis and reporting of the study.

Abstract

Aim: To assess the feasibility and effectiveness of depot antipsychotic (flupenthixol decanoate) combined with an assertive monitoring programme (AMP) in first-episode schizophrenia.

Methods: This was a prospective, non-comparative, longitudinal study conducted over 12 months assessing patient acceptance, adherence, outcome in domains of psychopathology, functionality and quality of life, and tolerability.

Results: Of 207 participants, 149 (72%) completed 12 months of treatment. Acceptance of and adherence to depot was good. Treatment response was achieved by 170 (82%) participants and remission by 124 (60%). Thirty-three (19%) responders relapsed and 10 (5%) participants met a priori criteria for treatment resistance. Treatment was generally well tolerated.

Conclusions: Combination of depot antipsychotic with an AMP may be an effective and safe intervention in early phases of schizophrenia, and may be particularly suitable for resource-constrained settings.

Key words: antipsychotic, developing country, psychotic disorder, schizophrenia.

INTRODUCTION

As a major contributor to disability-adjusted life years globally,[1] schizophrenia imposes a disproportionate emotional and financial burden on affected individuals, their families and carers, health-care systems and society.[2] The situation is particularly severe in low and middle income countries (LMICs) where poverty exacerbates the burden,[3] and where the treatment gap for severe mental disorders is

enormous.[4] Whereas part of this gap is due to patients not seeking biomedical help,[5] another likely major contributor is non-adherence to prescribed treatment, particularly in the period after first hospitalization.[6] Depot antipsychotics were developed in the 1960s to address the adherence problem in schizophrenia. However, they were typically reserved for patients with demonstrated poor treatment adherence or multiple relapses – that is, those who had been ill for many years.[7] Their greatest benefits may in fact be observed early in the illness by improving adherence and preventing accruing morbidity.[8] On their own, depots do not necessarily improve adherence, as patients may still default on treatment. Their great advantage, however, is that they make adherence explicit, thereby permitting timeous intervention for those at risk of relapse. With these considerations in mind, we developed an intervention comprising the use of a conventional depot antipsychotic with the following innovations: (i) targeting the early phase of illness; (ii) initiating depot treatment in the acute treatment phase to reduce the risk of disengagement between acute and maintenance phase treatment; (iii) using the lowest possible dose to minimize tolerability problems; and (iv) most importantly, exploiting the overt nature of adherence with depot by means of a simple assertive monitoring programme (AMP) suitable for resource-constrained settings. This study explored the acceptability, feasibility, efficacy and tolerability of this intervention in a collaborative two-site study conducted in Cape Town, South Africa, and Ibadan, Nigeria.

METHODS

This was an exploratory, non-comparative study assessing flexible doses of a conventional depot antipsychotic (flupenthixol decanoate) combined with an AMP as first-line treatment in first-episode schizophrenia. We report here the 12-month outcome results. Approval to conduct the study was obtained from the Stellenbosch University Faculty of Medicine and Health Sciences Human Research Ethics Committee and the University of Ibadan/University College Hospital Ethics Committee. The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice.[9]

Participants

Subjects were recruited from first referrals to psychiatric hospitals and community clinics within our catchment areas in Cape Town and Ibadan between April 2007 and March 2011. Patients and/or their legal guardians provided written, informed consent. Eligible participants were men and women, in- or outpatients, aged 16–45 years, with a first episode of psychosis meeting DSM-IV[10] (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnostic criteria for schizophreniform disorder, schizophrenia or schizoaffective disorder. Patients were excluded if they had, during their lifetime, been exposed to greater than 4 weeks of antipsychotic medication, been treated with a depot antipsychotic, and had a serious or unstable medical condition, mental retardation or current substance abuse.

Assessments

At baseline we obtained demographic information, psychiatric and collateral history, and records of previous and current treatment. All participants were assessed with the Structured Clinical Interview for DSM-IV (SCID).[11] Efficacy assessments comprised Positive and Negative Syndrome Scale (PANSS),[12] Clinical Global Impression (CGI) scale,[13] Calgary Depression Scale for Schizophrenia (CDSS),[14] Social and Occupational Functioning Assessment Scale (SOFAS)[10] and the World Health Organization Quality of Life-BREF (WHOQOL-BREF) Scale.[15] Duration of untreated psychosis (DUP) was estimated from the onset of continuous positive psychotic symptoms to initiation of adequate treatment. Adequate treatment was defined as the start of structured treatment with antipsychotic medication.[16] Subjects underwent physical examination. Tolerability measures comprised adverse event (AE) reporting, Extrapyramidal Symptom Rating Scale (ESRS),[17] weight, height and waist circumference. There were nine scheduled visits over the 12-month period – at baseline, weeks 1, 2, 4 and 6 and at months 3, 6, 9 and 12. Unscheduled visits took place at the investigators' discretion. Subjects were evaluated with the PANSS, CGI, CDSS and ESRS at each scheduled visit and with the SOFAS and WHOQOL-BREF at 0, 6 and 12 months. Investigators were trained in the use of the assessment instruments and underwent interrater reliability (IRR) testing prior to commencing the study. The IRR was >75% for all scales.

Interventions

Medication

There was a washout phase of up to 7 days during which all psychotropic medications were

discontinued. Patients were treated with oral flupenthixol 0.5–4 mg day^{-1} for 1 week prior to the first flupenthixol decanoate dose to test for hypersensitivity. The starting dose of flupenthixol decanoate was 10 mg two weekly deep intramuscular injection (IMI), with six weekly increments of 10 mg two weekly IMI permitted, to a maximum of 30 mg two weekly IMI. The starting dose could be reduced to 5 mg two weekly IMI in patients younger than 18 years. In the event of additional antipsychotic medication being required between visits, oral flupenthixol was allowed at the discretion of the investigator. Investigators were encouraged not to increase the dose of flupenthixol decanoate too rapidly, but rather prescribe lorazepam up to 12 mg day^{-1} for agitation during the acute phase of the study, and thereafter up to 4 mg day^{-1}. Other permitted concomitant medications included orphenadrine, trihexyphenidyl or biperiden for parkinsonism or dystonia; propranolol for akathisia; and antidepressants and medication for medical conditions at the investigators' discretion. Other antipsychotics, mood stabilizers and psychostimulants were not permitted.

AMP

The study coordinators (mental health nurses) were responsible for the AMP. They established good relations with patients and carers and provided psychoeducation with a structured approach emphasizing the need for continuous treatment. Study participation was by means of a shared decision-making process, involving family members where possible. A register was kept with patient appointment dates. Reminders were sent out by mobile phone text messaging. In the event of a missed appointment, patients or their carers were contacted telephonically by the mental health nurse and encouraged to come in for treatment. Where necessary, community health-care nurses were requested to contact the patient, and if all else failed, to conduct home visits.

Data analysis and outcome measures

We recorded all of the data in electronic case record forms. All entries were double-checked. Analyses were conducted using Statistica 11 (StatSoft, Inc) software. We used descriptive statistics, reporting means (SD). For efficacy and tolerability evaluations, we compared changes in scores from baseline to 12 months (per protocol population) and to end-point (intent to treat population, last observation carried forward) by Wilcoxon signed rank two-tailed test. Treatment response was defined as ≥50% reduction of PANSS total scores from baseline, calculated as (baseline score – end-point score)/baseline score – 30.[18] We defined remission according to Remission in Schizophrenia Work Group criteria.[19] We calculated relapse rates for those patients who had achieved a treatment response using relapse criteria adapted from those of Csernansky *et al.*[20] comprising any of: (i) 25% increase in PANSS total score from the previous visit; (ii) an increase of 10 points if the PANSS total score was less than 40; or (iii) a score of 6 ('much worse') or 7 ('very much worse') on the CGI scale. Treatment resistance was defined a priori as any one of: (i) study discontinuation due to poor response as judged by the investigator; (ii) end-point treatment response <20%; or (iii) end-point PANSS total score >70. For (ii) and (iii) criteria, patients were only considered treatment resistant if they had completed at least 3 months of treatment, and had not experienced a relapse. Adherence to depot was calculated as the percentage of actual injections received divided by the prescribed number of injections. To investigate predictors of remission and relapse, we conducted logistic regression using the following selected demographic and baseline clinical variables: age, gender, highest educational level, family history of schizophrenia, DSM-IV diagnosis, DUP, substance abuse in the past 3 months, PANSS positive/negative and general psychopathology subscale scores, CDSS total score, SOFAS score and WHOQOL-BREF transformed scores for domains 1–4.

RESULTS

We evaluated 328 patients, 91 of whom were not eligible, 15 declined participation, and 5 absconded prior to enrolment. A further 10 patients were excluded as they no longer met the inclusion/exclusion criteria before receiving study treatment. Therefore, 207 participants were included in the analyses – 126 patients from Cape Town and 81 from Ibadan. The majority of the patients had schizophrenia (149; 72%); 54 (26%) patients had schizophreniform disorder; and 4 (2%) patients had schizoaffective disorder. Table 1 presents the demographic and baseline clinical details of the sample.

Feasibility, acceptability, adherence

Each study coordinator was able to effectively manage a caseload of up to 70 patients with the AMP. Acceptance of depot treatment was good. Two

TABLE 1. Demographic details of the 207 participants

Age, years: mean (SD)	25.87 (6.92)
Gender, *n* (%)	
Male	137 (66)
Female	70 (34)
Ethnicity, *n* (%)	
Black African	99 (48)
Mixed ancestry	98 (47)
White	10 (5)
Marital status, *n* (%)	
Single	164 (79)
Married	30 (14)
Divorced	10 (5)
Widowed	2 (1)
Cohabiting	1 (1)
Employment status, *n* (%)	
Unemployed	177 (86)
Full-time employment	25 (12)
Casual employment	5 (2)
Diagnosis, *n* (%)	
Paranoid schizophrenia	78 (38)
Undifferentiated schizophrenia	44 (21)
Disorganized schizophrenia	25 (12)
Catatonic schizophrenia	2 (1)
Schizophreniform disorder	54 (26)
Schizoaffective disorder	4 (2)
Family history of schizophrenia, *n* (%)†	
Yes	81 (40)
No	123 (60)
Duration of untreated psychosis, weeks: mean (SD)	78.38 (147.65)
Duration of untreated illness, weeks: mean (SD)	120.09 (154.06)
Lifetime history of illicit substance abuse, *n* (%)‡	
Yes	80 (41)
No	116 (59)
Previous exposure to antipsychotic medication, *n* (%)	
Yes	61 (29)
No	146 (71)
Duration of antipsychotic exposure for the 61 subjects, days: mean (SD)	10.50 (7.10)
Hospitalized at start of study, *n* (%)	
Yes	47 (23)
No	160 (77)

†*N* = 204.
‡*N* = 196.

patients refused study participation because of fear of needles, and no injection site-related AEs were reported. All but one of our patients received their flupenthixol depot injections at two weekly intervals. (One patient switched to four weekly injections from week 40 to week 48 due to work commitments.) Our window period for the biweekly injections was 3 days. Although patients occasionally went beyond this period, overall adherence was good. One hundred and ninety-two (93%) patients received 100% of the prescribed depot injections (including patients who discontinued early), and the other 15 (7%) received a mean of 84% of the injections. (Fourteen patients at the Cape Town site received long-acting risperidone injection in place of flupenthixol depot injection for the first 12 weeks of the study as part of a sub-study. They were subsequently switched to flupenthixol decanoate.) The mean (SD) biweekly dose of flupenthixol decanoate was 11.6 (4.6) mg at 12 months for the per protocol patients and 11.5 (4.3) mg at end-point. Regarding concomitant medication, 109 (52%) patients were prescribed benzodiazepines and 31 (15%) antidepressants.

Efficacy

One hundred and forty-nine (72%) participants completed the 12 months of treatment. For the 58 (28%) who discontinued, reasons given were lost to follow up (n = 19, 9%), consent withdrawal (n = 16, 8%), poor response as judged by the investigator (n = 9, 4%), relocation (n = 7, 3%), medication side effects (n = 3, 1%), change of diagnosis (to bipolar disorder) (n = 2, 1%), persistent substance abuse (n = 1, 1%) and others (n = 2, 1%). Forty-seven (23%) patients were hospitalized at the start of the study, and eight (4%) required hospitalization during the course of the study, for worsening of psychosis (n = 2, 1%), hostility and aggression (n = 2, 1%), attempted suicide (n = 1, 1%), severe depression (n = 1, 1%), victim of assault (n = 1, 1%) and general medical condition (n = 1, 1%).

Treatment response (≥50% PANSS total score improvement) was achieved at some point by 170 (82%) of the 207 participants. Of the patients who responded, 33 (19%) relapsed according to our broadly defined criteria.[20] Most of the relapses were mild and did not require hospitalization. One hundred and twenty-eight (62%) patients met cross-sectional remission criteria and 124 (60%) achieved full remission (i.e. maintained for 6 months)[19] at 12 months. Ten (5%) participants met our a priori criteria for treatment resistance. For the logistic regression analyses, a lower baseline PANSS negative subscale score (odds ratio (OR) 1.2, 95% confidence interval (CI) 0.7–1.0, P = 0.009) and lower baseline CDSS score (OR 1.3, 95% CI 0.53–0.97, P = 0.01) significantly predicted remission, and female gender (OR 4.4, 95% CI 3.1–5.8, P = 0.03) predicted relapse.

Table 2 provides details of key efficacy and tolerability measures at baseline, 12 months (per protocol) and end-point.

