EFFECTS OF ANTIPSYCHOTIC DOSE REDUCTION ON METABOLIC SYNDROME IN PATIENTS WITH FIRST EPISODE PSYCHOSIS TREATED WITH A LONG-ACTING INJECTABLE ANTIPSYCHOTIC

By

Ziyanda Lynn Ndlangisa

Student number 213508630

Email 213508630@stu.ukzn.ac.za

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School of Medical Science

College of Health Sciences

University of KwaZulu Natal

Durban

4000

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Supervisor: Prof M Mabandla

Co-supervisor: Prof B Chiliza

As the candidate's supervisor, I have/have not approved this thesis/dissertation for submission.

Signed: _____ Date: _____

ABSTRACT

Background: The introduction of antipsychotics has been a significant milestone in the treatment of schizophrenia. However, these agents have several important side effects, such as metabolic syndrome. Options to curb these side effects include a change in the treatment option, changes in patients' lifestyle, and the addition of other medications such as metformin, among others. Thus, this study investigated whether dose reduction of an injectable antipsychotic, flupenthixol decanoate, would result in improvement of metabolic syndrome parameters in a cohort of first-episode schizophrenia patients in South Africa.

Methods: The study included 33 participants recruited at the Tygerberg and Stikland Hospitals in the Western Cape Province, South Africa. The metabolic syndrome profiles of all 33 participants were compared at baseline and at point of relapse. All participants were given a monthly dose of an injectable antipsychotic, flupenthixol decanoate, which was gradually reduced until the participant relapsed or was off treatment. Adherence to treatment was guaranteed as all participants had to visit the healthcare facility to receive their injectable.

Results: The majority of the participants were colored (75.8%). Most (64%) of the participants were overweight. The mean time to relapse was 39.2 weeks, and by week 32, almost half of the participants had relapsed. A significant change was observed for weight ($p = 0.018$), waist circumference ($p = 0.006$) and fasting glucose ($p = 0.045$). There were no significant changes in the lipid parameters following the antipsychotic dose reduction.

Conclusion: Antipsychotic dose reduction resulted in weight loss; however, the majority of patients relapsed with some having important consequences. Further studies are needed to understand the dynamics of treatment discontinuation in schizophrenia patients; however, clinicians should closely monitor patients taking antipsychotics as metabolic syndrome negatively impacts on the patients' quality of life.

PREFACE

The current research was part of a broader study which was a randomized, double-blinded, placebo-controlled investigation that involved subjects who had been successfully treated for 2 to 3 years after a first episode of schizophrenia, schizoaffective or schizophreniform disorder and who voluntarily opted to discontinue antipsychotic treatment under supervision (Emsley *et al.*, 2014).The data for this study were collected from patients recruited at Tygerberg and Stikland Hospitals catchment area in the Western Cape, South Africa. This is a secondary quantitative study which looked into whether treatment discontinuation had any effect on the individual metabolic syndrome parameters. The secondary analysis of the data was done under the supervision of Professor Bonginkosi Chiliza who was an investigator in the original study.

This study uses data collected by other researchers; however, has never been submitted under the current topic and investigating the parameters earlier mentioned to any tertiary institution. Where the use of other people's work has been done, this has been acknowledged in the text.

DECLARATION - PLAGIARISM

I, Ziyanda Lynn Ndlangisa, declare that:

1. The research reported in this thesis, except where otherwise indicated, is my original research.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons' data, pictures, graphs or other information unless specifically acknowledged as being sourced from other persons.

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LIST OF ABBREVIATIONS

SGA	: Second-generation antipsychotic
FGA	: First-generation antipsychotic
HDL	: High-density lipoprotein
LDL	: Low-density lipoprotein
VLDL	: Very low-density lipoproteins
HMG-CoA reductase	: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
AN	: Arcuate nucleus
AgRP	: Agouti-related protein
TG	: Triglycerides
MetS	: Metabolic syndrome
BMI	: Body mass index
FBG	: Fasting blood glucose
DBP	: Diastolic blood pressure
SBP	: Systolic blood pressure
SD	: Standard deviation
SE	: Standard error
DSM-IV	: Diagnostic and statistical manual of mental disorders, fourth edition
Tdp	: torsades de pointes

LIST OF PARAMETERS AND UNITS USED TO MEASURE

Parameter measured	Unit of measurement
BMI (body mass index)	: Kg/m^2
Diastolic blood pressure	: mmHg
Fasting blood glucose	: mmol/L
HDL (high densisity lipoprotein)	: mmol/L
LDL (low density lipoprotein)	: Mm/L
Systolic blood pressure	: mmHg
Triglycerides	: mmol/L
Waist circumference	: Cm
Weight	: Kg

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CHAPTER 1

GENERAL INTRODUCTION

1.1 Background

Antipsychotics have been a great milestone in the treatment of schizophrenia. From the discovery of the first antipsychotic chlorpromazine to the further discovery of more and differentiating into different classes, namely "first-generation antipsychotics" to "second-generation antipsychotics." However, these agents present with several serious untoward effects. The life expectancy of people suffering from mental illness is reduced by at least 7-24 years according to a systematic review published in 2014 (Chesney, Goodwin and Fazel, 2014). The study also noted that suicide among this population is ten times higher than the general population. Unfortunately, this figure is further fueled by the association of mental illness and substance abuse (Whiteford *et al.*, 2013).

Antipsychotics are widely used for the treatment of schizophrenia and other psychiatric disorders (Chang and Lu, 2012); however, they contribute to the public health problem of metabolic syndrome as well as its increasing prevalence (Chadda *et al.*, 2013). The increase in prevalence may also be attributed to modern civilization (Wang *et al.*, 2010). Metabolic syndrome involves a cluster of abnormalities including elevated fasting blood glucose, low HDL, increased LDL, obesity and elevated blood pressure (Grundy *et al.*, 2004). These adversities lead to cerebrovascular disease, diabetes mellitus and cardiovascular complications (Kannel and Daniel, 2012) further leading to the high rates of mortality in people with schizophrenia (Schoepf *et al.*, 2012).

There is inadequate literature available on antipsychotic dose reduction. However, a study in China (Wu *et al.*, 2014) not only examined the effects of antipsychotics on glucose and lipid metabolic parameters on a cohort of 131 Chinese patients with schizophrenia but also looked at the effects of antipsychotic discontinuation on these parameters. The study comprised of drug naïve participants, those treated with antipsychotics as well as participants who were treated and later discontinued treatment. Unfortunately, the study only confirmed what is already known of the metabolic adversities caused by antipsychotics. No improvement was noted in the glucose and lipid profiles of participants who had discontinued antipsychotic treatment. Most of the available literature looks at individual metabolic syndrome (MetS) risk factors instead of looking at individuals with full-blown MetS (people who meet at least three

of the five criteria), and not many of those studies have investigated dose tapering as a way to undo MetS.

The above-mentioned study is similar to our study, in which we examined the glucose and lipid profiles of participants with schizophrenia who had undergone remission. The participants were weaned off treatment in monthly intervals (reduction factor 0,75 for all participants). Glucose and lipid profiles were recorded at baseline and 6 monthly intervals. This study was conducted in an attempt to find out if gradual antipsychotic medication withdrawal could reverse metabolic adversities.

1.2 Research question

Does dose reduction of an injectable antipsychotic result in weight loss?

1.3 Problem statement

Various studies in the literature have investigated the effects of antipsychotics on weight and BMI and the management thereof. Of interest in the current study were the effects of dose reduction on the major phenotypical aspects of metabolic syndrome such as weight gain and lipid profile. The findings of this study may assist in determining which parameters to monitor when discontinuing antipsychotic therapy.

1.4 Aim

The aim of this study was to investigate the effects of antipsychotic treatment dose reduction on the participants' metabolic parameters.

1.5 Specific objectives

To compare participants' metabolic syndrome criteria at baseline and point of relapse.

To determine whether there is a relationship between metabolic syndrome and socio-demographic factors.

To determine the prevalence of metabolic syndrome across different socio-demographic factors.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

According to the DSM-V, schizophrenia is diagnosed when an individual experiences two or more of the following symptoms for at least one month (or longer): delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms. Although no definite etiological basis for this condition has been found, it is thought that factors such as environment, genetics, neurodevelopment could be the cause (Weinberger, 2017). To support the latter statement, Koenig et al. (2002) discovered that this condition may be genetic or even develop as a result of the unborn baby being exposed to prenatal stress during the second or third trimester of pregnancy. However, there are quite a few infectious disease studies that have found a link between schizophrenia and elevated *Toxoplasma gondi* antibodies in patients with schizophrenia (Yolken *et al.*, 2002; Ghorbanpoor *et al.*, 2010).

Before the development of antipsychotics, patients who had psychosis would have been institutionalized until their symptoms improved (Gronfein, 2012). This probably had a toll on the health system. Fortunately, the development of antipsychotics meant that patients could now be treated at home and only required hospitalization when their symptoms worsened (Kane, 1988a). With that being said, antipsychotics did come with a whole host of adverse effects and the most well-known being metabolic syndrome (Tschoner *et al.*, 2007), which has been observed at therapeutic doses. Not all antipsychotics contribute equally to this adverse effect and research has shown that compared to older generation antipsychotics, the newer generation antipsychotics are more likely to cause metabolic syndrome (Kane, 1988a).

Metabolic syndrome (MetS) further complicates the treatment of schizophrenia as it is likely to contribute to high rates of mortality (Saloojee, Burns and Motala, 2016). Mortality arises from the secondary complications of metabolic syndrome such as diabetes and cardiovascular adversities. Some patients may present with risk factors before treatment, and in most cases, lifestyle behaviors of people with schizophrenia such as inactivity and poor diet have an additive effect on MetS (Chadda *et al.*, 2013). The increased risk of metabolic syndrome in young patients with first-episode psychosis could also be due to elevated clinical markers such as LDL, HDL, triglycerides and fasting blood glucose in addition to unhealthy lifestyle

behaviors (Smith, Griffiths and Horne, 2016). This could result in high rates of non-adherence to treatment amongst patients as well as relapse (Tschoner *et al.*, 2007). Drugs have been developed recently (sertindole) to minimize adverse events, but this has not always proven successful, and newer agents are not necessarily more superior than their older counterparts (Cincotta and Rodefer, 2010).

Apart from metabolic syndrome, some researchers believe antipsychotics could be associated with a reduction in brain volume as well as dopamine receptor sensitization which could lead to relapse and illness progression(Goff *et al.*, 2017). Treatment of schizophrenia is based on the phase of illness (acute or maintenance phase)(Hui *et al.*, 2019). Some researchers believe maintenance treatment is the gold standard in antipsychotic therapy (Emsley, Kilian and Phahladira, 2016). However, one should be aware that guidelines vary based on the country of origin, and there is no one size fits all approach in the treatment of schizophrenia(Hui *et al.*, 2019). The same systematic review (Hui *et al.*, 2019) discovered that some guidelines suggest a two-year or 2-5 year period on maintenance therapy while others suggested maintenance treatment indefinitely.

2.2 Metabolic Syndrome overview

Metabolic syndrome, an umbrella term to describe hypertension, reduced high-density lipoprotein, hyperglycemia, hypertriglyceridemia as well as an increase in waist circumference (Kane, 1988a; Chadda *et al.*, 2013), has been noted to be a significant contributor to the mortality of patients with schizophrenia (Grundy *et al.*, 2004; Factors *et al.*, 2011; Fleischhacker *et al.*, 2013; Young, Taylor and Lawrie, 2015; Saloojee, Burns and Motala, 2016). Although some researchers might argue that MetS is intrinsic to schizophrenia (Freyberg *et al.*, 2017), given the sedentary lifestyle of most people with schizophrenia, others claim antipsychotic medicines do not cause metabolic syndrome but facilitate its progression (Factors *et al.*, 2011). Wysokiński, Dzienniak, and Kłoszewska (2013) found that disturbances in lipid and glucose profile contributed to worsening cognitive function in patients with schizophrenia. Diabetes, hypertension and obesity have shown to have similar susceptibility genes (Cheung and Li, 2012). The tragedy is that the manifestation of multiple factors that cause MetS in a person, may aggravate depression in such patients and thus presenting a challenge for clinical improvement (Vallance, 2009). Several factors lead to metabolic syndrome (resulting in cardiac complications as well), e.g. smoking, obesity, hypertension and

dyslipidemia. However, there is no clear answer as to whether all these factors are additive to the cause of MetS or they work together, eventually causing metabolic syndrome (Holt and Mitchell, 2015). Different criteria have been identified to determine if an individual should be considered as suffering from metabolic syndrome (Table 1).

Table 1: Criteria for metabolic syndrome according to the South African dyslipidemia guideline consensus statement: 2018. A person is said to have metabolic syndrome when they meet 3/5 criterion

Criterion	Specification
Fasting glucose	>5.6 mmol/L
Hypertriglyceridemia	>1.7 mmol/L
Low density lipoprotein cholesterol	<1 mmol/L men, <1.3 mmol/L women
Systolic blood pressure	>130 mmHg
Diastolic blood pressure	>85 mmHg
Waist circumference	>90 cm men, >80 cm women

Table from the South African dyslipidemia guideline consensus statement: 2018

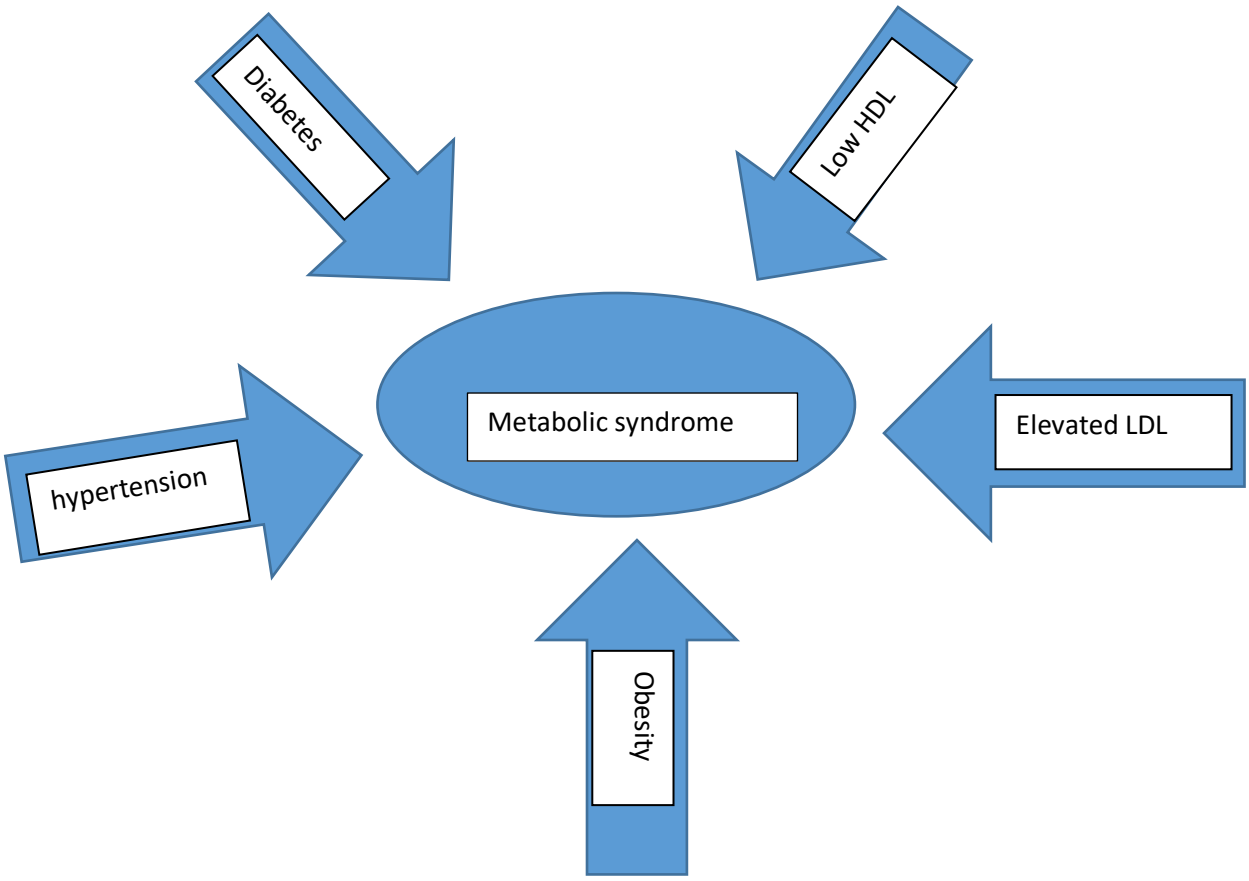

Figure 1: Factors contributing to metabolic syndrome.

2.2.1 Prevalence of antipsychotic-induced Metabolic Syndrome

Comparing prevalence studies by different researchers poses a challenge since there are varying definitions of MetS (Cameron, Shaw and Zimmet, 2004). The global prevalence of MetS was reported as 32.5% (Mitchell *et al.*, 2013). In their study, at least 1 out of 3 patients with schizophrenia who were included in prevalence studies had MetS (Mitchell *et al.*, 2013). These people were often from low- and middle-income countries where there might be very few physicians who can diagnose schizophrenia; some patients do not even present themselves to a healthcare facility at all. There are global studies looking into MetS in schizophrenia (Saloojee, Burns and Motala, 2016). However, one study was able to document prevalence in 27 countries(Mitchell *et al.*, 2013). A different study noted that MetS was more prevalent in the younger generation receiving second-generation antipsychotics(Chadda *et al.*, 2013). Young people on antipsychotics present with an incidence rate of 0.20/1000/year (Messias, Chen and Eaton, 2007). About 50% of patients with schizophrenia are overweight (Mitchell *et al.*, 2013). There seem to be contradictory findings when it comes to prevalence according to gender (Chiliza *et al.*, 2015). Some studies found MetS more prevalent amongst females (De Hert, Schreurs and D, 2008; Chadda *et al.*, 2013; Saklayen, 2018). Contrarily, Fleischhacker et

al. (2013) discovered that MetS was more prevalent amongst males. An increase in BMI was, however, associated with non-substance use (Chiliza *et al.*, 2015). Age did not necessarily have a significant contribution to prevalence; it was the duration of treatment that had an influence (Mitchell *et al.*, 2013).

About 15% of the world's population resides in Africa, and the figures are estimated to increase to approximately 40% by the end of the current century (Frankema and Waijenburg, 2018). However, only 0.001% of all schizophrenia patients recruited in global studies are from Africa (Purgato, Adams and Barbui, 2012). Therefore, information on antipsychotic-induced MetS in Black African people is limited (Saloojee, Burns and Motala, 2016). A recent cross-sectional study done in South Africa documented a metabolic syndrome prevalence rate of 23,2% in their cohort, with South African Indians being at a higher risk of MetS compared to people of Black African (Saloojee, Burns and Motala, 2016). Race seems to also play a role in studies that included people of different ethnic groups (Cameron, Shaw and Zimmet, 2004). Low- and middle-income countries may experience difficulty in estimating prevalence since many cases remain undocumented as patients never make it to healthcare facilities for treatment (Saloojee, Burns and Motala, 2016). Prevalence studies might also fail to deliver a clear global picture in the sense that they compare different populations subjected to varying inclusion criteria and study designs (Cameron, Shaw and Zimmet, 2004; Chadda *et al.*, 2013).

2.3 Antipsychotics

Before the successful discovery of the first effective antipsychotic chlorpromazine, in the late 1949's, scientists had several failed attempts in treating psychosis using (Chang and Lu, 2012; Gronfein, 2012). However, these failed attempts led to the realization that there was a need for other phenothiazine derivatives with similar effects, and eventually, chlorpromazine was successfully synthesized (Dimitrelis and Shankar, 2016). Antipsychotics have not only improved the treatment of mental illnesses such as schizophrenia but have also decreased the need for hospitalization because patients can now receive their treatment at home (Gronfein, 2012). This has improved compared to the past, where patients had to be hospitalized for long periods while receiving treatment (Abdelmawla and Mitchell, 2006). These drugs also happen to be one of the most prescribed drugs on the market today (Balt *et al.*, 2011). In South Africa, 17 drugs have been approved for the treatment of psychosis (Rossiter *et al.*, 2016). A list of these side effects are shown in Figure 2. The top 6 frequently encountered side effects

associated with the antipsychotics registered for use in South Africa include extrapyramidal effects, orthostatic hypotension, weight gain, dizziness, headache and sedation (Figure 2).