TABLE 2. Mean (SD) efficacy and tolerability scores at baseline, 12 months and end-point

	Baseline (n = 207)	12 months† (n = 149)	P	End-point‡ (n = 207)	P
Positive and negative symptom scores					
Total	86.5 (19.2)	42.5 (11.4)	<0.0001	48.8 (17.2)	<0.0001
Positive subscale	22.3 (5.8)	8.8 (3.0)	<0.0001	11.0 (5.4)	<0.0001
Negative subscale	23.2 (8.1)	12.2 (4.7)	<0.0001	13.7 (6.0)	<0.0001
General psychopathology subscale	40.9 (10.1)	21.5 (5.7)	<0.0001	24.0 (8.1)	<0.0001
Clinical global impressions					
Severity	5.1 (0.8)	2.3 (0.9)	<0.0001	2.7 (1.2)	<0.0001
Improvement	–	1.4 (0.6)	–	–	
Calgary depression scale for schizophrenia	2.8 (3.9)	1.4 (3.0)	<0.0001	1.4 (2.9)	<0.0001
Social and occupational functioning scale	43.9 (11.9)	70.1 (13.3)	<0.0001	63.7 (16.6)	<0.0001
WHO Quality of Life-BREF Scale					
Domain 1 transformed score	12.0 (2.4)	13.0 (2.3)	<0.0001	12.7 (2.4)	<0.0001
Domain 2 transformed score	12.6 (2.7)	13.4 (2.1)	<0.0001	13.2 (2.3)	<0.0001
Domain 3 transformed score	10.7 (4.3)	12.6 (3.9)	<0.0001	12.3 (4.1)	<0.0001
Domain 4 transformed score	11.5 (3.1)	13.7 (2.4)	<0.0001	13.3 (2.9)	<0.0001
Extrapyramidal Symptom Rating Scale§					
Total	2.0 (4.7)	2.1 (4.8)§	0.7		
Questionnaire	0.5 (1.2)	2 (2.4)§	<0.0001		
Parkinsonism	1.2 (3.2)	3.6 (5.6)§	<0.0001		
Dystonia	0 (0)	0.1 (0.8)§	0.03		
Dyskinesia	0.1 (0.4)	0.2 (0.8)§	0.01		
Akathisia	0.07 (0.3)	0.5 (1.1)	<0.0001		
Weight (kg)	58.4 (11.8)	66.8 (13.7)	<0.0001	65.2 (13.8)	<0.0001
Body mass index (kg m^{-2})	21.0 (3.6)	24.1 (4.8)	<0.0001	23.4 (4.7)	<0.0001
Waist circumference (cm)	76.8 (10.5)	84.5 (12.4)	<0.0001	82.2 (12.2)	<0.0001

†Per protocol.
‡Intention to treat, last observation carried forward.
§Highest score at any visit.

Tolerability and safety

Extrapyramidal symptoms

Mean (SD) ESRS total and subscale change scores from baseline to maximum scores showed some significant increases, particularly for parkinsonism and akathisia subscales (Table 2). Sixty eight (33%) patients reported 132 Extrapyramidal symptoms-related AEs (akathisia [n = 26, 13%], parkinsonism [n = 28, 14%], stiffness [n = 18, 9%], tremor [n = 22, 11%], dystonia [n = 20, 10%], dyskinesia [n = 10, 5%] and unspecified [n = 9, 4%]). Most of these AEs were mild. Six (3%) patients developed mild, transient dyskinesia. Sixty-nine (33%) patients were prescribed anticholinergics or propranolol for extrapyramidal symptoms.

Body mass

There were substantial increases in weight, body mass index and waist circumference (Table 2). One hundred and fifteen (56%) patients had weight gain of 7% or greater. Two patients (1%) had diabetes mellitus prior to study entry but there were no emergent cases reported during the study.

The following additional AEs were reported in >10% of the participants: depression (n = 68, 33%), excitement (n = 27, 13%) and anxiety (n = 21, 10%). There was one (0.5%) attempted suicide.

DISCUSSION

Feasibility, acceptability, adherence

The results of this study suggest that depot antipsychotic combined with an AMP is feasible, and may be an effective intervention in first-episode schizophrenia in resource-constrained settings. The simplicity of the AMP means that community healthcare providers can deliver it without the necessity for extensive training, and it permits effective management of large caseloads simultaneously. This approach enables a large proportion of the care of patients with schizophrenia to be provided by primary care workers under the supervision of general physicians and mental health specialists, wherever available. This task shifting may greatly improve access to effective treatment. Shared decision-making contributed to good patient and carer acceptance of injections. In this regard, depot

antipsychotics may be particularly suited to LMICs, where attitudes towards injectable medications may be more favourable.[21] Additionally, the psychoeducation and shared decision-making components of our AMP by trained mental health nurses are likely to have led to a higher rate of acceptance of the depot antipsychotic.

Study retention rates were high and adherence good – an important finding given that non-adherence is a major preventable cause of morbidity. Although non-adherence prevalence rates of 41–49% have been reported in higher income countries,[22] the rates are likely to be even higher in LMICs where factors such as lack of education, poor understanding of medical disease models and inaccessibility of services prevail – for example, studies in Nigeria and South Africa show that only about 1 in 5 of such persons receive any treatment in a 12-month period.[4]

Efficacy

As would be anticipated in a first-episode schizophrenia sample,[23] symptom improvements were generally robust. There were high response and remission rates, with accompanying improvements in social and occupational functioning and quality of life. Although caution is mandatory when comparing results across studies, outcomes from our study compared favourably with those reported for the European First-Episode Schizophrenia Trial (EUFEST) in which several second-generation oral antipsychotics and haloperidol were compared over 12 months of treatment. For example, for our study versus EUFEST, respectively, all-cause discontinuation rates were 28% versus 33–72%; response rates (50% PANSS total score improvement, calculated with the same correction as in the present study) were 82% versus 37–67%; and remission rates 60% versus 17–41%.[24,25] Furthermore, although several of our patients experienced relapses, few were treatment refractory. The favourable outcomes in the present study may be ascribable to the higher study retention rates and assured adherence associated with a long-acting injectable antipsychotic, as previously reported in a first-episode sample treated with long-acting risperidone injection.[26] However, other factors could equally explain the observed differences, including study design (open label, non-comparative vs. randomized, comparative) and cultural/ethnic differences in treatment response. The low mean dose of flupenthixol decanoate that patients received is consistent with previous reports that first-episode patients require lower antipsychotic doses[27] and that low doses of first-generation antipsychotics are just as effective as high doses in first-episode patients.[28]

Tolerability

Although several patients experienced emergent extrapyramidal symptoms and weight gain, the treatment was generally well tolerated – particularly when considering the exquisite sensitivity to antipsychotics of first-episode patients[29] and that flupenthixol is a first-generation antipsychotic. Indeed, the frequency and severity of extrapyramidal symptoms – the most problematic side effect of first-generation antipsychotics – was not dissimilar to that reported with some second-generation antipsychotics in longitudinal studies in first-episode samples,[24,26,30,31] and the mean weight gain of 8.4 kg over 12 months was less than that reported for olanzapine (13.9 kg), quetiapine (10.5 kg) and amisulpride (9.7 kg), but greater than haloperidol (7.3 kg) and ziprasidone (4.8 kg) in the EUFEST study.[24] The relatively favourable tolerability of the treatment could be ascribed to both our low-dosing strategy and the fact that flupenthixol has been described as a 'partially atypical' antipsychotic.[32] The demonstration of favourable tolerability is important, given that the high acquisition costs of second-generation antipsychotics put them beyond the reach of most patients in LMICs.[33] Indeed, a recent Cochrane review of flupenthixol recommended that this inexpensive drug may well be worthy of careful investigation.[34]

Maximizing the advantage of depot antipsychotics

Surprisingly, clinical studies have failed to unequivocally demonstrate the superiority of depot over oral antipsychotics. Systematic reviews report few outcome advantages for depots versus oral antipsychotics.[35,36] Indeed, the most recent systematic review and meta-analysis of randomized controlled trials of depot versus oral antipsychotics in schizophrenia reported that pooled depots did not reduce relapse rates compared with oral antipsychotics.[37] These reviews highlight several methodological challenges and shortcomings of previous studies such as small samples, short study duration and, particularly, selection bias. Non-adherent patients, although being the most likely to benefit from depot antipsychotic treatment, are less likely to consent to participate. However, there are other reasons why depot antipsychotics may have failed to demonstrate advantages. First, most studies have been conducted in chronic, multi-

episode samples. Response to treatment is better in the first episode compared with subsequent episodes,[38] and the first 2–5 years have been proposed as a 'critical period' during which the illness at its most aggressive and the risk for relapse, disease progression and suicide is greatest.[39] Non-adherence is very common during the early stages of treatment.[40] Therefore, addressing adherence in early phase of illness with a depot antipsychotic would be consistent with contemporary public health principles of early effective intervention and prevention of accruing morbidity. The risk of treatment discontinuation seems to be particularly high in the period between acute and maintenance treatment, often after discharge from hospital.[6] Therefore, initiating depot treatment during the acute treatment phase may help bridge the treatment gap over this crucial transitional phase. A second possible reason for the failure of depot antipsychotics to demonstrate clear advantages is that on their own they may not improve adherence, as patients may still default on treatment. Addition of an AMP exploits the transparency of depot treatment and may be the critical component to improving adherence. Third, doses of conventional depot antipsychotics were frequently excessive in the past and resultant side effects may have contributed to the high dropout rates observed in clinical trials. We have found that low doses of conventional oral antipsychotics had equal efficacy and superior tolerability to higher doses in first-episode schizophrenia.[28] The low-dosing strategy comprised initiating antipsychotic treatment at the lowest possible dose, treating initial agitation with a benzodiazepine rather than increasing the antipsychotic dose, and gradual upward titration of antipsychotic dose as necessary until optimal response was obtained.[41]

Considerations when using depot antipsychotics in early illness

Despite general recognition of the enormity of the non-adherence problem in schizophrenia, depot antipsychotics are only prescribed in a small proportion of patients in clinical practice.[42] Particularly, their use in the early stages of illness has been limited. Systematic reviews of depot antipsychotics in first-episode and early schizophrenia report that most studies to date were post-hoc analyses of larger datasets and involved second-generation long-acting injectable antipsychotics[43,44] that are beyond the reach of patients in LMICs. The use of depot antipsychotic in first-episode schizophrenia is controversial presumably due to concerns regarding individual autonomy, coercion and dignity,[43] and the preconceived view of some psychiatrists that patients are unwilling to accept injections in the early stages of illness.[45] A counter-argument would be that the best way to promote individual autonomy and dignity is to achieve sustained remission by means of continuous treatment, and studies have reported considerable patient preference for depots, with those who receive depots being generally satisfied with this treatment.[46] Indeed, patients with a high level of insight, favourable attitude towards drug treatment and good understanding of the disease may choose depot rather than oral antipsychotic treatment.[47]

The use of a depot antipsychotic in acute phase illness and in first-episode patients may also raise some safety concerns, given the increased sensitivity of these individuals to antipsychotics and the fact that depot antipsychotic blood levels persist for a long time after discontinuation. Drug sensitivity reactions are a concern, as are severe extrapyramidal side effects including neuroleptic malignant syndrome. For this reason, it is obligatory to test for hypersensitivity with oral medication before initiating depot treatment. Importantly, no increased risk of extrapyramidal side effects including neuroleptic malignant syndrome has been reported with depot antipsychotics compared with their oral counterparts.[35,48] There may also be a concern that introducing a depot as first-line treatment in the first episode may result in some patients receiving unnecessary long-term antipsychotic exposure. However, guidelines generally recommend treatment of a first episode of schizophrenia for at least 12–24 months for those who achieve symptom stabilization,[49,50] and our own and others' experience with first-episode schizophrenia (including schizophreniform disorder) was that the vast majority relapsed when antipsychotic treatment was discontinued.[51–53] Given the enormous risks associated with relapse and the absence of reliable relapse predictors, longer periods of treatment are increasingly advocated.[5] Clinicians may however sometimes decide to discontinue antipsychotic treatment in a particular patient, for example, due to uncertain or changed diagnosis. In such a situation, as with oral antipsychotics, depot antipsychotics may be discontinued at any stage of treatment. Finally, use of a depot plus AMP could be construed as overemphasizing the pharmacological aspects of treating schizophrenia and neglecting the importance of psychosocial interventions. Psychosocial interventions in conjunction with antipsychotic treatment are effective in improving adherence and reducing relapse rates,[54] and as such should be part of the comprehensive package of care provided to patients

with schizophrenia. However, many of these interventions are time consuming and costly, and frequently require the availability of health-care workers with high levels of skills. Consequently, many health-care settings around the world are not able to provide these services. The AMP has several important psychosocial components, including psychoeducation, shared decision-making, and establishing positive relationships with patients and carers that enhance adherence and outcome. Furthermore, the AMP does not preclude inclusion in any other psychosocial interventions that may be available to patients.

Limitations and future directions

Our findings are not necessarily generalizable to other clinical settings where, for example, attitudes to injections and access to services may differ. However, the combination of low-dose conventional antipsychotic depot with AMP may be an effective and cost-effective way of managing early-phase schizophrenia in settings beyond those in LMICs. The major limitation of this study is that it was non-comparative, and as such was not designed to compare depot versus oral antipsychotic treatment, or conventional versus second-generation antipsychotics. Rather, it aimed to assess the feasibility and effectiveness of using low-dose first-generation depot antipsychotic plus AMP as first-line acute and maintenance treatment in first-episode schizophrenia. The logical next step would be to conduct a pragmatic randomized controlled trial comparing depot antipsychotic plus AMP with depot without AMP and with oral antipsychotic with and without AMP in order to determine whether, as we suspect, the addition of AMP is the critical factor. A further study limitation is the possibility of sample selection bias. It is possible that the patients who agreed to participate in the study were those with a better prognosis. We were unable to compare the baseline characteristics of patients who agreed to participate with those who declined, as we did not collect baseline characteristics of participants who declined participation.