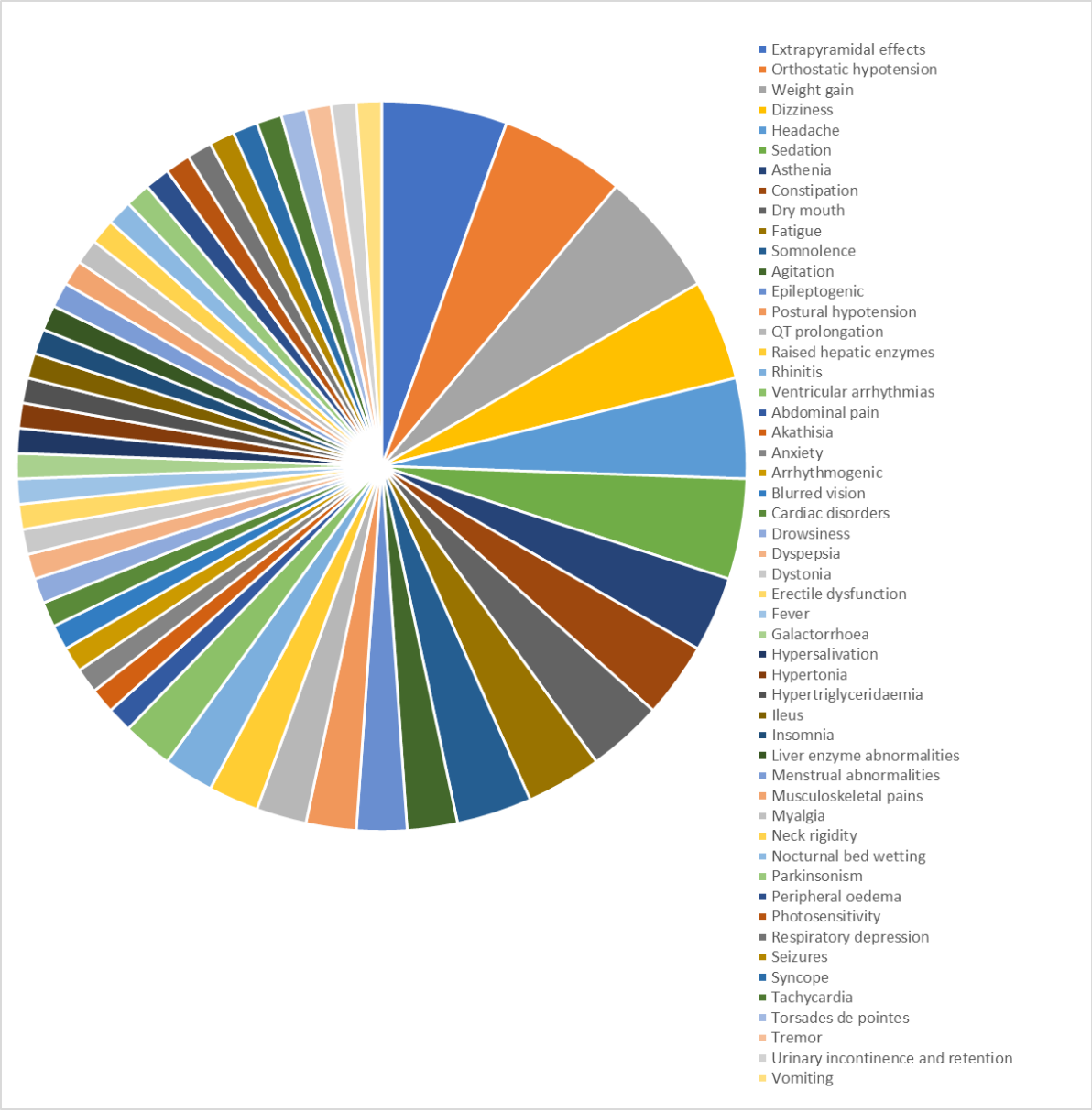

Figure 2 : S*ource:* (Rossiter *et al.*, 2016)

2.3.1 Advancement to newer drugs

Schizophrenia is not only one of the most distressing mental illness for both patient and caregiver, but also quite costly to treat (Chisholm *et al.*, 2008). The degree to which different antipsychotics contribute to the different metabolic adversities differs (Stroup *et al.*, 2011). Hence clinicians could decide to switch from one antipsychotic to one better tolerated by the patient (de Silva *et al.*, 2016). During recent years, there has been a shift from first-generation

antipsychotics (FGA) to the second-generation (Leucht, Kissling and Davis, 2009) antipsychotics (SGA). The main difference between FGA and SGA is that FGA highly antagonizes at the dopamine D2 receptors; newer drugs (SGA) have more affinity for other neuro-receptors such as serotonin (Tashkin *et al.*, 2008). Another point to note is that SGA present with a better tolerability profile compared to FGA, as well as a reduction in cognitive impairment (Kane, 1988a). However, SGA have been linked to weight gain and metabolic syndrome (Kane, 1988a; Factors *et al.*, 2011). This could potentially affect treatment adherence (Tschoner *et al.*, 2007) since these medicines often come with a warning of possible hyperglycemia and diabetes (Factors *et al.*, 2011). Therefore patients taking antipsychotics require regular monitoring by the treating clinicians. The use of antipsychotic drugs is not limited to schizophrenia alone. Despite all the side effects of SGA, they remain the treatment of choice for most psychiatrists (Leucht, Kissling and Davis, 2009). However, due to cost, many lower- and middle-income countries still use first-generation antipsychotics as they are more affordable (Chisholm *et al.*, 2008). The cost of these agents (SGA) might have caused the spark in the debate about their superiority to first-generation antipsychotics (Leucht *et al.*, 2009).

All clinicians would agree that the most important decision when treating schizophrenia lies in which antipsychotic will best work for the patient(Davis, Chen and Glick, 2003). First-generation antipsychotics are believed to effectively treat positive symptoms in schizophrenia which include delusions and hallucinations while they are less effective in treating the negative symptoms and this is where second-generation antipsychotics are thought to be quite effective (Chang and Lu, 2012). In a systematic review comparing antipsychotic efficacy, Leucht et al. discovered that four (amisulpride, clozapine, olanzapine and risperidone) out of nine second-generation antipsychotics were more effective in primary outcomes compared to first-generation antipsychotics (Leucht *et al.*, 2009). Extrapyramidal side effects remained the main concern with first-generation antipsychotics; however, when it came to metabolic side effects such as weight gain, there was no superiority (in terms of side effect profile) of second-generation antipsychotics compared to the first-generation antipsychotics. The study also noted that SGAs cause just as much weight gain as FGAs except for aripiprazole and ziprasidone which were more weight neutral. One thing is sure, regardless of whether an antipsychotic is an SGA or FGA, the effect it has on the different metabolic syndrome parameters differs(Chadda *et al.*, 2013).

The introduction of second-generation antipsychotics gave an impression of new, safer and more efficacious drugs into the market. In 1996 a Dutch-manufactured atypical antipsychotic drug, sertindole, was introduced into the market and had passed as a better-tolerated drug in clinical trials (Cincotta and Rodefer, 2010). Its reign was, however, short-lived when it was later withdrawn in 1998 because of discovering that it caused prolongation of the QT interval (Cincotta and Rodefer, 2010). This shows that even with newer drugs being introduced, it does not necessarily mean they are superior to older antipsychotics. Sertindole was later brought back into the market by certain European countries because of specific characteristics that were found more desirable and overshadowed its safety concerns (Cincotta and Rodefer, 2010). In a double-blinded study by Leucht et al. again sertindole was found not to be any more superior to the first generation antipsychotics in treating both positive and negative symptoms (Leucht *et al.*, 2009).

2.4 Complications presented by antipsychotics

2.4.1 Weight gain

Antipsychotic use is associated with weight gain(de Silva *et al.*, 2016). It is commonly believed that the main contributors to weight gain or obesity are lack of exercise, or physical inactivity and consumption of too many calories (Manu *et al.*, 2015). Weight gain can be determined by measuring weight, however measuring waist circumference is useful when measuring the increase in abdominal fat deposition and this approach is much more efficient in determining risks of developing secondary illnesses such as type two diabetes (Fleischhacker *et al.*, 2013). People on antipsychotics are generally more prone to weight gain or obesity compared to the general population (Chang and Lu, 2012). Antipsychotics can cause metabolic syndrome in ways that cannot be explained by weight gain alone (Kang and Lee, 2015). This is supported by evidence in a study that discovered that unlike the prevalence of weight gain, the prevalence of metabolic syndrome differed for the three groups that were being studied, revealing that weight gain does not always correlate with disturbances in lipid and glucose homeostasis (Kang and Lee, 2015). One of the theories of antipsychotic-induced weight gain is that weight gain is mediated through peripheral messengers which act through pathways in the hypothalamic region known as the arcuate nucleus (AN) which causes secretions of a peptide hormone (ghrelin) from the stomach mucosa which results in the expression of neuropeptide Y (NPY) and agouti-related protein (AgRP) by the hypothalamus (Luquet *et al.*, 2005; Balt *et al.*, 2011).

These neurons are responsible for appetite and weight gain. Balt et al. (2011) were also able to cite gene alleles (*HTR2C* −759C and the *LEP* −2548G) that were most likely to predispose patients to weight gain. When different atypical antipsychotics were compared to one another, it was found that the extent to which each antipsychotic contributed to weight gain differed (Fleischhacker *et al.*, 2013).

Although antipsychotics may contribute to an increase in BMI (Chiliza *et al.*, 2015), the increase was found to be related to improved cognition and memory performance (Luckhoff *et al.*, 2019), which was however independent of the degree of antipsychotic exposure. An increase in BMI, although not physically appealing, appears to improve cognitive function in patients with schizophrenia. Studies on clozapine have shown that it has more significant metabolic adversities compared to other antipsychotics; however, it has been found to be more superior in treatment-resistant schizophrenia (Nielsen, Skadhede and Correll, 2010a).

Pharmacological strategies to counteract weight gain have been proposed, especially for cases where switching antipsychotics to those with less cardio-metabolic adversities is not feasible (De Hert *et al.*, 2008). These strategies involve the use of antidiabetic drug metformin (Mahmood, Naeem and Rahimnajjad, 2013; Mizuno *et al.*, 2014; de Silva *et al.*, 2016). Other strategies include exercise, a balanced diet as well as switching antipsychotics from those that have a high tendency of causing weight gain to those which are more weight neutral.

2.4.2 Diabetes

2.4.2.1 Glucose homeostasis

Like most systems in the body, glucose homeostasis is regulated through a negative feedback mechanism. This feedback mechanism involves the *B* cells which are found on the islets of Langerhans in the pancreas, which have four types of cells which produce four different hormones (Pandol, 2015), namely:

- Beta cells - insulin
- Alpha cells - glucagon
- Omega cells - somatostatin
- F cell - pancreatic polypeptide

The *B* cells work with the insulin-sensitive cells in the body. When glucose levels rise in the body, the *B* cells of the pancreas are stimulated to secrete insulin which sensitizes cells to

glucose (Laurie Kelly, 2005). Muscles use glucose as the primary source of energy, and in order to absorb glucose, they require insulin to facilitate the transport of glucose into the cells. Thus, the increase in insulin results in glucose uptake by the cells maintaining homeostasis. In the case of insulin resistance, as seen in the majority of obese people, the *B* cells are stimulated to secrete increased amounts of insulin in response to the reduced sensitivity of the cells (to overcome insulin resistance) in order to maintain homeostasis. Eventually, because of insulin resistance, the *B* cells are unable to meet the increased demand for insulin, and this results in elevated plasma glucose levels (hyperinsulinemia). The elevation in plasma glucose initially causes impaired glucose tolerance and further damage to the *B cells* causing further increases in plasma glucose, and eventually, full-blown type two diabetes develops (Kahn, Cooper and Del Prato, 2014). The long-term consequences of hyperglycemia are thickening of capillary membranes as well as narrowing of blood vessels that supply vital organs with blood, and this can lead to atherosclerosis, retinopathy, neuropathy and ulceration or gangrene. Severe peripheral neuropathy puts the patient at risk of lower extremity amputations (Pemayun *et al.*, 2015).

2.4.2.2 Diabetes mellitus in patients taking antipsychotics

Although there are genetic factors involved in some cases of diabetes mellitus globally, we have witnessed an increase in cases of obesity and as a result, this has contributed to the increased prevalence of type 2 diabetes (Kahn, Cooper and Del Prato, 2014), not to forget environmental factors involved. Environmental factors can include but are not limited to a sedentary lifestyle and a high-calorie diet. Some researchers believe disturbances in glucose homeostasis in patients taking antipsychotics is a result of "antipsychotic-induced weight gain"; this is an indirect association which could be explained by the decrease in peripheral insulin sensitivity (Nielsen, Skadhede and Correll, 2010b). Another exciting discovery was that schizophrenia and type 2 diabetes mellitus share the same intrinsic inflammatory pathways (Perry *et al.*, 2016), this was justified by first episode psychosis later developing into full-blown schizophrenia and likewise pre-diabetes later on leading to diabetes. Both these events occur concurrently in people diagnosed with both schizophrenia and type 2 diabetes mellitus.

However, there are many cases of diabetes mellitus in people living with schizophrenia that remain undiagnosed making it difficult to determine prevalence rates as schizophrenia and diabetes share similar risk factors (Fernandez-Egea *et al.*, 2009). Literature has remained quite

consistent though in reporting a two to three-fold higher diabetes mellitus rate in schizophrenia patients compared to the general population (Holt and Mitchell, 2015). As mentioned earlier, some researchers believe that MetS could be intrinsic to schizophrenia (Cohn *et al.*, 2006; Venkatasubramanian *et al.*, 2007). At least 10% of patients with schizophrenia develop diabetes in their lifetime, putting people with schizophrenia at 2.5 times greater risk of developing diabetes compared to the general population (Pillinger *et al.*, 2017). Fernandez-Egea *et al.* (2009) discovered that drug-naïve patients with psychosis displayed abnormal glucose tolerance before being exposed to any antipsychotic medication. It seems that insulin plays a crucial role in the development of MetS and diabetes mellitus in patients (Tomono *et al.*, 2008). Venkatasubramanian et al. (2007) believe that the answer lies in the deficiency of insulin growth factor-1 (crucial for insulin sensitivity) which they found to exist in antipsychotic-naïve patients with schizophrenia. A deficiency in IGF-1 could potentially result in insulin resistance leading to diabetes. Fleischhacker et al. (2013) also concluded that 5.9% of their participants had pre-existing metabolic syndrome at baseline prior to any treatment, however, their explanation was attributed to unhealthy behaviors like smoking, alcohol, sedentary lifestyle which is in line with the other researchers findings in earlier studies (Factors *et al.*, 2011).

2.4.3 Dyslipidemia

Hepatic lipase, which is found in the liver, is responsible for the hydrolysis of triglycerides (TG) and phospholipids into low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles. This process results in smaller and denser LDL particles (carry cholesterol to tissues and results in artery plaque formation) and a higher reduction in HDL (removes cholesterol from circulation and returns it to the liver for excretion). The human body requires higher levels of HDL, the so-called “good cholesterol” and lower levels of LDL, which is known as “bad cholesterol”. The next stage is an increased synthesis of apolipoprotein B, which leads to an increase in triglyceride containing very low density lipoprotein (VLDL) particles (Ayyobi and Brunzell, 2003).

Dyslipidemia is the major contributing factor to the complications of metabolic syndrome, which is mainly high levels of free fatty acids, TG, LDL and rather low levels of HDL (Kolovou, Anagnostopoulou and Cokkinos, 2005). Secondary causes of dyslipidemia include:

- Liver disease

- Hypothyroidism
- Kidney disease
- Excessive alcohol consumption
- Diabetes mellitus
- Steroid drugs
- Progestins
- Antiretrovirals, e.g. stavudine
- retinoids

2.4.3.1 Pathophysiology of Dyslipidemia

Cholesterol is notoriously known for causing cardiac conditions as well as blocking arteries; however, the body requires cholesterol to synthesize hormones, bile acid, plasma membranes and myelin sheath of neurons (Zhang and Liu, 2015). An imbalance in lipid profile has been known to cause coronary heart disease, atherosclerosis, cerebrovascular disease as well as peripheral vascular disease.

Dyslipidemia is caused by both environmental (sedentary lifestyle, diet, smoking) and genetic factors.

When LDL remains in plasma for too long, it becomes oxidized generating free radicals, and that oxidation renders it atherogenic which causes atherosclerosis and even worsens the inflammation of blood vessels. Most atherosclerosis-related deaths are as a result of coronary heart disease (Weisfeldt and Zieman, 2007). Weight gain, as well as insulin resistance, are the main driving forces predisposing individuals to dyslipidemia (Ayyobi and Brunzell, 2003; Kang and Lee, 2015). The adipose tissue of overweight individuals produces adipokines (cytokines), which also contribute to the development of metabolic syndrome (Tomono *et al.*, 2008). People with increased intra-abdominal fat have increased hepatic lipase activity, which results in hydrolysis of HDL and LDL (Ayyobi and Brunzell, 2003). People with obesity release reduced amounts of adiponectin from adipose tissue, which is believed to be the cause of insulin resistance and a fatty liver (Buechler, Wanninger and Neumeier, 2011). Adipokines cause atherogenesis directly by acting on the arterial walls or through other metabolic risk factors. HDL primarily disturbs the process of atherogenesis through reverse transportation of LDL and VLDL (Hao and Friedman, 2014). Plaque buildup can also cause thrombosis when the plaque on the vessel ruptures worsening coronary heart disease. Incorporating exercise,

maintaining a healthy weight and reducing alcohol consumption are just some of the ways individuals can improve lipid imbalance (Kolovou, Anagnostopoulou and Cokkinos, 2005). Dyslipidemia is pharmacologically treated using a class of drugs called statins. These drugs act by binding and inhibiting an enzyme HMG-CoA reductase; this increases the hepatic extraction of LDL from the blood, therefore, reducing free-flowing LDL (McFarland *et al.*, 2014).

2.4.4 Hypertension

2.4.4.1 Normal blood pressure

Blood pressure is regulated by a system called the renin-angiotensin system which uses aldosterone to control the movement of sodium through the distal tubule of the nephron by increasing the number of sodium permeable channels as well as activating the sodium-potassium ATPase pump. The pump removes sodium from the lumen into the extracellular cavity returning sodium particles into circulation. The movement of sodium is accompanied by water. The presence of sodium and water in the extracellular cavities results in a larger blood volume increasing the mean arterial pressure. When sodium is retained, potassium is excreted. An increase in extracellular potassium, on the other hand, results in the activation of angiotensin II (from precursor enzyme angiotensin from the liver) which results in the stimulation of the kidneys adrenal cortex to release aldosterone which in turn brings blood potassium levels back to normal (Harrison-Bernard, 2009).

2.4.4.2 Hypertension in metabolic syndrome

People with metabolic syndrome have been found to display defective baroreceptor responses (Brozmanova *et al.*, 2009). The mechanism by which hypertension occurs in metabolic syndrome is not clear (Tomono *et al.*, 2008). An increase in visceral fat, as well as insulin resistance, have been thought to be the major contributors to increased blood pressure (Ferrannini *et al.*, 1997). Visceral fat can secrete adipocytokines, namely:

- interleukin-6
- necrosis factor alpha
- non-esterified fatty acids
- tumor necrosis factor alpha;

These adipocytokines, through their different mechanisms, result in hypertension (Katagiri, Yamada and Oka, 2007). The renin angiotensin aldosterone system also plays a pivotal role in the development of cardiovascular events (Li, 2006). The byproduct of this system (angiotensin II), induces the release of cytokines and pro-inflammatory transcription factors (nuclear factor *B*) which result in the release of free radicals including reactive oxygen species (Grote, Luchtefeld and Schieffer, 2005). Free radicals (ROS) are formed through cellular oxidative systems that produce superoxides causing vascular oxidative stress (Grote, Luchtefeld and Schieffer, 2005). There are several mechanisms involved which also include vasoconstriction, cell growth and vascular inflammation (Li, 2006). Often diabetes and hypertension have overlapping disease mechanisms which could explain why some patients with hypertension would also have diabetes(Cheung and Li, 2012). Both of these diseases can be characterized by chronic inflammation.