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Chapter 4

Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic

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Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic

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ABSTRACT

Objectives: To assess changes in body mass and metabolic profiles in patients with first-episode schizophrenia receiving standardised, assured treatment and to identify predictors and moderators of the effects.
Methods: We investigated the changes in body mass, fasting blood glucose and lipids in 107 largely antipsychotic naïve, first-episode schizophrenia patients who were treated according to a standard algorithm with long-acting injectable flupenthixol decanoate over 12 months.
Results: Eighty-three (78%) participants completed the 12 months of treatment, and 104 (97%) received 100% of the prescribed injections during their participation. There were significant increases in BMI ($P < .0001$), waist circumference ($P = 0.0006$) and triglycerides ($P = 0.03$) and decrease in HDL ($P = 0.005$), while systolic ($P = 0.7$) and diastolic blood pressure ($P = 0.8$), LDL ($P = 0.1$), cholesterol ($P = 0.3$), and glucose ($P = 0.9$) values did not change over time. The triglyceride: HDL ratio increased by 91%. Change in BMI was only correlated with change in triglycerides ($P = .008$). The only significant predictor of BMI increase was non-substance abuse ($P = .002$).
Conclusions: The risks of weight gain and metabolic syndrome associated with antipsychotic treatment in first-episode schizophrenia are not restricted to second generation antipsychotics. This is a global problem, and developing communities may be particularly susceptible.

1. Introduction

Patients with schizophrenia are at increased risk of weight gain, metabolic syndrome (MetS), cardiovascular disease and mortality [29]. While factors such as sedentary lifestyle [6], smoking and poor diet play a role [41], it is now recognised that antipsychotics, via their adipogenic and dysmetabolic effects, are major contributors [10,15]. Young people experiencing a first-episode of psychosis with no or limited previous antipsychotic exposure are most susceptible [4,9,17,35,48]. The risk of weight gain varies amongst individuals and this may be genetically determined [27]. Also, the risk varies between individual antipsychotics. While most attention has focused on second-generation antipsychotics (SGAs), low potency first-generation antipsychotics (FGAs) are reported to carry a similar risk [26]. Other FGAs have not been associated with weight gain and, apart from haloperidol, have not generally been studied–despite the fact that they continue to be extensively used, particularly in lower-income countries. Considerable attempts have been made to identify clinical and laboratory predictors of weight gain. Predicting patients at risk for weight gain would be beneficial as interventions could then be tailored specifically to those patients who are at highest risk of weight gain. Previously identified predictors of weight gain have included sex, age, ethnicity and low BMI [48], however there have been conflicting results. Advances in pharmacogenomics have yielded the most promising results in predicting severe weight gain in some individuals [8].

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Estimates of the effects of antipsychotics on body mass and metabolic profiles are confounded by many factors, thereby making it impossible to draw firm conclusions from much of the published literature [18]. Many studies are limited by factors such as small sample sizes, brief evaluation periods, poorly characterised patient samples, non-standardisation of treatment and failure to assess the effects of dosage and non-adherence. Furthermore, interpretation of study results is often complicated by the use of inappropriate statistical analyses. For example, last-observation carried forward (LOCF) analyses are likely to underestimate drug effects [18,21,48], as longitudinal studies frequently have high rates of discontinuation. Similarly, observed cases, or per protocol samples may be biased as reasons for study discontinuation may not be random. Non-adherence is also likely to be a major cause of underreporting of effects of antipsychotics on body mass and metabolic profiles, with most studies either not assessing adherence, or utilising methods with inherent inaccuracies [46]. Non-adherence may be particularly relevant in early psychosis, given the very high rates reported in early phases of treatment of schizophrenia [18,45]. Finally, notwithstanding the fact that comorbid substance abuse is very common in schizophrenia, many studies either excluded these patients from their samples, or failed to assess their effects on body mass and metabolic changes. The above limitations have been highlighted and additional recommendations made, including the testing for dosage effects, controlling for age and sex and adoption of Consolidated Standards of Reporting Trials (CONSORT) [38] or Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [47] guidelines to increase accuracy of reporting and of interpreting [18].

We conducted a study that was able to address several of these potential confounders. We selected first-episode, largely treatment-naïve patients and conducted regular, standardised assessments of body mass and metabolic profile during the course of treatment according to a standard protocol, with a single long-acting injectable antipsychotic which provided assured medication adherence. Also, we excluded comorbid medical conditions and carefully assessed the role of substance abuse. Studies to date have involved predominantly Caucasian and Chinese patient samples [44]. As far as we are aware, this is the first longitudinal study assessing weight-gain and its metabolic concomitants in an African sample, and the cohort, comprising largely individuals of mixed ancestry from the greater Cape Town region, may represent an economically emerging, particularly at-risk community for metabolic syndrome [14]. Finally, to the best of our knowledge this is the first study prospectively assessing the effects of flupenthixol on body mass and metabolic profiles.

Our study aimed to assess changes in body mass and metabolic profiles in patients with first-episode schizophrenia receiving standardised, assured treatment over 12 months, and to identify predictors and moderators of these effects. We hypothesised that there would be substantial weight gain which would be significantly correlated with changes in lipid and glucose profiles, and emergent cases of MetS.

2. Methods

This was a single-site cohort study. Approval was obtained from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences. The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice (GCP) [23] and was registered at the South African National Clinical Trials Register (DOH-27-0710-1957), URL: www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx.

3. Participants

Subjects were recruited from first-admissions to psychiatric hospitals and community clinics within our catchment areas in Cape Town between April 2007 and March 2011. Patients and/or their legal guardians provided written, informed consent. Eligible participants were men and women, in- or outpatients, aged 16 to 45 years, meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) [5] diagnostic criteria for schizophreniform disorder, schizophrenia or schizo-affective disorder. Patients were excluded if they had, during their lifetime, been exposed to >4 weeks of antipsychotic medication, been treated with a long-acting depot antipsychotic, had a serious or unstable medical condition, mental retardation or overt substance abuse.

4. Assessments

A physical examination was conducted at the start and completion of the study. For anthropometric measurements patients removed all surplus clothing including shoes and socks and were weighed on a regularly calibrated electronic scale. Waist circumference (WC) was measured between the lowest rib and the iliac crest with patients standing upright and breathing normally. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Weight was assessed at baseline, week 6, and months 3, 6, 9 and 12. Laboratory tests were conducted at baseline, 3, 6 and 12 months. Laboratory tests comprised fasting glucose, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides and total cholesterol, as well as urine toxicology for cannabis, methaphetamines and methaqualone. For these tests patients fasted for at least 8 hours overnight and rested for 10 min prior to venipuncture. We used the Adult Treatment Panel (ATP III-A) criteria proposed by the American Heart Association for MetS [2]. MetS criteria comprise raised blood pressure, raised triglycerides, lowered high-density lipoprotein cholesterol, raised fasting blood glucose, and central obesity according to WC. Cut-off values for WC (≥ 90 cm men, ≥ 80 cm women) were adapted to our specific population norms [28]. Abnormal values for any 3 of the 5 criteria would qualify an individual for MetS.

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) [16] and psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) [24] and the Calgary Depression Scale for Schizophrenia (CDSS) [1]. Clinical outcomes will be reported separately.

5. Treatment

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 hours prior to assessments. Medications not permitted included other antipsychotics, mood stabilizers and psychostimulants.

6. Statistical methods

Analyses were performed on a modified intent-to-treat basis, meaning that all patients were included in the analysis if they had a

baseline and at least one post-baseline measure. We performed a Kolmogorov-Smirnov test for weight, waist circumference, systolic and diastolic blood pressure and none of the variables had a *P*-value of < 0.05. We employed linear mixed effect models for continuous repeated measures (MMRM) to assess the changes in BMI and metabolic indices over time. Visit-wise changes were assessed using a model that included fixed terms of age, gender, baseline measure, substance abuse and endpoint flupenthixol dose. Due to some deviations from normal distribution, we also performed the analyses on log transformed data. These results are not reported as they did not differ from the non-transformed results. We conducted Pearson correlational coefficient analyses to explore associations between changes in BMI and metabolic indices. Change scores were calculated by subtracting the baseline score from the endpoint (LOCF) score. We conducted a predictor analysis to identify demographic and baseline variables that best predicted change in BMI. The variables we considered were age, gender, ethnicity, duration of untreated psychosis (DUP), baseline scores for PANSS positive subscale, PANSS negative subscale, PANSS general subscale, CDSS, BMI, fasting glucose, HDL, LDL, triglycerides and cholesterol. As there was an indication of multicollinearity, we conducted best subsets regression analysis. To assess the effect of antipsychotic dose on body mass, we calculated least squares means for BMI according to the endpoint dose of flupenthixol decanoate. All tests were 2-tailed and a significance level of .05 was used throughout. None of the analyses were corrected for multiple comparisons. Descriptive statistics are reported as the mean (SD) at baseline, at 12 months (per protocol) and endpoint (LOCF).

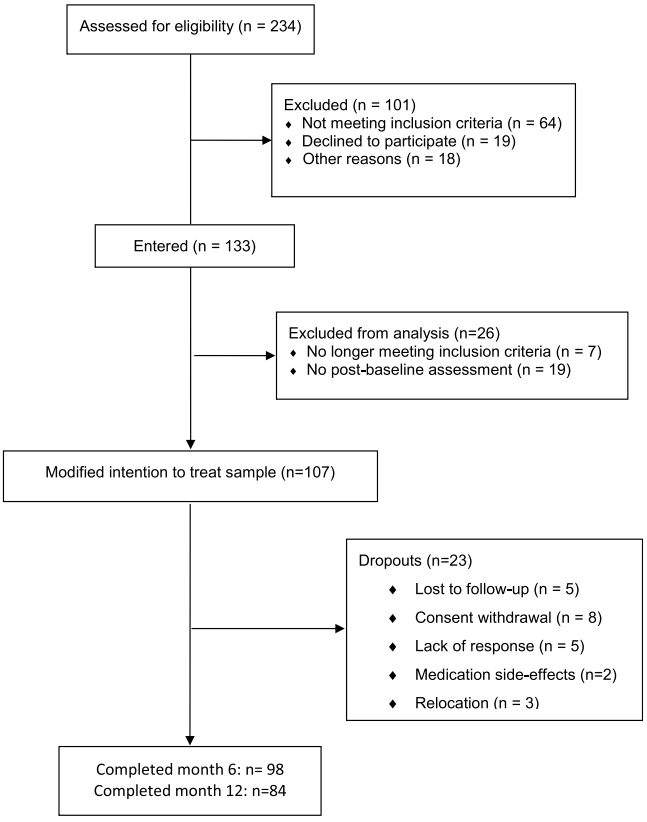

Fig. 1. Study profile diagram.

7. Results

The study profile diagram is provided as Fig. 1. The sample analysed ($n = 107$) comprised 77 (72%) men and 30 (28%) women with a mean age of 24 (SD 6.5) years. Race distribution was as follows: mixed ancestry ($n = 82$, 77%), black ($n = 15$, 14%) and white ($n = 10$, 9%). The South African mixed ancestry population, or so-called South African Coloured population, is a unique population with a complex genetic history that is largely made up of Khoisan genes admixed with African, European and a smaller Asian contribution [11]. Patients who self-identified as South African Coloured were included under mixed ancestry category. DSM IV diagnoses were schizophrenia ($n = 61$, 59%), schizophreniform disorder ($n = 43$, 40%) and schizo-affective disorder ($n = 1$, 1%). Mean DUP was 34 (SD 43.2) weeks and the mean baseline PANSS total score was 95 (SD 16.1). Fifty (47%) patients had a history of substance abuse and 48 (45%) had previous exposure to antipsychotics, for a mean duration of 11 (SD 6.8) days. Our window period for the 2-weekly injections was 3 days. While patients sometimes went beyond this period, treatment adherence, calculated as the number of actual injections received divided by the prescribed number of injections, was 100% for 104 (97%) patients, and 60%, 56% and 55% for one patient each.

Details of the results for physical and laboratory assessments at baseline, 12 months and endpoint are provided in Table 1. There were statistically significant increases in BMI, weight, WC and triglycerides and significant decrease in HDL, while systolic and diastolic blood pressure, LDL, cholesterol and glucose values did not change significantly over time. The number of patients with individual MetS risk factors, as well as those meeting full MetS criteria [2] at baseline, month 12 and endpoint, are provided in

Table 1
Mean (SD) baseline, 12-month (per protocol) and endpoint (LOCF) values for anthropometric, blood pressure and metabolic measures.

	Baseline ($n = 107$)		12 months ($n = 83$)		Endpoint ($n = 107$)		*P*
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	
BMI (kg/m^2)	21.6	3.9	24.5	5.1	24.3	4.9	$<.0001^{*}$
Weight (kg)	61	12	69	14	68	14	$<.0001^{**}$
WC (cm)	77	11	84	12	83	12	0.0006^{**}
Systolic BP (mmHg)	121	14	123	13	122	14	0.7^{**}
Diastolic BP (mmHg)	80	10	80	10	79	11	0.8^{**}
Glucose (mmol/L)	4.8	0.7	5.0	1.5	5.0	1.4	0.9^{*}
HDL (mmol/L)	1.2	0.6	1.0	0.3	1.0	0.3	0.005^{*}
LDL (mmol/L)	2.7	0.9	2.8	0.8	2.8	0.9	0.1^{*}
Triglycerides (mmol/L)	0.9	0.5	1.2	0.8	1.2	0.9	0.03^{*}
Cholesterol (mmol/L)	4.2	1.1	4.3	0.9	4.3	0.9	0.3^{*}
Tryglyceride/HDL	0.9	0.7	1.3	1.0	1.4	1.2	0.003^{*}

WC = waist circumference; BP = blood pressure; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol.
* Linear mixed effect models for continuous repeated measures (MMRM).
** *t*-test baseline vs. endpoint.