Recent evidence shows that insulin causes sodium retention in the distal tubules of the nephron (Miller and Bogdonoff, 2019). This phenomenon is exacerbated in individuals with insulin resistance (Reaven and Hoffman, 1987), and as mentioned earlier, an increase in extracellular sodium increases blood volume causing an increase in blood pressure, resulting in vascular injury.

2.4.5 Cardiovascular complications

Cardiovascular adversities arise mainly from the effects (remodeling) exerted on the vascular system (Grote, Luchtefeld and Schieffer, 2005). One study estimated a reduction in life expectancy of 20% in patients with schizophrenia compared to the general population (Newman and Bland, 1991). Adverse effects of antipsychotics increase the risk of cardiovascular disease, especially in patients who already present with atherosclerosis or type 2 diabetes (Buckley and Sanders, 2000; Tschoner *et al.*, 2007). Adverse effects include tachycardia, heart arrhythmias, postural hypotension, palpitation and heart failure which was the case in almost 75% of patients receiving antipsychotics at therapeutic doses in clinical trials or observational studies (Buckley and Sanders, 2000). Apart from suicide and possible accidental deaths (Buckley and Sanders, 2000), many patients with schizophrenia demise, possibly because the complications associated with metabolic syndrome occur at a molecular level. They are not always evident without the appropriate diagnosis, and some people may not be aware of the molecular changes occurring in the body leading to death (Vancampfort *et al.*, 2013; Chiu *et al.*, 2016). Thus, such complications entail different mechanisms. These

mechanisms can include direct blockage of muscarinic receptors and 1-adrenoceptors as well as sodium, potassium, calcium channels. There is also an indirect blockade mechanism that involves blockade of 2-adrenoceptors in the nervous system (Buckley and Sanders, 2000).

2.5 Interventions to combat antipsychotic-induced weight gain

Weight gain has been associated with treatment non-adherence in patients with schizophrenia (Dayabandara *et al.*, 2017). Strategies to counteract weight gain in schizophrenia include providing those affected and on antipsychotic therapy with health education (Manu *et al.*, 2015). Health education includes the promotion of healthy lifestyles behaviours, opting for healthier nutritional alternatives and physical activity (Dayabandara *et al.*, 2017). Health education is the first step before considering pharmacological interventions.

It has been proposed that physical activity and a healthy diet should be the main aim of counteracting some of the effects of MetS (Li *et al.*, 2017). Lifestyle interventions such as exercise have been investigated as potential solutions, especially for diabetes and hypertension (Cheung and Li, 2012). The type of physical activities that were deemed suitable for patients on antipsychotic therapy was found to be aerobics as well as moderate to high resistance training (Curtis *et al.*, 2016), in the same study weight loss was seen after 12 weeks of participating in the program. However, of the 28 participants enrolled in the study, only 13% of the participants had a significant loss in weight. Although physical activity might work one study revealed this intervention was not sustainable in patients with antipsychotic-induced weight gain/metabolic syndrome (Bruins *et al.*, 2014).

The second step is to switch antipsychotics, where possible. Significant weight gain has been noted in patients taking clozapine (Bobes et al., 2003), which has proven efficacious in treatment-resistant schizophrenia (Kane, 1988a). Ziprasidone, according to a meta-analysis study, was the antipsychotic least associated with weight gain (Rummel-Kluge et al., 2010). After taking into account side effects, efficacy and the patients preference, physicians are able to switch patients to a more weight neutral antipsychotic (Dayabandara et al., 2017). Switching antipsychotics to more weight neutral ones has proven effective in some studies (Mukundan et al., 1996). Patients who were switched to weight-neutral antipsychotics generally lost weight (Mukundan et al., 2007). However, switching from one antipsychotic to another has been associated with treatment non-adherence and increased risk of relapse (Stroup et al., 2011), hence close monitoring after treatment switch is crucial.

Recently, clinicians have adopted a pharmacological approach to treating metabolic adversities caused by antipsychotics. A systematic review that looked at the effects of pharmacological interventions in the treatment of weight gain discovered that topiramate, sibutramine, aripiprazole, reboxetine were effective, while metformin was the most effective agent(Mizuno *et al.*, 2014). Most literature supports the use of metformin (Mizuno *et al.*, 2014; Chiu *et al.*, 2016; de Silva *et al.*, 2016), a biguanide which acts by reducing intestinal glucose uptake as well as reducing the hepatic synthesis of glucose (Pharmacology, 2006). Metformin has been confirmed to be highly effective in treating antipsychotic-induced weight gain (de Silva *et al.*, 2016). Although metformin has proven to be the superior pharmacological intervention in treating antipsychotic-induced weight gain (Zheng *et al.*, 2015), statins have been found to be useful in lowering LDL cholesterol(Stroup *et al.*, 2011). The use of metformin presents some disadvantages such as lactic acidosis especially in elderly patients (Silvestre *et al.*, 2007). These adversities are yet to be researched further in patients taking antipsychotics.

2.5.1 Treatment discontinuation

It has been proven that the use of antipsychotics improves the lives of people with psychotic episodes despite the adversities mentioned earlier (Ventriglio *et al.*, 2015). Of the available studies that looked at treatment discontinuation as a method of correcting metabolic syndrome, a Chinese study which recruited 131 patients discovered that there was no significant change in fasting glucose as well as lipid parameters following antipsychotic treatment discontinuation (Wu *et al.*, 2014). With treatment discontinuation comes the added risk of relapse (Chiliza *et al.*, 2015). With antipsychotic discontinuation, relapse often follows regardless of how long the person has been on treatment (Emsley *et al.*, 2013). Relapse does not only complicate the course of treatment for the patient, but it often results in hospitalization which has financial implications (Ascher-Svanum *et al.*, 2010). Not many studies have investigated the consequences of relapse; however, some authors believe relapse results in psychotic exacerbations, functional deterioration as well as treatment resistance (Donoghue *et al.*, 2016; Emsley, Kilian and Phahladira, 2016). Therefore, patients who show improvement while on treatment should not be discontinued from therapy as maintenance treatment often prevents relapse, especially if side effects are minimal (Barnes, 2011).

Treatment non-adherence was found to be the major contributor to relapse in patients experiencing first-episode psychosis (Alvarez-Jimenez *et al.*, 2012). On the other hand, some

patients relapse while on treatment (Alphs *et al.*, 2012), although some might argue that there is no guaranteed method of measuring treatment adherence. Chen et al. (2010) noted that relapse rates were higher (79%) in patients who discontinued treatment compared to those on maintenance therapy. There are varying definitions of relapse in literature. Some researchers use hospital admissions as an indicator of relapse and a flaw in this method is that admission rates can be determined by the availability of hospital beds or the ability to provide treatment (Donoghue *et al.*, 2016). The same study also noted that a lower relapse threshold resulted in higher rates of relapse.

CHAPTER 3

MATERIALS AND METHODS

3.1 Study site

The participants of the current study were recruited from the inpatient and outpatient departments of Stikland and Tygerberg Hospitals, as well as the clinics and day hospitals within the catchment area.

3.2 Study population and data collection

The current research was part of a broader study which was a randomized, double-blinded, placebo-controlled investigation that involved subjects who had been successfully treated for 2 to 3 years after a first episode of schizophrenia, schizoaffective or schizophreniform disorder and who voluntarily opted to discontinue antipsychotic treatment under supervision. Thus, the procedures for data collection and the study population had previously been reported (Emsley *et al.*, 2014). Briefly, for inclusion in the study, participants could be either male or female aged between 16 and 50 years old and had been exposed to at least two years of uninterrupted antipsychotic therapy. Participants had a DSM-IV diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder. Participants were followed from start or baseline (remission) until the point of relapse. Follow-up assessments were done every month to determine symptom severity, but laboratory samples and measurements were done every six months.

All participants signed informed consent before inclusion in the study. The study was approved by the Institution Review Board (Ethics Committee) of Stellenbosch University.

The following data was obtained from the participants at baseline and endpoint (point of relapse)

1) Sociodemographic data
    - Sex

- Age of participant
- Level of education
- Employment status
- Type of accommodation
- Number of children
- Psychiatric diagnosis

Laboratory measurements

- BMI
- Weight
- Waist circumference
- Blood glucose
- Cholesterol

Treatment

Participants were all given the injectable long-acting antipsychotic flupenthixol decanoate in their respective doses as determined by the participants' psychiatrist during routine clinical care assessment reviews. Each month the flupenthixol decanoate dose was reduced by a factor of 0,75 (however, the dose was rounded off to the nearest 10mg for ease of administration). Compliance was guaranteed since participants had to visit the healthcare facility to get the injection.

3.3 Data analysis

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, version 20.0; IBM Corporation, Armonk, New York, USA). Descriptive statistics were performed to obtain frequencies of the various parameters. A paired sample Student t-test was used to check for any differences between the initial and the endpoint values of all measured parameters. Percentages, means and standard deviation of numeric data was determined as well as the percentages of categorical data. Chi-square tests were used to compare the categorical variables. In order to assess the factors affecting BMI (body mass index), regression (such as logistic, linear) were performed to examine the factors. Variables that were significant in

bivariate analysis were included in further analyses. Results were considered statistically significant at a 95% confidence limit. A statistical test was considered significant if $p<0.05$.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Results

4.1.1 Sample characteristics

The total sample in the current study included 33 patients in the age range of 21 years and above. The proportion of patients who had secondary school education was 60.6%, 78.8% were single, and the majority of the patients were colored (75.8%). Also, 66.7% of the patients spoke English, with 78.8% being unemployed. Most of the patients (48.5%) had no children with 24.5% having at least one child, and 84.8% of the patients lived in their own family house (Table 2).