Table 2
Number (%) of patients with individual MetS criteria, and those meeting full MetS criteria (3/5 criteria) at baseline, month 12 (per protocol) and endpoint (LOCF).

	Baseline ($n = 107$)	Month 12 ($n = 83$)	Endpoint ($n = 107$)
Elevated WC (>90 cm men, >80 cm women)	13 (12%)	26 (31%)	29 (27%)
Elevated triglycerides (>1.7 mmol/L)	6 (6%)	11 (13%)	15 (14%)
Low HDL (<1 mmol/L men, <1.3 mmol/L women)	62 (58%)	53 (64%)	71 (66%)
Elevated systolic BP (>130 mmHg)	28 (26%)	27 (33%)	33 (31%)
Elevated diastolic BP (>85 mmHg)	38 (36%)	29 (35%)	37 (35%)
Elevated fasting glucose (>5.5 mmol/L)	6 (6%)	7 (8%)	9 (8%)
At least 1 MetS criterion	86 (80%)	73 (88%)	94 (88%)
MetS full criteria (any 3/5 risk factors)	17 (16%)	21 (25%)	26 (24%)

WC = waist circumference; HDL = high density lipoprotein cholesterol; BP = blood pressure; MetS = metabolic syndrome.

Table 2. Fig. 2 shows the least squares mean BMI by MMRM over the 12 month treatment period. The increase in BMI was highly significant. There were no significant effects for age ($P = .8$), sex ($P = .6$), history of substance abuse ($P = .2$) or endpoint flupenthixol dose ($P = .1$). There were no significant differences between the ethnic groups regarding BMI ($P = 0.4$) and the metabolic parameters ($P = 0.2$ to 0.9). We repeated the analysis on the subset of patients who had never been exposed to previous antipsychotic treatment ($n = 59$; 55%) and the results were similar ($F[5,214] = 14.344$, $P < .0001$). Twenty-three participants were prescribed antidepressants at some point in the study. To assess whether this could have had an effect on our results, we compared them with the rest of the sample regarding changes in BMI and metabolic indices from baseline to endpoint. No evidence for an effect was found insofar as there were no significant differences for changes in BMI ($P = 0.3$), fasting glucose ($P = 0.9$), HDL ($P = 0.3$), LDL ($P = 0.7$), triglycerides ($P = 0.8$) and total cholesterol ($P = 0.6$).

For the correlational analyses for changes from baseline to endpoint, change in BMI was significantly correlated with change in WC ($r = .8$, $P < .0001$) and triglycerides ($r = .34$, $P = .008$), but not with change in glucose ($r = .1$, $P = .3$), HDL ($r = -.1$, $P = .3$), LDL ($r = .2$, $P = .1$) or total cholesterol ($r = .2$, $P = .1$). To better examine the relationships between change in BMI and changes in the metabolic measures over time we conducted MMRM analyses fo,r the percentage change values over 12 months for these variables (Fig. 3). The greatest magnitudes of change were observed in triglyceride increases and HDL reductions, and this is reflected in a 91% increase in the triglyceride/HDL ratio. For the prediction analysis, the only significant predictor of BMI increase was absence of history of substance abuse ($P = .002$). A model incorporating age, sex, previous antipsychotic treatment, substance abuse, baseline BMI, baseline fasting glucose, triglycerides, total cholesterol, HDL and LDL provided an $R^2 = .22$. The relationships between the endpoint dose of flupenthixol decanoate and least squares means for BMI are provided in Fig. 4.

8. Discussion

Our cohort of first-episode schizophrenia patients gained considerable weight over their first 12 months of antipsychotic treatment. The mean baseline BMI of our sample of 21.6 (SD 3.9) is somewhat lower than the adult population norm for South Africans of 28.5 [39], which is consistent with their relatively young age. The baseline BMI of our sample is very similar to that of a first-episode schizophrenia sample from Europe [25]. The increase in body mass was already substantial at 6 weeks, and continued throughout the study period. These results are consistent with previous studies showing extensive weight gain in first-episode samples [4,8,42,44,47] and emphasise the exquisite sensitivity of these individuals to the adipogenic effects of antipsychotics. While most attention has focussed on the weight gain risk associated with SGAs and to a lesser extent low-potency FGAs [26], our study shows that, in first-episode patients, a similar risk exists even when treated with an FGA that is not generally associated with weight gain and has been reported not to cause weight gain in patients with chronic schizophrenia [30].

We were able to make several important observations from our study. First, we could assess the true weight-gain effects of an antipsychotic when adherence was assured. Non-adherence is one of the major potential confounders in longitudinal studies of weight gain, and this may be particularly the case in the first year of

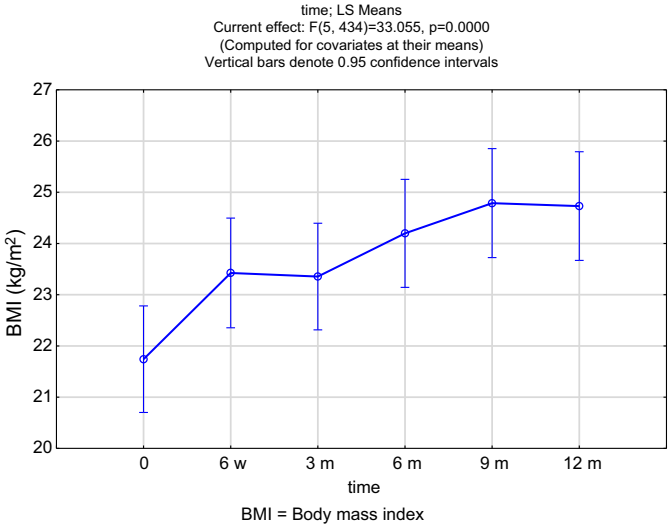

Fig. 2. Least squares mean BMI over 12 months.

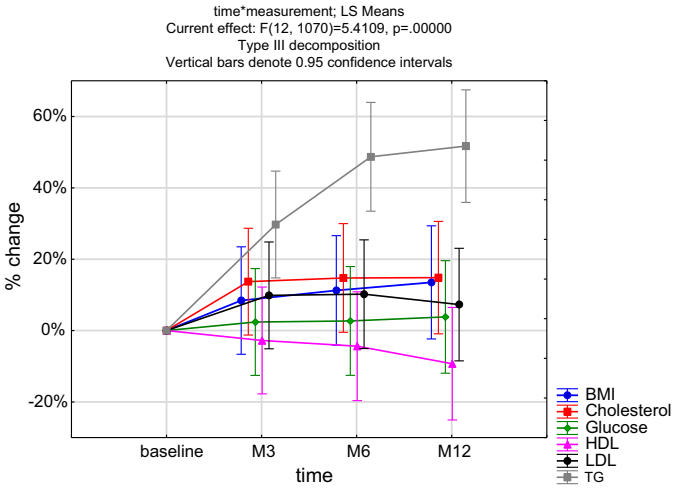

Fig. 3. Percentage change of BMI and metabolic indices from baseline to 12 months.

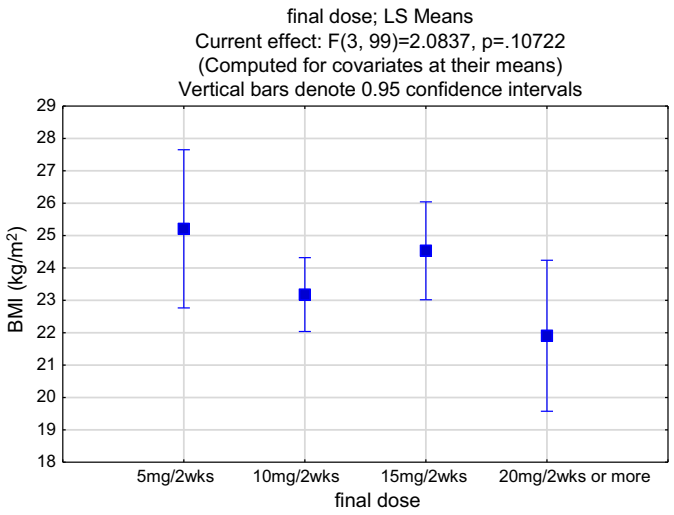

Fig. 4. Least squares mean BMI according to the final dose of flupenthixol decanoate.

treatment [7] and soon after discharge after first hospitalisation [45]. Second, another difficulty in determining the longer term weight-gain effects of antipsychotics is the role of reduced drug exposure and missing values due to high discontinuation rates frequently associated with longitudinal studies [18]. Our relatively high study retention rate (78%) allowed us to better assess the long-term effects of an antipsychotic on weight-gain. Also, by conducting MMRM as well as reporting per-protocol and endpoint results, we were able to assess the impact of missing values. Perhaps surprisingly, although endpoint BMI values were lower than the per protocol and MMRM results the differences were not marked, suggesting that, at least in our sample, early discontinuation did not have a major impact on overall results. Finally, we were able to demonstrate that the weight-gain effect was unrelated to antipsychotic dose. The finding that fully adherent patients may not be at much greater risk of weight gain than those who are partially non-adherent is perhaps not surprising as the vast majority of our patients (97%) were fully adherent to treatment. Together these findings suggest that weight-gain is unlikely to be a useful marker of antipsychotic adherence and that dose-reduction may not be an effective strategy in dealing with weight gain.

It is not known whether changes in lipid profiles or blood glucose levels in the first-episode of psychosis are independent of weight changes [18]. We were able to address the temporal relationships between these variables in our study. Together with the increase in BMI we observed some significant changes in the lipid profiles of our patients. Particularly, the increases in TG and reductions in HDL were significant and together they gave rise to an alarming increase in the TG/HDL ratio. This is of concern given that the TG/HDL ratio is an atherogenic marker [13,19] and a powerful independent predictor of all-cause mortality and cardiovascular events [34]. Our findings of greatly elevated TG/HDL ratio are therefore consistent with, and provide a rational basis for the finding that the most common cause of death in schizophrenia is cardiovascular disease [34]. The fact that the weight and metabolic changes occurred in patients treated with an FGA is consistent with work that suggests that, while individual antipsychotics differ in their effects on body weight, lipids and glucose regulation in chronic schizophrenia, first-episode patients may be susceptible to these effects with a wider range of antipsychotics [9,48]. Indeed, a recent systematic review found no evidence of significant differences between FGAs and SGAs in terms of weight gain after 1 year [18], and it has been reported that cardiometabolic outcomes were not different across different antipsychotic treatments [36]. Another notable finding in the present study was the increase in numbers of patients with individual MetS risk factors as well as those meeting full MetS criteria. The baseline MetS rate of 16% in our sample is considerably higher than that reported in unmedicated (9.8%) and first-episode (9.9%) patients in a meta-analysis using similar MetS criteria to ours [32]. This may reflect the particular risk of MetS even in young individuals in emerging economies globally [22]. Our cohort comprised largely individuals of mixed ethnicity in the greater Cape Town area – a community where the prevalence of MetS and diabetes has hugely increased in recent years and is predicted to reach epidemic proportions [14]. We did not find any ethnic differences on weight and other metabolic parameters in our cohort; however other studies have found that African patients are at higher risk of antipsychotic induced weight gain [43]. After 12 months of treatment the prevalence of MetS in our cohort had increased to 25% and the percentage of patients with at least one MetS risk factor had increased from 80% at baseline to 88% after 12 months. The most frequently occurring risk factors in our sample were low HDL and elevated blood-pressure. Unexpectedly, we did not observe a significant elevation in fasting blood glucose levels during the 12-month treatment period, suggesting that glycaemic dysregulation is a later complication of antipsychotic treatment. This finding is in contrast to a study reporting substantial worsening of fasting blood glucose levels over 52 weeks of treatment with several SGAs and haloperidol in European first-episode patients [17], but is consistent with a reported lack of correlation between weight gain and blood glucose levels with both olanzapine and haloperidol treatment in first-episode patients treated over 12 months [18,48]. Our failure to identify significant correlations between BMI change and metabolic changes other than triglycerides supports the proposal that different mechanisms may be involved and at least some metabolic effects of antipsychotics are weight-independent [31].

Not all patients are at equal risk of weight gain with antipsychotics and reliable markers for those at risk would be hugely beneficial. The fact that we were only able to identify one significant predictor highlights the difficulty in identifying reliable clinical and laboratory predictors of weight gain with antipsychotic treatment [48]. Female sex has been reported as a risk factor for weight gain with antipsychotic treatment [20]. However, we and others [9,48] did not find such an association, and our results suggest that sex effects may be confounded by substance abuse, given that the only significant predictor of BMI increase that we identified was non-substance abuse. Substance abuse is more common in men than in women in patients with first-episode schizophrenia [33]. Also, an inverse relationship has been reported between baseline BMI and the magnitude of subsequent weight gain during antipsychotic treatment [37]. However, it has been proposed that this may be a spurious finding and could be explained by a statistical artefact, namely regression to the mean [3]. The small degree of variability explained by our predictor model (22%) highlights our inability to accurately identify which individuals are at risk of weight gain [26,48] and suggests that factors other than those included in our model should be examined for their predictive power. In future, pharmacogenetic strategies may be especially useful, and new developments in genomics are providing informative data on the genes associated with psychotropic drug weight gain [8]. For example, it has been reported that a subset of approximately one quarter of patients experience severe weight gain when treated with SGAs, and that this risk may be genetically conferred, with common variants at a locus near the melanocortin 4 receptor gene being specifically implicated [27]. In that study, severe weight gain was defined as $>14\%$ gain from

baseline after 12 weeks of treatment. It is of interest that, when we applied the same criteria to our own sample we found a similar result – 23% of our patients met these criteria for severe weight gain at 12 weeks.

Flupenthixol, first introduced almost 50 years ago, is widely available and remains a popular choice by psychiatrists in both high and low income settings for treating people with psychosis. Flupenthixol, belonging to the thioxanthene class, is a high potency FGA. However, its receptor binding profile is not dissimilar to several SGAs, as it antagonises $D_{1\text{-}5}$ dopamine, 5-HT_2, H_1 histamine and alpha$_1$ adrenergic receptors [12]. Its use is based on anecdotal experience rather than well-conducted clinical studies and little is known about its tolerability and efficacy profile. According to a recent Cochrane review there are few data from clinical trials investigating its absolute effects, and the authors concluded that flupenthixol may well be worthy of careful investigation, partly to ensure that this inexpensive active drug is not forgotten [40].

Strengths of the study include the fact that this was a largely unmedicated first-episode sample, thereby circumventing possible effects of disease chronicity and previous antipsychotic exposure. Also, by following a standard treatment protocol with a single antipsychotic, we avoided the confounding differential weight-gain effects of different antipsychotics. Finally, using a long-acting injectable antipsychotic addressed the problem of partial and non-adherence, and the consequent high rates of study retention enhanced our ability to assess true long-term weight-gain and metabolic effects by reducing the numbers of missing variables.

Limitations include the absence of a healthy control group which meant that we were unable to assess the changes in weight and metabolic profile over time in young people in the community from which our patients were recruited. We did not measure fasting insulin levels which could have informed us about insulin resistance which is usually a precursor to increased fasting glucose. Also, we did not assess the effects of smoking, diet or the levels of activity in our patients. Finally, our findings may not be generalisable to antipsychotics other than flupenthixol, and also to populations other than the one studied here. Nevertheless, results from this carefully selected, treated and assessed cohort provide several insights into effects of an antipsychotic on weight and metabolic profiles. The results highlight the magnitude of the problem, that the risk is not restricted to those patients treated with SGAs or low-potency FGAs and that this represents a global health challenge, affecting both high and low income communities.

Disclosure of interest

L.A., Y.vN., R.E., M.K. and A.M. declare that they have no conflicts of interest concerning this article. B.C. has received honoraria from Sandoz and Janssen for speaking at educational meetings. P.O. has received honoraria from Pfizer, Lundbeck, Astra-Zeneca and Cipla for speaking at educational meetings. R.A.E has received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Organon, Pfizer, Servier, Otsuka and Wyeth for participating in advisory boards and speaking at educational meetings, and has received research funding from Janssen, Lundbeck and AstraZeneca.

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Chapter 5

Rate and predictors of non-response to first-line antipsychotic treatment in first-episode schizophrenia

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Rate and predictors of non-response to first-line antipsychotic treatment in first-episode schizophrenia†

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Objective The goals of this study were to (i) estimate the rate of non-response to first-line treatment in first-episode schizophrenia, (ii) evaluate other outcomes associated with symptom non-response and (iii) identify demographic, baseline clinical and early treatment response predictors of non-response.
Methods This was a single-site, longitudinal cohort study assessing the effects of treatment with flupenthixol decanoate according to a standardised protocol over 12 months in patients with schizophrenia, schizophreniform and schizo-affective disorders.
Results Of 126 patients who received at least one dose of study medication, 84 (67%) completed the study. Fifteen (12%) met our predefined criteria for non-response. Non-responders were younger and at baseline had more prominent disorganised symptoms, poorer social and occupational functioning, poorer quality of life for psychological, social and environmental domains, more prominent neurological soft signs (NSS) and lower body mass index. At endpoint, the non-responders were characterised by higher levels of symptomatology in all domains, poorer functional outcome, poorer quality of life and greater cognitive impairments. They also had more prominent NSS and lower body mass index. The strongest predictors of non-response were more prominent baseline NSS and poor early (7 weeks) treatment response.
Conclusions Results are consistent with a lower rate of refractoriness to treatment in first-episode schizophrenia compared with multi-episode samples. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—non-response; first-episode psychosis; predictors; outcome; neurological soft signs

INTRODUCTION

Treatment outcome has been extensively studied in first-episode schizophrenia. However, the majority of studies have primarily focused on favourable outcome measures such as response, remission and recovery. Others have investigated relapse in patients who have responded to treatment. Few studies have investigated non-response from the outset as the primary outcome in first-episode samples (Menezes *et al*., 2006), notwithstanding the fact that there are good reasons to do so. Persistence of psychotic symptoms causes ongoing distress, diminished autonomy, poor quality of life and increased morbidity and mortality for affected individuals. It also places emotional and financial burdens on carers and excessive demands on healthcare services (Van Sant and Buckley, 2011; Kennedy *et al*., 2014).

The importance of early, effective treatment in optimising the long-term outcome of the illness is well recognised (Amminger *et al*., 2011). The early identification of individuals failing to respond to their initial antipsychotic treatment would enable the consideration of alternative interventions at an earlier phase of illness to prevent accruing morbidity. In a well-designed study where a standardised treatment algorithm was used, only a small number of patients (23%) responded to a second antipsychotic trial after failing to respond to first-line antipsychotics (Agid *et al*., 2007). However, the majority of patients (77%) who went on to clozapine after two failed antipsychotic trials had a robust response. Therefore, switching to clozapine earlier has been a proposed solution, as failure to respond to a first antipsychotic is highly predictive of failure to respond to a subsequent antipsychotic, other than clozapine (Remington *et al*., 2013).

Another reason for investigating treatment non-response in first-episode patients is to further elucidate the evolution of treatment refractoriness in schizophrenia. It has been proposed that most cases of treatment refractoriness emerge in previously responsive patients as the illness progresses (Lieberman, 1999). If that is the case, then the rates of non-response to treatment

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in first-episode schizophrenia should be lower than in multi-episode samples. Poor response to treatment is common in chronic, multi-episode samples with almost 60% of patients failing to achieve response after 6 months on antipsychotic drug therapy (Kennedy *et al.*, 2014), and up to half are regarded as refractory to antipsychotic treatment (Conley and Kelly, 2001; Caspi *et al.*, 2004). In contrast, treatment response in first-episode schizophrenia is frequently favourable (Robinson *et al.*, 1999). A systematic review calculated the average rate of poor outcome in first-episode samples as 27%, although rates varied considerably across studies (Menezes *et al.*, 2006). The inconsistency is likely due to factors such as differences in criteria applied to define non-response, varying study durations, non-standardisation of treatment and dosage, medication non-adherence and varying rates of dropout. We addressed several of these methodological issues by defining an a priori criterion for non-response, treating patients according to a standard algorithm with a single antipsychotic, ensuring adherence by way of depot injection and carefully monitoring the cohort to facilitate study retention. Participants were comprehensively assessed, which enabled us to explore multiple putative predictors and clinical concomitants of treatment non-response. The aims of the study were to estimate the rate of non-response to first-line treatment in first-episode schizophrenia, to evaluate other outcomes associated with symptom non-response and to identify demographic, baseline clinical and early treatment response predictors of non-response.

METHODS

This was a single-site, longitudinal cohort study assessing the effects of treatment with flupenthixol decanoate according to a standardised protocol over 12 months in a convenience sample of patients with first-episode schizophrenia. Approval to conduct the study was obtained from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences. The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice (International Conference on Harmonization, 1996) and was registered at the South African National Clinical Trials Register (DOH-27-0710-1957) URL: www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx

Participants

Patients were recruited between April 2007 and March 2011 from first hospital admissions and community clinics in the Greater Cape Town area. Patients from the area are treated at community clinics by psychiatry residents and community psychiatry nurses. There are no specific first-episode psychosis/early intervention services, and it is very difficult to access inpatient services. The vast majority of inpatients are admitted as involuntary hospital users, under the Mental Health Care Act, when they are deemed to be a danger to themselves or others. Written, informed consent was obtained from the patients and/or their legal guardians. Inclusion criteria included men and women, inpatients or outpatients, aged 16–45 years, experiencing a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (American Psychiatric Association, 1994a) diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder, for convenience of reporting referred to as first-episode schizophrenia. Exclusion criteria were lifetime exposure to >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.

Treatment

There was a 1-week lead-in period of oral flupenthixol 1–3 mg per day followed by long-acting flupenthixol decanoate injections every 2 weeks for the duration of the study. The starting dose of flupenthixol decanoate was 10 mg 2-weekly, with 6-weekly increments of 10 mg permitted, to a maximum of 30 mg 2-weekly or the maximum tolerated dose. The dose was increased at week 6 if patients failed to achieve an adequate response (at least 20% decrease in the total positive and negative symptom scale score and minimal improvement on the clinical global impression–improvement (CGI) scale). The dose could be further increased at week 12 and every 6 weeks thereafter if patients failed to achieve cross-sectional criteria for remission (Andreasen *et al.*, 2005) and a CGI score of much or very much improved. More rapid upward or downward titration was permitted if deemed necessary. 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, however, to use lorazepam up to 12 mg during the acute phase and thereafter up to 4 mg per day for agitation. The treatment goal was to achieve symptom remission. Therefore, for patients with persistent symptoms, the dose was increased either until remission was achieved or until the maximum allowed dose or the maximum tolerated dose was reached. Flupenthixol decanoate was chosen as it is widely

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available, affordable and remains a popular choice by psychiatrists in both high-income and low-income settings for treating people with psychosis. Flupenthixol, belonging to the thioxanthene class, is a high potency first-generation antipsychotic. However, its receptor binding profile is not dissimilar to several second-generation antipsychotics, as it antagonises D1-5 dopamine, 5-HT2, H1 histamine and alpha1 adrenergic receptors (de Wit, 2010). Flupenthixol decanoate has also been shown to be more cost-effective than long-acting injectable risperidone (Frey *et al*., 2014). Permitted concomitant treatment included lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms, propranolol for akathisia, antidepressants for depression and medication for general medical conditions. Prohibited medications included other antipsychotics, mood stabilisers and psychostimulants.

Assessments

Patients were assessed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (First *et al*., 1994), the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987), the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994b), the Calgary Depression Scale for Schizophrenia (Addington and Addington, 1993), the Birchwood Insight Scale (Birchwood *et al*., 1994), the Premorbid Adjustment Scale (Cannon-Spoor *et al*., 1982), the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989), the Extrapyramidal Symptom Rating Scale (Chouinard and Margolese, 2005), the World Health Organisation quality of life-BREF scale (The WHOQOL Group, 1998) and the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB) (Green *et al*., 2004). Duration of untreated psychosis (DUP) and duration of untreated illness were estimated, respectively, from the onset of continuous positive psychotic symptoms and the onset of first recognisable symptoms to the initiation of treatment. Substance abuse was measured with a structured substance abuse questionnaire. Furthermore, patients had urine toxicology for cannabis, methamphetamine and methaqualone at baseline, 3, 6 and 12 months.

Statistical methods

Analyses were performed on all participants who received at least one dose of study medication with last observation carried forward. For differences between groups, the *T*-test and the chi-square test were used to compare continuous and categorical variables, respectively. All tests were two tailed. The significance level was set at 0.05 and not adjusted as these were considered preliminary analyses to identify the most suitable predictor variables. To investigate predictors of non-response, we conducted linear regression, entering demographic, baseline clinical and early (7 weeks) response variables that were selected from the preliminary analyses together with additional variables that we considered relevant.

Defining treatment non-response

We aimed to identify all of the participants who experienced prominent persistent symptoms despite an adequate first-line antipsychotic treatment trial. Non-response was defined a priori as any one of the following: (i) study discontinuation due to poor response as judged by the investigator and an assessment panel consisting of three experienced psychiatrists. All reasonable measures were taken to keep the patients in the study and to adhere to the treatment algorithm; (ii) endpoint treatment response $<25\%$ in PANSS total score (recommended minimum response rate for defining refractory patients (Leucht *et al*., 2009)); or (iii) endpoint PANSS total score >70. For criteria (ii) and (iii), patients were only considered to be non-responders if they had completed at least 3 months of treatment and had not experienced a relapse. We chose a minimum treatment period of 3 months because, although it is well recognised that antipsychotics act rapidly (Kinon *et al*., 2010) and a treatment period of minimum 6 weeks has been proposed (Suzuki *et al*., 2011), a subset of first-episode patients responds to treatment more slowly (Emsley *et al*., 2006b). In keeping with recommendations to include a broader range of symptoms when assessing non-response to treatment (Marder, 1995), we selected the PANSS total score as the primary measure of psychopathology rather than selected items or domains. Early treatment response was calculated as corrected percentage change in PANSS total score at week 7 (baseline score − week 7 score)/(baseline score − 30). To assess symptom categories, we calculated scores for the PANSS factor analysis-derived positive, negative and disorganised excitement/hostility and depression/anxiety domains (Emsley *et al*., 2003). We defined remission according to Remission in Schizophrenia Work Group criteria (Andreasen *et al*., 2005). Adherence to depot was calculated as the percentage of actual injections received divided by the prescribed number of injections.