Table2: Socio-demographic characteristics of the study population

Characteristic	Frequency (n)	Percentage
Age group		
21-25 years	13	39.4
26-30 years	9	27.3
31 year and above	11	33.3
Gender		
Male	24	72.7
Female	9	27.3
Ethnic group		
Black African	5	15.2
Colored	25	75.8
White	3	9.1
Level of education		
Elementary school	4	12.1
Secondary school	20	60.6
Matric	8	24.2
Technical	1	3

Home language		
Afrikaans	6	18.2
English	22	66.7
isiXhosa	4	12.1
Other	1	3
Marital status		
Single	26	78.8
Married	3	9.1
Divorced	3	9.1
Cohabiting	1	3
Number of children		
0	16	48.5
1	8	24.5
2	5	15.2
3	2	6.1
4	1	3
5	1	3
Employment status		
Unemployed	26	78.8
Casual employment	1	3
Full time		
Current accommodation	6	18.2
Rented room	3	9.1
Rented house	2	6.1
Own family house	28	84.8

4.1.2 Number of weeks it took participants to relapse

The mean number of weeks to relapse was 39.2 weeks following the gradual discontinuation of the antipsychotic treatment (Table 3). The maximum number of weeks before relapse was 96 weeks while the minimum number of weeks before relapse was 1. By week 32, almost half of the study participants had relapsed.

Table 3 Number of weeks it took participants to relapse

Number of weeks to relapse	**Number of participants who relapsed**
4	1
12	4
16	2
20	3
24	3
28	2
32	1
36	1
40	4
44	3
48	1
52	1
64	2
76	1
88	3
96	1
Mean time to relapse 39.2 weeks	Total number of participants 33

4.1.2 Changes in measured parameters

An overall comparison of the initial and the endpoint values of the eight parameters measured in the current study are represented in Figure 3.

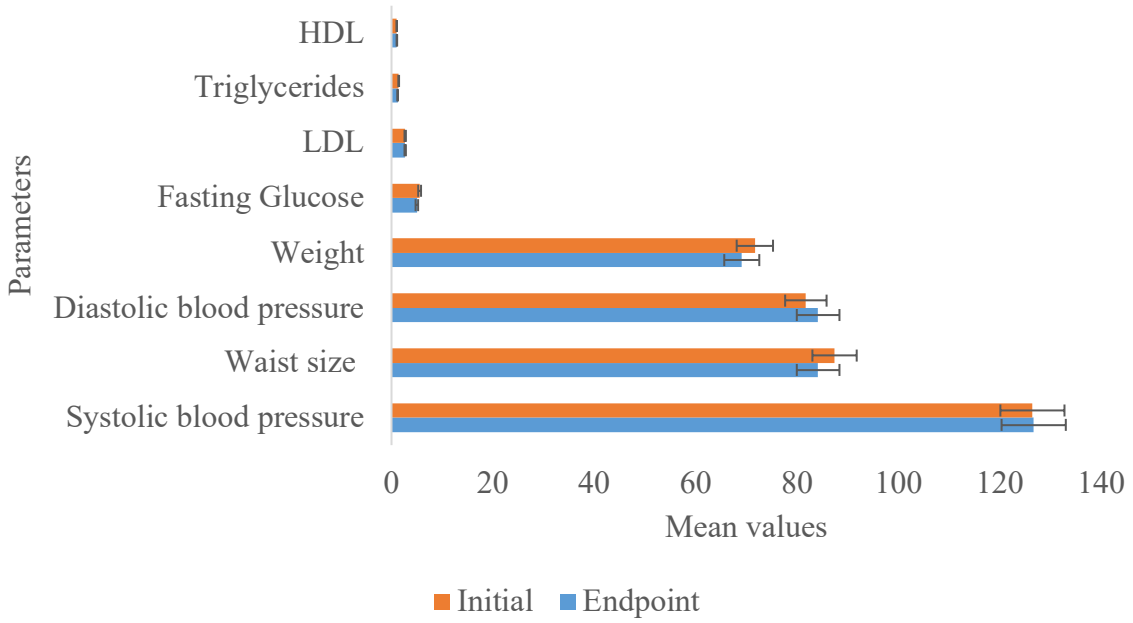

Figure 3: Mean change in measured parameters over time following a change in drug regime. The error bars represent the standard deviations from the mean

Following the dose reduction, there was an overall decrease in the patients' mean waist size, weight, fasting blood glucose (FBG) and triglyceride values (Table 4). On the other hand, increases were observed with systolic blood pressure (SBP), diastolic blood pressure (DBP) and HDL. Only the mean LDL values remain unchanged following treatment.

Despite these changes, the paired sample t-test analysis revealed that only the changes in FBG ($p = 0.450$), weight ($p = 0.018$) and waist size ($p = 0.006$) were statistically significant ($p < 0.05$) (Table 5). No statistically significant differences ($p > 0.05$) were observed between the mean HDL, LDL, SBP, DBP and Triglycerides values.

Table 4: Overall change in metabolic syndrome parameters between initial and endpoint, following dose reduction

	Initial					Endpoint				
Parameter	**N**	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**	**N**	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Weight	33	49	99	71.67	13.817	33	50	97	69.09	13.333
Fasting Glucose	33	4	15	5.55	2.346	33	3	10	5.00	1.275
Systolic Blood Pressure	33	110	151	126.42	11.530	33	95	156	126.67	14.192
Diastolic Blood Pressure	33	59	98	81.73	9.398	33	66	118	84.15	11.662
Triglycerides	33	0	7	1.42	1.370	33	0	3	1.21	0.740
Waist	33	68	118	87.39	14.213	33	66	110	84.15	12.711
HDL	33	1	2	1.03	0.174	33	1	2	1.06	0.242
LDL	33	1	4	2.70	0.984	33	1	6	2.70	1.159

Table 5: Comparison between initial and endpoint parameters following dose reduction

Parameters		Paired Differences					T	df	*P*-value
		Mean	SD*	SE**	95% Confidence Interval of the Difference				
					Lower	Upper			
1	Initial FBG - Endpoint FBG	0.545	1.502	0.261	0.013	1.078	2.086	32	**0.045**
2	Initial HDL - Endpoint HDL	-0.030	0.305	0.053	-0.138	0.078	-0.571	32	0.572
3	Initial LDL – Endpoint LDL	0.000	0.935	0.163	-0.332	0.332	0.000	32	1.000
4	Initial SBP – Endpoint SBP	-0.242	12.627	2.198	-4.720	4.235	-0.110	32	0.913
5	Initial DBP – Endpoint DBP	-2.424	12.065	2.100	-6.702	1.854	-1.154	32	0.257
6	Initial Triglycerides – Endpoint Triglycerides	0.212	1.244	0.217	-0.229	0.653	0.980	32	0.335
7	Initial Weight – Endpoint Weight	2.576	5.911	1.029	0.480	4.672	2.503	32	**0.018**
8	Initial Waist size – Endpoint waist size	3.242	6.260	1.090	1.023	5.462	2.975	32	**0.006**

*SD: Standard deviation; **SE: Standard error of the mean. Highlighted values indicate statistical significance

4.1.2.1 BMI of participants at first visit versus predictor variables

Table 6 displays the cross-tabulation of BMI at first visit versus predictor variables. BMI was categorized as 18.5-24.9 (normal weight), >=25 (overweight). 64% of participants aged 31 years and above were >= 25 (overweight), 89% of females were overweight. The observed prevalence of normal weight was higher among patients who were never married, while the overweight was more predominant amongst the married patients. Considering the racial groups, the study found that white patients were more overweight compared to their colored counterparts. In the case of employment status, the findings of this study highlight that patients who had fulltime jobs were more overweight while the highest proportion of normal weight was found amongst the patients with casual employment.

Table 6: Cross-tabulation of BMI at first visit versus predictor variables

BMI	**18.5 – 24.9**		**>=25**			
BMI (first visit) Characteristic	**N**	**%**	**N**	**%**	***p*-value**	**Chi-square**
Age group						
21-25 years	6	46	7	54		
26-30 years	4	44	5	56	0.881	0.254
31 year and above	4	36	7	64		
Gender						
Male	13	54	11	46	0.26	4.968
Female	1	11	8	89		
Ethnic group						
Black African	2	40	3	60		
Colored	11	44	14	56	0.933	0.139
White	1	33	2	67		
Level of education						
Elementary school	3	75	1	25		
Secondary school	8	40	12	60	0.247	4.137
Matric	2	25	6	75		

Technical	1	100	0	0		
Marital status						
Single	14	54	12	46		
Married	0	0	3	100	0.88	6.547
Divorced	0	0	3	100		
Cohabiting	0	0	1	100		
Employment status						
Unemployed	11	42	15	58		
Casual employment	1	100	0	0	0.458	1.560
Full time	2	33	4	67		

4.1.2.2 BMI of participants at endpoint versus predictor variables

Table 7 shows predictor variables at the endpoint. There was an overall decrease in BMI with some participants being recorded as being underweight.

Table 7: Socio-demographic factors associated with BMI among participants in South Africa

BMI	**Underweight**		**Normal**		**Overweight**			
BMI (first visit) Characteristic	**N**	**%**	**N**	**%**	**n**	**%**	**P-value**	**Chi-square**
Age group								
21-25 years	2	15	7	54	4	31	0.228	5.634
26-30 years	0	0	7	78	2	22		
31 year and above	0	0	5	45	6	55		
Gender								
Male	2	8	16	67	6	25	0.077	5.138
Female	0	0	3	33	6	67		
Ethnic group								
Black African	0	0	3	60	2	40	0.340	4.524

Colored	1	4	15	60	9	36		
White	1	33	1	33	1	34		
Level of education								
Elementary school	1	25	3	75	0	0	0.430	5.938
Secondary school	1	5	10	50	9	45		
Matric	0	0	5	63	3	38		
Technical	0	0	1	100	0	0		
Marital status								
Single	2	8	17	65	7	27	0.510	5.268
Married	0	0	1	33	2	67		
Divorced	0	0	1	33	2	67		
Cohabiting	0	0	0	0	1	100		
Employment status								
Unemployed	2	8	15	58	9	34	0.808	1.603
Casual employment	0	0	1	100	0	0		
Full time	0	0	3	50	3	50		

4.1.2.3 Diabetes mellitus status according to the general characteristics of patients

Table 8 displays the total observed prevalence of diabetes mellitus status, as well as the prevalence of each according to the general characteristics of the participants in the sample. The prevalence of normal fasting blood glucose is 66.7%, pre-diabetes was 27.3%, and the diagnosis of diabetes mellitus was 6%. Among the different age groups, normal fasting blood glucose was the highest among the 21-25 year-old (45.5%), and similarly for diagnosis of diabetes which was 100% in the age groups 31 years and above. The observed normal fasting blood glucose was observed amongst patients who had matric and technical education while those with elementary education had 75%. Normal fasting blood glucose was significantly higher amongst white participants. However, Black African patients had the lowest pre-diabetes and diagnosis of diabetes. According to the univariate chi-square p-values of table 2, all the independent variables were significantly associated with various diabetes except race at a 1% level of significance (p-value <0.001).