RESULTS

The study flow diagram is provided in Figure 1. Of the 126 patients who received at least one dose of study medication, 85 (67%) patients were recruited from community clinics, and 41 (33%) were hospitalised at

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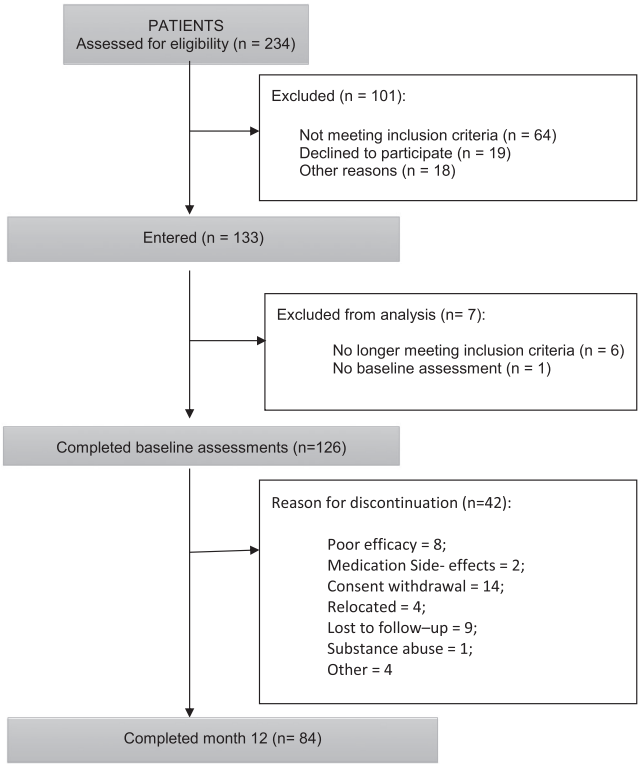

Figure 1. Flow diagram of the study

the start of the study. Fifteen patients (12%) met our criteria for non-response. Of the 84 (67%) patients who completed the study, 61 (48%) achieved remission, and 23 (18%) improved but did not achieve remission. Thirty (24%) patients dropped out of the study for reasons other than non-response. The baseline demographic and clinical characteristics of the non-responders versus the rest of the sample are provided in Table 1. Endpoint (last observation carried forward) values for outcome variables are presented in Table 2. As anticipated, the non-responders were characterised by, in addition to higher levels of symptomatology in all domains, poorer functional outcome, poorer quality of life and greater cognitive impairments. They also had more prominent neurological soft signs (NSS) and lower body mass index (BMI). They did not differ from the rest of the cohort in terms of depression symptoms, levels of insight, extrapyramidal symptoms and endpoint flupenthixol dose. However, they used more benzodiazepines as concomitant medication. The selected linear regression model included the following domains: age, DUP, PANSS disorganised factor, SOFAS, World Health Organisation Quality of Life-BREF Scale domains 2 and 3, NES total, MCCB working memory domain, PANSS total score change at 7 weeks, gender and substance abuse. The model explained 26% of the variance ($R=0.51$; $R^2=0.26$, $p=0.01$), and NES scores ($p=0.003$) and PANSS total score change at 7 weeks ($p=0.03$) were significant independent predictors of non-response.

In a post-hoc analysis, we applied more stringent criteria for treatment refractoriness adapted from Suzuki *et al.* (2012). According to these criteria, four patients were classified as "treatment intolerant" rather than non-responders, and two patients who discontinued because of lack of response were excluded because of not having completed 6 weeks of treatment. These criteria identified 10 (8%) treatment-refractory patients.

Our window period for the biweekly injections was 3 days. Although patients sometimes went beyond this period, overall adherence was good. One hundred and twenty-three (98%) patients received 100% of the prescribed depot injections (including patients who discontinued early), and the other three (2%) patients received a mean of 61% of the injections.

DISCUSSION

Rate of non-response to first antipsychotic treatment

The present study identified the prevalence of treatment non-response to first antipsychotic treatment in our first-episode schizophrenia cohort as 12%. A study in a first-episode psychosis programme in Canada, which utilised a treatment algorithm-based approach and measured response as a CGI improvement score of much or very much improved or Brief Psychiatric Rating Scale thought disorder subscale (conceptual disorganisation, hallucinatory behaviour, suspiciousness and unusual thought content) less than 6, found that 24% of first-episode psychosis patients did not respond to the first treatment trial (Agid *et al.*, 2007). However, there may have been poor adherence and other confounders influencing the results. In a recent Nordic outcome study in first-episode psychosis, rates of persistence of psychosis were reported as 16.4% over 2 years (Simonsen *et al.*, 2010). The study was conducted in a naturalistic setting, and patients were treated with various first-generation and second-generation antipsychotics. Psychosis was defined broadly and included affective psychosis with mood-incongruent delusions. Symptom persistence was defined as a score of 4 or more on at least one of PANSS items P1, 3, 5, 6 and G9. Mean estimated reported medication adherence was 76% over the 2-year study period, suggesting that some patients with persistent symptoms may have been poorly adherent rather than non-responsive. In a Canadian naturalistic study, 15% of first-episode patients were found to have

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Table 1. Comparison of socio-demographic, baseline clinical assessments and early treatment non-response and the rest of the sample

Variable	The rest of the sample ($n = 111$)	Non-responders ($n = 15$)	T-value/Chi squared	P*
Age (years), mean (SD)	**24.5 (6.8)**	**20.5 (3.7)**	**2.2**	**0.026**
Sex				
Male	82 (74%)	11 (73%)	0.001	0.964
Ethnicity				
Mixed	84 (76%)	14 (93%)	2.99	0.233
Black	18 (16%)	0 (0)		
White	9 (8%)	1 (7%)		
Highest education level				
Junior	7 (6%)	2 (13%)	3.88	0.421
Senior	67 (60%)	9 (60%)		
Completed Grade 12	24 (22%)	1 (7%)		
Tertiary	13 (12%)	3 (20%)		
Employment status				
Unemployed	88 (79%)	14 (93%)	1.72	0.421
Informal	2 (2%)	0 (0%)		
Full time	21 (19%)	1 (7%)		
Family history of schizophrenia	42 (38%)	10 (67%)	0.17	0.678
DSM-IV diagnoses				
Schizophreniform disorder	34 (31%)	6 (40%)	0.75	0.687
Schizophrenia	75 (68%)	9 (60%)		
Schizo-affective	2 (2%)	0 (0%)		
Hospitalised at study entry	33 (30%)	8 (53%)	3.35	0.067
Substance abuse	46 (41%)	6 (40%)	0.20	0.654
DUP (weeks), mean (SD)	35.2 (44.7)	28.4 (31.0)	0.6	0.569
DUI (weeks), mean (SD)	81.5 (77.7)	103.6 (123.8)	−1.0	0.341
PANSS negative factor, mean (SD)	17.3 (4.7)	19.4 (5.2)	−1.6	0.116
PANSS depression anxiety factor, mean (SD)	9.2 (4.3)	9.0 (3.4)	0.2	0.877
PANSS positive factor, mean (SD)	13.5 (2.8)	13.9 (2.5)	−0.5	0.607
PANSS excitement/hostility factor, mean (SD)	8.3 (3.8)	10.3 (4.1)	−1.9	0.058
PANSS disorganised factor, mean (SD)	**17.8 (4.3)**	**21.4 (4.8)**	**−3.0**	**0.003**
PANSS total score, mean (SD)	**93.7 (15.9)**	**102.7 (19.3)**	**−2.0**	**0.048**
PANSS total change (7 weeks), mean (SD)	0.4 (0.2)	0.3 (0.2)	2.0	0.050
CGI S, mean (SD)	5.0 (0.8)	5.2 (0.6)	−1.0	0.310
CDSS total score, mean (SD)	3.3 (4.1)	4.0 (3.9)	−0.6	0.528
SOFAS, mean (SD)	**44.8 (11.7)**	**38.1 (8.8)**	**2.2**	**0.032**
WHOQOL-BREF domain 1, mean (SD)	12.0 (2.4)	11.5 (2.1)	0.8	0.404
WHOQOL-BREF domain 2, mean (SD)	**13.2 (2.7)**	**11.2 (2.7)**	**2.7**	**0.009**
WHOQOL-BREF domain 3, mean (SD)	**12.2 (4.1)**	**9.4 (4.2)**	**2.5**	**0.016**
WHOQOL-BREF domain 4, mean (SD)	11.9 (3.3)	10.1 (3.1)	2.0	**0.051**
NES sensory integration, mean (SD)	**2.5 (2.3)**	**5.3 (2.9)**	**−4.3**	**0.000**
NES motor coordination, mean (SD)	**1.2 (1.3)**	**3.2 (2.4)**	**−5.1**	**0.000**
NES sequencing of motor acts, mean (SD)	**2.7 (2.3)**	**4.9 (2.6)**	**−3.5**	**0.001**
NES total, mean (SD)	**13.9 (7.0)**	**23.6 (9.5)**	**−4.8**	**0.000**
PAS total child, mean (SD)	0.2 (0.2)	0.2 (0.1)	1.4	0.178
PAS total EAdol, mean (SD)	0.3 (0.2)	0.3 (0.2)	0.2	0.806
PAS total LAdol, mean (SD)	0.4 (0.2)	0.3 (0.2)	0.6	0.545
PAS total adult, mean (SD)	0.4 (0.2)	0.4 (0.3)	−0.7	0.464
PAS total general, mean (SD)	0.5 (0.2)	0.6 (0.2)	−1.7	0.095
PAS overall, mean (SD)	0.4 (0.1)	0.4 (0.1)	0.0	0.960
BIS subscale 1, mean (SD)	2.3 (1.1)	2.2 (0.6)	0.3	0.784
BIS subscale 2, mean (SD)	1.6 (1.3)	1.3 (1.0)	0.9	0.372
BIS subscale 3, mean (SD)	2.2 (1.0)	2.0 (0.9)	0.6	0.548
BIS total, mean (SD)	6.0 (2.1)	5.4 (1.7)	1.0	0.323
ESRS total parkinsonism, mean (SD)	1.7 (3.6)	2.1 (4.7)	−0.4	0.684
ESRS total, mean (SD)	2.5 (5.1)	3.9 (8.1)	−0.9	0.382
BMI, mean (SD)	21.8 (3.9)	19.8 (3.2)	2.0	**0.053**
MCCB SOP, mean (SD)	18.2 (16.2)	10.9 (14.2)	1.5	0.130
MCCB AV, mean (SD)	26.3 (11.8)	20.1 (10.1)	1.7	0.097
MCCB WM, mean (SD)	**24.5 (915.6)**	**15.2 (11.7)**	**2.1**	**0.042**
MCCB Vrbl Lrng, mean (SD)	34.8 (8.6)	31.6 (6.9)	1.3	0.209
MCCB Vis Lrng, mean (SD)	29.9 (15.3)	23.1 (15.1)	1.5	0.134
MCCB RPS, mean (SD)	31.8 (8.7)	32.5 (10.3)	−0.3	0.773
MCCB SC, mean (SD)	29.7 (11.8)	23.3 (6.0)	1.8	0.070
MCCB comp score, mean (SD)	14.0 (15.7)	4.5 (9.8)	1.9	0.055

DSM-IV, Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition; SD, standard deviation; MATRICS, measurement and treatment research to improve cognition in schizophrenia; MCCB, MATRICS consensus cognitive battery; MCCB SOP, MATRICS consensus cognitive battery speed of processing; MCCB AV, MATRICS consensus cognitive battery attention/vigilance; MCCB WM, MATRICS consensus cognitive battery working memory; MCCB Vrbl Lrng, MATRICS consensus cognitive battery verbal learning; MCCB Vis Lrng, MATRICS consensus cognitive battery visual learning; MCCB RPS, MATRICS consensus cognitive battery reasoning and problem solving; MCCB SC, MATRICS consensus cognitive battery 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; PAS EAdol, premorbid adjustment scale early adolescence; PAS LAdol, premorbid adjustment scale late adolescence; NES, neurological evaluation scale, ESRS, extrapyramidal symptom rating scale; WHOQOL-BREF, World Health Organisation quality of life-BREF scale; CGI S, clinical global impression severity scale.
P, significance value; *T*-test, for continuous variables; chi squared, for categorical variables.
Significance level was set at 0.05.

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Table 2. Comparison of endpoint (last observation carried forward) clinical and cognitive scores and study and concomitant medication use between non-responders and the rest of the sample

Variable	The rest of the sample ($n = 111$)	Non-responders ($n = 15$)	*T*-value or chi square*	*P*
PANSS total, mean (SD)	**49 (14.7)**	**82.6 (12.7)**	**−8.4**	**<0.0001**
PANSS disorganised factor, mean (SD)	**6.5 (2.4)**	**11.4 (2.2)**	**−7.5**	**<0.0001**
PANSS positive factor, mean (SD)	**6.6 (4.1)**	**12.3 (2.5)**	**−5.2**	**<0.0001**
PANSS depression/anxiety factor, mean (SD)	**5.4 (2.5)**	**7.1 (3.6)**	**−2.4**	**0.02**
PANSS negative factor, mean (SD)	**11.2 (4.1)**	**20.8 (5.3)**	**−8.2**	**<0.0001**
PANSS excitement/hostility factor, mean (SD)	**5 (2.1)**	**6.5 (3.2)**	**−2.3**	**0.02**
CGI S, mean (SD)	**2.5 (1)**	**4.3 (0.7)**	**−6.5**	**<0.0001**
CGI improvement, mean (SD)	**1.6 (0.8)**	**2.9 (0.9)**	**−6.0**	**<0.0001**
CDSS total, mean (SD)	1.2 (2.8)	1.9 (2.4)	−1.0	0.3
SOFAS, mean (SD)	**62.2 (12.8)**	**46.7 (7.7)**	**4.6**	**<0.0001**
WHOQOL-BREF domain 1, mean (SD)	**12.6 (2.7)**	**10.9 (2.4)**	**2.3**	**0.03**
WHOQOL-BREF domain 2, mean (SD)	**13.5 (2.5)**	**11.4 (2)**	**3.1**	**0.003**
WHOQOL-BREF domain 3, mean (SD)	**13.7 (3.8)**	**11.2 (4.2)**	**2.4**	**0.02**
WHOQOL-BREF domain 4, mean (SD)	**13.7 (3.1)**	**11.3 (4)**	**2.8**	**0.006**
NES sensory integration, mean (SD)	**1.4 (2)**	**3.1 (2.7)**	**−2.9**	**0.004**
NES motor co-ordination, mean (SD)	**0.8 (1.2)**	**2.1 (2)**	**−3.9**	**<0.0001**
NES sequencing of motor Acts, mean (SD)	**1.6 (1.9)**	**4.1 (2.9)**	**−4.4**	**<0.0001**
NES total, mean (SD)	**9.7 (5.7)**	**18.3 (8.6)**	**−5.2**	**<0.0001**
BIS 1, mean (SD)	2.1 (1.1)	2.2 (0.6)	−0.1	0.9
BIS 2, mean (SD)	1.6 (1.3)	1.4 (1.3)	0.5	0.6
BIS 3, mean (SD)	2.5 (1)	2.6 (0.8)	−0.1	0.9
BIS total, mean (SD)	6.2 (2.3)	6.1 (2.1)	0.2	0.9
ESRS change parkinsonism, mean (SD)	1.6 (3.5)	0.3 (2.7)	1.3	0.2
ESRS change total, mean (SD)	2.3 (4.8)	1.1 (3.9)	0.9	0.4
BMI, mean (SD)	24.2 (4.8)	20.5 (3.9)	2.8	**0.006**
Fluanxol dose, mean (SD)	11.9 (5.4)	10.4 (6.2)	1.0	0.3
Anticholinergics, number (%)	12 (11%)	4 (30%)	3.4	0.07
Antidepressants, number (%)	17 (15%)	1 (7%)	0.7	0.4
Benzodiazepines, number (%)	**11 (10%)**	**4 (30%)**	**4.0**	**0.05**
Completed week, mean (SD)	**38.3 (16.6)**	**22.2 (17.6)**	**3.5**	**0.001**
MCCB SOP, mean (SD)	**27 (15.3)**	**13.2 (15.1)**	**3.1**	**0.003**
MCCB AV, mean (SD)	**34.9 (10.9)**	**24.1 (9.6)**	**3.3**	**0.001**
MCCB WM, mean (SD)	**32.5 (13.3)**	**20.4 (13.4)**	**3.1**	**0.003**
MCCB Vrbl Lrng, mean (SD)	**37.6 (7.9)**	**31.9 (3.6)**	**2.6**	**0.01**
MCCB Vis Lrng, mean (SD)	**37.1 (13.3)**	**27.6 (13.6)**	**2.4**	**0.02**
MCCB RPS, mean (SD)	37.5 (10.2)	32.8 (10.2)	1.6	0.1
MCCB SC, mean (SD)	**33.2 (12.2)**	**24.8 (12.6)**	**2.2**	**0.03**
MCCB comp score, mean (SD)	**23.4 (14.6)**	**8.7 (13.2)**	**3.3**	**0.001**

SD, standard deviation; MATRICS, measurement and treatment research to improve cognition in schizophrenia; MCCB, MATRICS consensus cognitive battery; MCCB SOP, MATRICS consensus cognitive battery speed of processing; MCCB AV, MATRICS consensus cognitive battery attention/vigilance; MCCB WM, MATRICS consensus cognitive battery working memory; MCCB Vrbl Lrng, MATRICS consensus cognitive battery verbal learning; MCCB Vis Lrng, MATRICS consensus cognitive battery visual learning; MCCB RPS, MATRICS consensus cognitive battery reasoning and problem solving; MCCB SC, MATRICS consensus cognitive battery 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; NES, neurological evaluation scale, ESRS, extrapyramidal symptom rating scale; WHOQOL-BREF, World Health Organisation quality of life-BREF scale; BMI, body mass index; CGI S, clinical global impression severity scale.
Significance level was set at 0.05
**T*-value and chi square for continuous and categorical variable comparisons, respectively.

persistent psychosis, defined as a rating of 3 or more on any subscale of Scale for Assessment of Positive Symptoms at baseline, 1 and 2 years, and no period of full recovery of symptoms at any time during the 2-year period (Manchanda *et al.*, 2005). In the New York Hillside Hospital cohort study conducted over 5 years (Robinson *et al.*, 1999), the authors reported an 87% cumulative response rate for patients who were moved through a treatment algorithm with various antipsychotics if necessary, including clozapine. They identified 10 patients (8% of the sample) who were refractory to treatment throughout. Our rate of non-response is more in line with these three latter studies, suggesting true treatment non-response rates of between 8% and 16% in first-treated patients with first-episode schizophrenia. With more stringent criteria and in the presence of adequate adherence, the rate of non-response to first-line treatment appears to be less than 10%.

Predictors of non-response

Given the clinical importance of early identification of treatment refractoriness, interest has focused on identifying demographic, clinical and biological predictors of treatment non-response. While numerous predictors have been reported, results are inconsistent and strength of the associations generally weak. Examples of previously reported predictors include male sex (Robinson *et al.*, 1999), early age of onset (Meltzer *et al.*, 1997), positive family history of schizophrenia (Malaspina *et al.*, 2000), obstetric complications (Alvir *et al.*,

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1999), longer DUP (Marshall *et al*., 2005) and tardive dyskinesia (Lieberman, 1993). In a regression analysis conducted on results of studies reporting predictors of poor outcome in first-episode samples, the only two factors predicting poor outcome were treatment with conventional antipsychotics and being treatment naïve at study entry (Menezes *et al*., 2006).

In the preliminary analyses, the findings of poorer functional outcome, quality of life and cognitive performance in the non-responder group were all anticipated, while the lower BMI was unanticipated. However, the lower BMI could be attributed to first, the younger age of the non-responders, and second, the shorter duration of exposure to the adipogenic effects of antipsychotic treatment due to their higher rate of dropout. Our linear regression model was only able to explain a relatively small portion of the variance (26%), indicating that other factors not assessed in the present study play a role in predicting non-response. The results replicate a previous study conducted by us in another first-episode sample in which both NSS and early treatment response were identified as significant predictors of outcome (Emsley *et al*., 2006a). The strongest predictor that we identified in the present study was prominent NSS. While several previous studies report no association between NSS and treatment outcome (Kolakowska *et al*., 1985; Sanders *et al*., 2004; Emsley *et al*., 2005), an association was found between persistence of NSS at 1 year following a first episode of schizophrenia and poor treatment response (Prikryl *et al*., 2007), and NSS improved to a lesser degree in the early stages of illness for patients with a poorer outcome (Bachmann *et al*., 2005). Also, fewer NSS significantly predicted later remission in a first-episode sample (Emsley *et al*., 2006a).

It is now well recognised that antipsychotic drugs exert their effects rapidly, with the greatest degree of symptom reduction occurring within the first few weeks of treatment (Agid *et al*., 2003). Also, early symptom improvement is strongly predictive of later treatment response (Kinon *et al*., 2010). However, the majority of these studies were of short duration, and those that were of longer duration focused on predicting favourable outcomes (Emsley *et al*., 2008). Our results therefore extend previous findings by indicating that poor early treatment response is significantly predictive of longer-term treatment non-response.

Do cases of treatment-emergent refractoriness occur?

It has been proposed that, in addition to its neurodevelopmental origins, schizophrenia is a progressive illness and that in most cases treatment refractoriness develops during the course of successive episodes (Lieberman, 1999). Arguing against this is that the evidence for disease progression is not strong and could be explained at least in part by secondary factors such as substance abuse and the effects of medication (Zipursky *et al*., 2013). Also, in studies assessing treatment outcome in first-episode schizophrenia, no increase in the rates of refractoriness was found in studies of longer duration (Menezes *et al*., 2006). On the other hand, there is accumulating evidence to suggest that treatment non-responsiveness does evolve in some individuals who previously responded to antipsychotic medication and that relapse events are critical to its development. Supportive evidence includes the following: (i) Estimates of refractoriness in multi-episode schizophrenia are consistently higher than in first-episode samples—being estimated as between one fifth to one half of patients (Conley and Kelly, 2001; Caspi *et al*., 2004)—however, this finding may be explained by selection bias. Multiple-episode samples may contain more severely ill patients as they are often recruited from hospital settings. (ii) Some long-term outcome studies report illness progression related to relapse events. In a 7-year follow-up study, 80% of patients with schizophrenia had deteriorated over time, and the degree of deterioration was significantly correlated with the number of relapses that patients experienced (Curson *et al*., 1985). In a 15-year follow-up study in a Dutch incidence cohort, Wiersma *et al*. (1998) reported a striking observation—that on average, one in six patients did not remit after each relapse, irrespective of which episode it was. Poor treatment response increased from 27% after the first psychotic episode to 47% after the fourth psychotic episode (Wiersma *et al*., 1998). (iii) Studies comparing pre-relapse and post-relapse treatment response report evidence of emergent non-responsiveness. A small study comparing treatment response times of first and subsequent episodes reported that, compared with the first episode, the time to remission was significantly longer for the second episode and third episode (Lieberman *et al*., 1996); in two studies comparing treatment response before and after relapse, one in a first episode (Emsley *et al*., 2013) and the other in a multi-episode sample (Emsley *et al*., 2012), evidence of emergent treatment failure was found in a subset of 16% of the first episode and 14% of the multi-episode samples, respectively. Whether these cases of "emergent non-responders" differ in any respect from the "inherent non-responders" remains to be determined.

Other outcome measures associated with non-response

Our results indicate that first-episode patients who fail to respond to treatment in terms of symptom reduction

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also do poorly in several other outcome measures. Compared with the rest of the sample, they were significantly worse in terms of social and occupational functioning, quality of life and cognitive performance and had significantly higher NES scores. The finding that they did not differ regarding insight scores is surprising, given that poor insight has been associated with poor outcome (Shad *et al*., 2007). Similarly, the finding that non-responders did not differ from the rest regarding the presence of depressive symptoms is in contrast to a previous study in which persistent symptoms of depression were associated with poor outcome (Oosthuizen *et al*., 2006).

Difficulties associated with defining treatment non-response

Accurate identification of treatment non-responders is frequently difficult. Factors such as covert non-adherence and comorbid disorders need to be carefully considered. Also, although we did not find substance abuse as a significant association of non-response in our sample, other studies have previously found higher rates of substance abuse in non-responders (Manchanda *et al*., 2005). Furthermore, inconsistencies in criteria applied to define non-response, particularly regarding the degree of symptom reduction and the spectrum of symptoms to be included, together with the dose and duration of what constitutes an adequate trial vary across studies, making it difficult to compare and interpret the data. Additionally, using percentage change in symptoms from baseline to define response can be misleading as patients with higher baseline scores may show considerable percentage reduction yet continue to experience prominent persistent symptoms. This is reflected in the finding that several of our patients achieved 25% and greater reduction in PANSS total score yet met our other criteria for non-response. For this reason, we consider it preferable to use threshold scores to define non-response and refractoriness, as is the case with the widely adopted remission criteria developed by the Remission in Schizophrenia Working Group (Andreasen *et al*., 2005). Another difficulty in defining non-response in first-episode patients concerns what constitutes an adequate treatment trial. Antipsychotics work rapidly, and early non-response to antipsychotic treatment is a robust predictor of subsequent lack of response (Kinon *et al*., 2008). Therefore, a 4–6-week period has been regarded as an adequate trial duration (Kane and Marder, 1993). However, for first-episode patients, a subset appears to respond more slowly. In a study assessing time to treatment response, response was not achieved until after 4 weeks in 22.5% and after 8 weeks in 11.2% (Emsley *et al*., 2006b). Therefore, a longer treatment trial is warranted in first-episode schizophrenia. Also, the typical minimum dose requirement of 600 mg chlorpromazine equivalents per day (Suzuki *et al*., 2012) may not be appropriate for first-episode patients. Excessive antipsychotic doses are not associated with additional therapeutic benefit in multi-episode samples, and this may be particularly the case in first-episode samples (Davis and Chen, 2004). First-episode patients are exquisitely sensitive to the effects of antipsychotic medication and require lower doses for optimal efficacy (McEvoy *et al*., 1991; Oosthuizen *et al*., 2004). Therefore, a lower minimum dose requirement may be appropriate for first-episode patients.

Several limitations need to be considered when interpreting the findings of this study. First, as a convenience sample, these patients are not representative of all first-episode schizophrenia patients. Second, it is possible that some of the patients who dropped out early for reasons other than non-response could have been refractory. There were 11 patients who dropped out for reasons other than non-response before 8 weeks. Similarly, it is possible that some of the early dropouts due to poor response could have become responders if they had been able to remain in the study. However, this is considered unlikely as the decision to discontinue because of poor response was only taken when the investigators were of the opinion that there was no realistic chance of improvement. Also, the long-term outcome of the 15 non-responders that we identified is not known and is the subject of an ongoing study. Finally, it is possible that some patients who discontinued because of poor tolerability may have responded on a second-generation antipsychotic. We did not utilise a crossover design where patients who did not respond to first-line treatment could be switched to a second antipsychotic trial, as we focused on response to first-line antipsychotic treatment where treatment was guaranteed my means of a depot antipsychotic. Strengths of the study include the fact that patients were either treatment naïve or minimally treated—the comprehensive battery of assessments and the standardised treatment algorithm. Also, by using depot antipsychotic medication, we were able to remove the potential confounding effect of non-adherence.