Table 8: Diabetes mellitus status according to the general characteristics of patients aged 21-50 years

	Normal		Pre-diabetes		Diabetic		
	N	**%**	**N**	**%**	**n**	**%**	***p*-value**
Age group							
21-25 years	10	45.5	3	33.3	0	0	0.007
26-30 years	8	36.4	1	11.1	0	0	
31 year and above	4	18.1	5	55.6	2	100	
Gender							
Male	16	72.7	7	77.8	1	50.0	0.045
Female	6	27.3	2	22.2	1	50.0	
Ethnic group							
Black African	3	60.0	1	20.0	1	20.0	0.710
Colored	17	68.0	7	28.0	1	4.0	
White	2	100	1	33.3	0	0	
Marital status							
Single	19	73.1	7	26.9	0	0	0.033
Married	1	33.3	1	33.3	1	33.3	
Divorced	1	33.3	1	33.3	1	33.3	
Cohabiting	1	100	0	0	0	0	
Education							
Elementary	3	75.0	1	25.0	0	0	0.021
Secondary	10	50.0	8	40.0	2	10.0	
Matric	8	100	0	0	0	0	
Technical	1	100	0	0	0	0	

Predictors of BMI at baseline

The results depicted in Table 9a show the estimates and odds ratios (OR) of socio-demographic factors in the outcome of interest (BMI). Out of all the covariates included in the current study, gender and marital status were the only significant covariates. Female participants were 1.57 times more likely to have a higher BMI at baseline (initial visit) compared to their male counterparts (OR=1.57, $p = 0.03$). Furthermore, married and divorced participants had a higher BMI compared to those who were single (OR=2.21, $p = 0.02$) and (OR=2.08, $p = 0.05$), respectively.

Table 9a: Estimates and odds ratios of socio-economic and demographic factors on first visit BMI

Predictors of BMI at endpoint

There were no statistically significant demographic predictors of baseline BMI (see table 9b). At the endpoint visit (point of relapse), married participants were 1.51 times more likely to have a higher BMI compared to participants who were not married. Additionally, female participants were more likely to have a higher BMI compared to male participants (OR=1.40).

Table 9b: Estimates and odds ratios of socio-economic and demographic factors on endpoint BMI

Variable	Estimate	OR	Standard error	*p*-value
Dependent variable: First Visit				
Age group in years (ref: 21-25)				
26-30	-1.17	0.31	0.21	0.44
31+	-0.29	0.75	0.24	0.24
Gender (ref: male)				
Female	0.45	1.57	0.20	**0.03**
Ethnic group (ref: Black African)				
White	0.21	1.23	0.36	0.57
Colored	0.13	1.14	0.26	0.62
Educational status (ref: elementary)				
Secondary	0.26	1.30	0.27	0.35
Matric	0.52	1.68	0.31	0.11
Technical	0.11	1.12	0.54	0.85
Marital status (ref: single)				
Married	0.79	2.20	0.31	**0.02**
Divorced	0.73	2.08	0.35	**0.05**
Cohabiting	0.02	7.40	0.53	0.97

Variable	Estimate	OR	Standard error	*p*-value
Dependent variable: Endpoint				
Age group in years (ref: 21-25)				
26-30	-0.12	0.89	0.27	0.69
31+	0.21	1.23	0.29	0.49
Gender (ref: male)				
Female	0.34	1.40	0.25	0.18
Ethnic group (ref: Black African)				
White	-0.28	0.76	0.25	0.54
Colored	-0.14	0.87	0.32	0.68
Educational status (ref: elementary)				
Secondary	0.56	1.75	0.34	0.11
Matric	0.41	1.51	0.38	0.29
Technical	0.17	1.19	0.67	0.81
Marital status (ref: single)				
Married	0.41	1.51	0.39	0.31
Divorced	0.37	1.45	0.43	0.40
Cohabiting	0.73	2.08	0.25	0.28

4.2 Discussion

There have been speculations on the potential effects of drug withdrawal on predictors of metabolic syndrome in patients experiencing psychosis. Thus, the current study aimed at establishing if there was a change in metabolic syndrome parameters following antipsychotic dose reduction in patients attending a hospital in the Western Cape, South Africa. The results of the study revealed that weight, fasting blood glucose, and BMI all decreased significantly from baseline to endpoint. On the other hand, lipids, diastolic and systolic blood pressure did not improve from baseline to endpoint. An overall decrease in BMI was observed in the majority of patients, following the reduction in the treatment dose. Females were more likely to have a higher BMI at baseline compared to males. Married and divorced participants were also more likely to have a higher BMI at baseline compared to those who were single.

Our study findings seem to differ from Wu et al., as their study reported an insignificant decrease in glucose; however, they also found an insignificant change in lipid parameters. Their study compared patients who were drug naïve and had schizophrenia, those who had first-episode psychosis and patients who had schizophrenia and were on treatment. They further concluded that antipsychotic discontinuation had no positive effect on glucose and lipid parameters (Wu *et al.*, 2014). Several factors could account for the difference between the findings of the current study and those of Wu and colleagues. Firstly, the sample sizes differed in that Wu et al. worked with 131 participants compared to 33 included in our study. This could have affected the strength of the statistics and, thus, the observed outcome in both studies. Secondly, the subjects in Wu et al. were not placed on the same antipsychotic, while our study only focused on participants who were put on flupenthixol treatment. Our study shows that antipsychotic discontinuation does improve fasting blood glucose, weight and BMI. The decrease in BMI is consistent with the findings of a recently published discontinuation study on adolescents, which revealed a significant decrease in BMI after treatment discontinuation (Upadhyay *et al.*, 2019). However, with that being said, the loss of weight following antipsychotic discontinuation needs to be balanced by the risks associated with relapse. Hence, recruitment of study participants for our study was stopped due to the high rates of relapse following treatment discontinuation with one patient attempting suicide (Emsley et al., 2014).

4.2.1 Participant's demographic information

Socio-demographic factors have been found to be associated with weight gain in upper-income countries; however, this has been more evident in low and middle countries where there is a stronger association between weight and socio-demographic factors (Ball and Crawford, 2005). The major risk factors associated with MetS were being a white female and older than 35 years and of white descent. These findings are similar to those of another study done in South Africa (Saloojee, Burns and Motala, 2016); however, due to the lack of Indian participants in the current study population, it not possible to determine the racial impact based on South Africa's diversity.

The majority of our participants were unemployed, which in keeping with other studies. One study done in the UK, Germany and France, recorded less than 12% of their participants who had schizophrenia were employed and capable of taking care of themselves financially without assistance from social welfare (Marwaha *et al.*, 2007). One would assume that this figure would be lower in low- and middle-income countries due to poverty and scarcity of employment even for those who are qualified and do not have a mental illness. However, the study mentioned above had most of the 12% in elementary occupations requiring the use of hand-held tools and physical effort, e.g. farm workers and only 1% in senior positions. The present study had 78.8% of the participants unemployed, apart from reasons related to mental health, South Africa currently has one of the highest rates of unemployment even for qualified graduates who can function well cognitively (Banerjee *et al.*, 2008). Not to tell people that suffer from schizophrenia do not make it through to technical education, as we have discovered a fair number (Marwaha *et al.*, 2007). However, they might experience challenges, especially those who have early-onset schizophrenia (Okasha, Kamel and Sadek, 1979). One participant in the current study had achieved a technical education level.

4.2.2 Overall change in patients' parameters

The major phenotypical signs of metabolic syndrome in schizophrenia patients taking antipsychotics are the increase in weight, BMI and waist circumference (Kane, 1988a; Reynolds and Kirk, 2010; Correll, Lencz and Malhotra, 2011; Wu *et al.*, 2014; Chiliza *et al.*, 2015). In the

current study, a significant change was observed for weight (p=0.018) and waist circumference (p = 0.006) following the discontinuation of antipsychotic therapy. The participants in our study had gained weight and experienced an increase in waist circumference; however, by reducing the dose of flupenthixol, it was discovered that there was an overall decrease in these parameters. This was more evident for those participants who took longer to relapse. Some researchers, however, believe that weight gain is not necessarily related to the dose of antipsychotics, therefore making dose reduction an unreliable strategy in dealing with weight gain (Chiliza *et al.*, 2015). Weight gain is probably one of the few modifiable risk factors in schizophrenia which require closer monitoring; however, there has been inadequate attention to this until recently (Allison *et al.*, 2009). Upadhyay et al. (2019) also noticed a reduction in BMI in their study population. It was also evident that although the participants' BMI decreased, the new BMI was not the same as their initial BMI prior to taking antipsychotics treatment which means that adolescents on antipsychotic treatment who had gained a considerable amount of weight could remain obese.

Lipid parameters such as HDL, LDL, and triglycerides revealed no statistically significant change. These findings are consistent with those obtained by Wu et al. (2014), revealing that there is no significant change in lipid profile in schizophrenia patients after treatment discontinuation. An alarming discovery was the increase in total cholesterol and triglycerides in a cohort of Taiwanese patients after only three weeks of antipsychotic therapy (Huang and Chen, 2005). Alterations in lipid profiles often result in coronary heart disease as well as type two diabetes. Such adversities have led to an estimated 20% reduction in the life expectancy of patients with schizophrenia compared to the general population (Newman and Bland, 1991; Huang and Chen, 2005; Ventriglio *et al.*, 2015).