In conclusion, this study identified a relatively low rate, 12%, of non-response to first-line antipsychotic treatment in first-episode schizophrenia, which is consistent with the proposal that some cases of treatment refractoriness emerge during the course of the illness in individuals who were initially responsive to treatment. Several demographic, baseline clinical and early treatment response variables may be useful in identifying these non-responders at an early stage of treatment.

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CONFLICTS OF INTEREST

Bonginkosi Chiliza has participated in speakers/advisory boards and received honoraria from Janssen and Sandoz. Laila Asmal, Sanja Kilian and Lebogang Phahladira have no conflict of interest to declare. Robin Emsley has participated in speakers/advisory boards and received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Organon, Pfizer, Servier, Otsuka and Wyeth. He has received research funding from Janssen, Lundbeck and AstraZeneca.

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Chapter 6

Conclusion

Conclusion

The overall aim of the dissertation was to study the clinical, biological and functional aspects of outcome in first episode schizophrenia. We were able to carefully assess, treat and follow up 207 patients (126 patients from our cohort in Cape Town, South Africa and 81 from Ibadan, Nigeria) with first episode schizophrenia over a period of 12 months. To date our study was the largest cohort of first-episode schizophrenia patients treated with a long-acting injectable antipsychotic published. Therefore, our main contribution to the literature was our ability to comprehensively study the outcome of first-episode schizophrenia patients on assured antipsychotic treatment in terms of clinical features (response, remission and relapse rates), biological (weight and metabolic changes) and functional aspects (social and occupational functioning and quality of life).

Long-acting injectable antipsychotics (LAIs) were developed in the 1960s specifically to address the problem of poor adherence in patients with schizophrenia. However, they are most often reserved for patients who have proven to be non-adherent or uncooperative, experienced multiple relapses, or are treatment refractory (Kane and Garcia-Ribera, 2009). We believe that LAIs are most useful and effective early in the course of schizophrenia (Emsley et al., 2013), because comprehensive intervention during the early course of illness is likely to change the long term trajectory and outcome of schizophrenia (Birchwood et al., 1998). This early or 'critical period', (i.e. the first two to five years of the illness), seems to be when the illness is most aggressive and is associated with multiple relapses and the greatest loss of functioning (Lieberman et al., 1993). Non- and partial-adherence to treatment is particularly predominant during the early course of treatment when patients are not yet convinced of the need for long-term treatment (Coldham et al., 2002). Yet the main predictor of relapse is treatment non-adherence or discontinuation (Robinson et al., 1999).

Therefore, multiple relapses and subsequent progression of illness and poorer functioning in the early course of illness is most likely due to treatment non-adherence. Consequently, a method of ensuring guaranteed antipsychotic delivery (e.g. utilizing LAIs) is ideally suited for first episode schizophrenia patients.

Early intervention in resource constrained settings

Our study was based within the large early intervention in psychosis movement. The early intervention wave has spread across many countries in Europe, North America, Australia and Asia (McGorry, 2015). However the majority of the early intervention research and services have been in upper income countries. There are very few studies that have examined the effects of early intervention of first episode schizophrenia in lower and middle income countries (LMICs). One of the key principles in early intervention in psychosis is the reduction of duration of untreated psychosis (DUP). Since the DUP is one of a few modifiable factors that influence long-term outcome, its reduction has been an important target for early intervention work. A recent systematic review showed that the DUP is in fact longer in LMICs than in upper income countries (Large et al., 2008). Additionally our literature review found that a long DUP is associated with poor outcome in these countries. Thus, there is a need to ensure those with first-episode schizophrenia receive psychosis treatment early in LMICs to improve long-term outcome.

A recent systematic review which analysed initiatives aimed at reducing DUP found, intensive public education and awareness plus changes to the health system to improve pathways to care can effectively reduce DUP (Lloyd-Evans et al., 2011). However less intensive intervention initiatives failed to reduce DUP due to significant logistical difficulties. Calls for early intervention in LMICs have argued that public awareness and education campaigns that target key informants, community

health workers, traditional and religious healers may be effective in reducing DUP (Farooq, 2013). Indeed, there is now ongoing research to examine whether the collaboration with traditional and complementary medicine practitioners will improve patient outcome (Gureje et al., 2015).

The second principle of early intervention is comprehensive treatment of first-episode schizophrenia patients after engaging with the services. We believe that in resource constrained settings with limited public funding like ours, one should focus on treating first episode schizophrenia patients as well as possible in order to improve the long-term outcome. We firmly believe the role for LAIs is crucial in treating first-episode schizophrenia patients. Our literature review of remission in LMICs showed that first-episode schizophrenia patients had high rates of remission despite a long DUP. This is likely due to the fact that some of the studies included in the review utilized LAIs for treating patients. Our study proved an older cost-effective antipsychotic, flupenthixol decanoate, can remarkably increase rates of remission, which gives further evidence for the utilization of LAIs in first episode schizophrenia within resource constrained settings.

Efficacy of a long-acting injectable antipsychotic

The majority of patients with first-episode schizophrenia have a robust response to antipsychotic treatment, unlike multi-episode patients (Robinson et al., 1999). However the response is typically not sustained for a sufficient duration to produce symptomatic remission. Our study found that by combining flupenthixol decanoate with a simple assertive monitoring programme, 82% of our patients responded to treatment, while 60% were able to meet the remission criteria by the end of the study. The rate of remission of our study is indeed remarkable as other studies have found lower remission rates (e.g. the large EUFEST study found remission rates varied from 17 – 41%) (Boter et al., 2009). Other studies where patients were treated within comprehensive early intervention

services also found low remission rates (e.g. Addington and Addington, 2008). Interestingly, in an earlier study from our research group, very similar rates of remission (64%) were found in a smaller cohort of first episode schizophrenia patients treated with long-acting injectable risperidone (Emsley et al., 2008). It is important to note, in our resource constrained setting, that flupenthixol decanoate has been found to be more cost-effective than long-acting injectable risperidone (Frey et al., 2014).

Our results support our view that long-acting injectable antipsychotics should be used as first line treatment in first-episode schizophrenia in order to improve patient outcome. Symptomatic remission has been associated with improved functioning and better quality of life. Therefore, we believe the continuous sustained delivery of an antipsychotic allowed the majority of our patients to achieve remission, thereby setting the stage for improved long-term outcome and even recovery.

Tolerability of a long-acting injectable antipsychotic

Since flupenthixol decanoate belongs to the first-generation class of antipsychotics, we were concerned that extrapyramidal effects would be one of the most significant side effects in our patients. We thus opted for a low-dose strategy as patients with first-episode schizophrenia are particularly sensitive to the side effects of antipsychotics (McEvoy et al., 1991). We found mild rates of extrapyramidal effects which were present in only a third of our cohort. The majority of the extrapyramidal effects were easily treated with anticholinergics or propranolol. Only 3% of our patients developed transient dyskinesia over the period of the study. We concluded that the low rates of extrapyramidal effects were due to the use of low dose of antipsychotics. With LAIs clinicians are able to titrate the dose of the medication such that minimum effective dosing is used. However the use of low doses of haloperidol in a previous study from our group did not protect patients from developing tardive dyskinesia (Oosthuizen et al., 2003). The second possible reason for

the low rates of extrapyramidal effects may be related to the improved pharmacokinetic properties of LAIs. The plasma concentrations of the medication are more consistent and more likely to stay within the effective plasma range. Oral medications often have more varied plasma concentrations related to administration timing and food effects, such that side effects associated with peak plasma levels are more common than with LAIs.

The extent of the weight and metabolic changes were however surprising. Our cohort gained considerable weight over 12 months of treatment. Weight gain was significant early on (at 6 weeks) and continued throughout the study. We know first-episode schizophrenia patients are sensitive to potential weight gain while taking antipsychotics (Alvarez-Jimenez et al., 2008), however the focus of most published studies has been on second generation antipsychotics. Flupenthixol has been characterised as being weight neutral among chronic schizophrenia samples, therefore the substantial mean weight gain was unexpected. There was a subset of patients (23%) who gained severe weight gain (measured as > 14% of body of weight), at 12 weeks. These patients could prove interesting for future pharmacogenomic predictor of weight gain studies, but also for clinicians who should place more clinical attention on these patients. Our future research will focus on these patients in order to determine if early severe weight gain could be predictive of later weight and metabolic changes, since we found no clinically meaningful predictors of weight gain.

Accompanying the weight and BMI changes, our cohort had significant changes in their lipid profiles. The increases in triglycerides (TG) and reductions in high density lipoproteins (HDL) gave rise to highly significant increases in the TG/HDL ratio. This is of particular concern as this ratio is an atherogenic marker and a predictor of cardiovascular disease. Our finding of an increase in the number of risk factors for metabolic syndrome is of further concern. Our study was able to

convincingly demonstrate the magnitude of the problem because the majority of our patients were fully adherent to treatment and completed the study. Interestingly, we did not find a significant increase in fasting blood glucose and there was no correlation between changes in BMI and metabolic markers, other than TG. These findings raise further questions for future studies particularly around the mechanisms of weight and metabolic changes. Future studies should also focus on interventions that ameliorate weight and metabolic changes, such as focusing on diet and lifestyle changes, exercise and smoking cessation.

Initial treatment refractoriness

The evolution of treatment refractoriness is poorly understood. Whilst some patients are non-responsive from the outset, others appear to respond initially and only develop refractoriness following a relapse (Emsley et al., 2013). Actual rates of true refractoriness are not known, as in many cases the persistence of positive symptoms could be due to non- or partial adherence to antipsychotic medication. The only way to control for the confounding effect of non- or partial compliance is to ensure antipsychotic medication is delivered by means of a long-acting injection.

Our study was able to carefully assess true rates of non-response to first line antipsychotic treatment. We found very low rates of non-response to treatment (12%), and it appears that these were patients were non-responders from the outset. These patients were more likely to have prominent neurological soft signs and showed poor early treatment response. Treatment non-responders are an important group of patients to identify early in order to avoid accruing morbidity and unnecessary treatment trials (Agid et al., 2007). Patients who failed to respond to a first line antipsychotic are also unlikely to respond to another antipsychotic. Therefore early use of clozapine in these patients has been recommended as early effective treatment and is associated with better

outcome (Remington et al., 2013). Future research should test this strategy by comparing patients with prominent neurological soft signs and poor early response to first line antipsychotics, who are later switched to clozapine and compared to those who stay on another non-clozapine antipsychotic.

Future research direction

Our research team plans to examine the effectiveness of the combination of LAI plus assertive monitoring program. This is best demonstrated by utilising a pragmatic cluster randomized trial where different community clinics are randomized to LAI management of first episode schizophrenia patients plus an assertive monitoring program or treatment as usual. This research design will not only ascertain whether our treatment strategy is effective when implemented within routine care, but also determine how to scale up the intervention. The simple assertive monitoring program is straightforward and can be delivered by primary health care providers, thus ideal for resource constrained settings. In order to have a broader impact on public health, these research findings should be disseminated to government to influence policy and treatment guidelines.

Our research team also plans to embark on a long-term follow up of this cohort of first-episode schizophrenia patients to assess whether our intervention during the critical period of treatment had any effects on long-term outcome. We will examine the course of illness, remission and recovery rates as well as functional aspects of outcome, including quality of life and social and occupational functioning. We shall also further examine the evolution of treatment refractoriness and long-term weight and metabolic features. We believe that this very carefully assessed and treated cohort will be able to give us a wealth of information on the early course of treatment as other recently published studies (e.g. Morgan et al., 2014). This long-term follow up will indeed give further

evidence as to whether early effective management of first-episode schizophrenia patients with assured antipsychotic delivery during the critical period influences long-term outcome.

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List of Abbreviations

AMP	assertive monitoring program
BIS	Birchwood insight scale
BMI	body mass index
BPRS	brief psychiatric rating scale
CDSS	Calgary depression scale for schizophrenia
CGI	clinical global impression
CONSORT	consolidated standards of reporting trials
DAI	drug attitude inventory
DSM-5	diagnostic and statistical manual of mental disorders, fifth edition
DSM-IV	diagnostic and statistical manual of mental disorders, fourth edition
DUI	duration of untreated illness
DUP	duration of untreated psychosis
EPPIC	early psychosis prevention and intervention centre
EPS	extrapyramidal side effects
ESRS	extrapyramidal symptom rating scale
FGA	first generation antipsychotics
GCP	good clinical practice

GDP	gross domestic product
HDL	high density lipoproteins
LAI	long-acting injectable antipsychotic
LDL	low density lipoprotein
LMIC	lower and middle income countries
LOCF	last observation carried forward
MCCB	measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery
MetS	metabolic syndrome
MMRM	mixed effect models for continuous repeated measures
NSS	neurological soft signs
PANSS	positive and negative symptom scale
PAS	premorbid adjustment scale
RSWG	remission in schizophrenia working group
QLS	quality of life scale
SANS	scale for assessment of negative symptoms
SAPS	scale for assessment of positive symptoms
SGA	second generation antipsychotic
SOFAS	social and occupational functioning assessment scale
STROBE	strengthening the reporting of observational studies in epidemiology

TG	triglycerides
WC	waist circumference
WHO	World Health Organization