No improvement was observed in blood pressure readings as well. There seems to be a lack of research in the alterations in blood pressure attributed to the use of antipsychotics. However, one study suggested that an increase in weight could be the driving force for hypertension. The mechanism by which blood pressure is elevated in patients with metabolic syndrome could be secondary to obesity and alterations in lipid profile (Re, 2009). Patients with increased weight usually require more pressure to move blood around the body, when fat is situated around the abdominal area, this thickens arteries, making them stiff further increasing pressure required to transport blood (Dr Robin Miller, 2011).

However, our study found an improvement in fasting glucose (p = 0.045) (SD = 1.502). Some researchers claim that glucose abnormalities might be intrinsic to schizophrenia even before any initiation of antipsychotic therapy (Guest *et al.*, 2010; Freyberg *et al.*, 2017). Wu et al. (2014) concluded that the disturbances that occur with glucose and lipid metabolism are associated with both schizophrenia and antipsychotics. The results of the current study support the potential contribution of antipsychotics to the increased rates of diabetes mellitus in people with schizophrenia, as diabetes mellitus is highly prevalent amongst people with schizophrenia compared to the general population (Schoepf *et al.*, 2012). Older participants were more likely to have diabetes compared to their younger counterparts (Selvin and Parrinello, 2013). This could be attributed to illness duration whereby older participants might have had schizophrenia for longer than the younger participants and hence increasing the chances of presenting with diabetes (De Hert *et al.*, 2006).

4.2.3 BMI of participants versus predictor variables

The burden of being overweight affected 64% of the participants and mostly those participants who were aged 31 and above. Participants who were 31 years and above had a higher BMI at baseline as well as an endpoint, although there was a general drop at endpoint this group still had most of its participants overweight. A positive correlation between age and weight has been observed in some studies (Kelly *et al.*, 2008; Hales *et al.*, 2015). An increase in BMI with age could be attributed to a more prolonged illness duration or increased exposure to predisposing factors. The CATIE study also had similar results where older participants were more likely to have metabolic syndrome, most of whom were white and female (Meyer *et al.*, 2005).

The results of our study revealed that females were more prone to weight gain compared to their male counterparts. This is in line with the findings of other studies which suggest that the female gender was more prone to weight gain (Burke *et al.*, 1996; Wang *et al.*, 2010; Chadda *et al.*, 2013). However, in lower- and middle-income countries (LMIC), this could differ depending on the economic status of the majority of people. In LMIC, weight gain is associated with a better economic standing whereas in the upper-income countries it is vice versa (Dinsa *et al.*, 2012). Although the present study did not adequately represent South Africa's diverse racial makeup,

(Saloojee, Burns and Motala, 2016) found that metabolic syndrome could also be race-dependent in which some racial groups are more prone to metabolic abnormalities compared to others. Their study confirmed that participants of Indian were more prone to MetS compared to Black Africans, which could be as a result of Indian participants having a high visceral fat deposition even at low BMI and being more prone to diabetes mellitus (Palaniappan *et al.*, 2011). It should, however, be noted that given the small number of participants examined in the current study, the results presented should be interpreted with caution. Also, we found that white females were obese compared to females of other racial groups although, Black African females were not too far behind. This is contrary to the findings made by Burke (Burke *et al.*, 1996), where it was found that people Black Africans were generally more overweight compared to white people. This could be attributed to the relatively small sample size of the current study. The same study by Burke observed weight gain changes in young participants for five years, and although many participants who were Black Africans presented obese at baseline, they still gained a considerable amount of weight during the study period. In some African cultures, women who carry more weight are considered healthier especially in regions where poverty is rife (Costello-Nichitas, 1987). Also, African women do not necessarily experience the same societal pressures experienced by white women when it comes to weight and therefore do not see the need for regular weight loss exercises compared to their white counterparts (Burke *et al.*, 1996). This might change due to globalization and adoption of the western culture by African females. Malnutrition and obesity are both considered public health problems (Harrison, 2006; Akadri *et al.*, 2016) and depending on the region one is at, one of the two usually dominates. Weight gain can cause obesity-related diseases in schizophrenia patients such as type 2 diabetes and cardiovascular disease (Ferrannini *et al.*, 1997; Mackin, Watkinson and Young, 2005; Reynolds and Kirk, 2010; Chang and Lu, 2012).

It was found that single (unmarried) participants were less prone to weight gain. There is evidence in the literature supporting the notion that changes in marital status affect changes in weight (Sobal, 1992). Other studies have stated explicitly that women who get married gain more weight compared to married males (Janghorbani *et al.*, 2008), which is contradictory to findings of other studies such as (Sobal, 1992) who found that males gained more weight than females. The reason for this could be that women who are single experience pressure in attracting a potential life partner

as well as being economically viable through appearance (McKinley and Hyde, 1996), although it could be the other way around depending on geographical region or culture.

4.2.4 Diabetes status according to the general characteristics of patients

Some researchers believe that the increased prevalence of Type 2 diabetes in schizophrenia patients might be as a result of Type 2 diabetes sharing a common intrinsic inflammatory disease pathway with schizophrenia (Perry *et al.*, 2016). Lorenzo et al. (2003) suggested that metabolic syndrome is a predictor of diabetes. Some studies discovered that the mean age of acquiring full diabetic status was 41 years of age (Cohen, 2007). A global study discovered that in developed countries, most people with diabetes were over 60 years of age, while in developing countries it was most common among the working class with age varying between 40 and 60 years (Whiting *et al.*, 2011). Although the age threshold of the patients in the current study was below 60, it was also observed that participants over the age of 31 were most likely to have diabetes compared to the younger participants. This could be a result of illness duration or even prolonged exposure to antipsychotic therapy which could have increased the patient's chances of having diabetes (Mitchell *et al.*, 2013). This is further supported by the observation that most people are diagnosed with schizophrenia in their mid-20s (Kam, Singh and Upthegrove, 2015). Insulin sensitivity decreases in both obese males and females as they get older (Gale and Gillespie, 2001). It was also discovered that patients who had schizophrenia but did not have diabetes were, in most cases, on antipsychotics that had low metabolic risks, e.g. ziprasidone (Nielsen, Skadhede and Correll, 2010a).

In Africa, the prevalence of diabetes is estimated to be 4.7% by 2030 and 7.7% globally in the same year (Whiting *et al.*, 2011). Previous literature associated increased risk of diabetes with being female; however, it has been proven that those studies were, in fact, biased (Gale and Gillespie, 2001). The present study discovered that diabetes was equally present in both gender groups. Normal fasting blood glucose was highest among participants between the ages of 21 and 25 years. Younger participants might have had a shorter illness duration to have been exposed to the predisposing factors of diabetes, including the duration on high metabolic syndrome risk antipsychotics which could lead to weight gain and later diabetes (Nielsen, Skadhede and Correll,

2010a). Older participants were at higher risk of diabetes, and this could be a result of other comorbidities such as hypertension and high cholesterol levels (Lorenzo *et al.*, 2003). Slamming high metabolic risk antipsychotics do not necessarily work in the best interest of the patient as some of these antipsychotics (clozapine) have been proven to be efficacious in the treatment of resistant schizophrenia, and therefore psychiatrists have to risk metabolic syndrome for a better quality of life (Kane, 1988b).

Overall diabetes did not seem to be a major health issue in the study population of the current study. The participant's race did not seem to play a role in the diabetes status of the participants (p>0.05). Saloojee et al. (2016) discovered that full metabolic status was more prevalent in Indian participants compared to other racial groups, which cannot be reported in the current study as it did not represent South Africa's racial diversity adequately. Obesity could have been one of the predisposing factors leading to diabetes in these participants (Saklayen, 2018). Black African participants had the lowest diagnosis of diabetes. This could be a result of socio-economic factors such as poverty, and in many instances, there is no luxury of choosing what to eat, meals are based on what is available.

CHAPTER 5

CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

5.1 Conclusion

The importance of monitoring patients taking antipsychotics is crucial and should be considered as part of routine patient clinical care. Patients taking antipsychotics are at risk of weight gain as well as the other disease burdens that come with obesity. In the current study, it was shown that dose reduction does overall decrease the BMI of participants taking a long-acting injectable antipsychotics. The lipid profiles of the participants were moderately affected by dose reduction and the change in blood pressure from the beginning of the study was insignificant. The issue of non-compliance and variations in weight gain attributed to the use of different antipsychotics was resolved by the use of the injectable antipsychotic. The study was able to keep almost all of its participants, although there were the inevitable cases of relapse. Although dose reduction might have worked in reducing BMI, the challenge that arose was that of relapse, making treatment with antipsychotics a difficult task of balancing a risk-benefit ratio scale.

5.2 Limitations

The present study presented with a number of limitations, the most evident being the relatively small sample size (N=33) that lacked a healthy control. Recruitment of more participants had to be stopped because participants started relapsing, with some even attempting suicide. Factors such as diet, smoking, level of physical activity and drug abuse were not measured. This study is also limited in that it only assessed metabolic syndrome in patients using only one antipsychotic (flupenthixol), which means results cannot be generalized for all first-episode psychosis patients. Another noteworthy factor would be the duration of the study might not have been long enough to significantly improve MetS, this factor is further hindered by relapse as patients tend to relapse soon before any changes can be observed. As soon as patients relapsed, they went back onto treatment to eliminate illness progression. Regardless of the above-mentioned limitations, there is

little research available on strategies to reverse metabolic risk factors and the few available studies are not particular on which antipsychotic the participants are on. The major strength of this study is that all the participants were given an injectable antipsychotic, which meant adherence to treatment was guaranteed, as the injectable was administered at a health facility.

5.3 Recommendations

Based on the findings of the current study, it is recommended that:

1. A more robust study be conducted to take into account a larger sample size and for a longer period. This should also involve different regions of the country so that a better appreciation of race can be achieved.
2. The lack of a healthy control population could also affect the overall conclusions drawn in the current study. As such, further studies would be required to ascertain that parameters such as weight gain were actually a result of treatment with antipsychotics.
3. Different dosages of antipsychotics present with different side effects and at different levels. This could affect the outcome of discontinuing treatment, as all the patients were not put on the same dosage. It would, therefore, be important to conduct further studies involving participants undergoing the same level of treatment.

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