THE PREVALENCE OF METABOLIC DISORDERS AND THEIR ASSOCIATED RISK FACTORS IN FORENSIC PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS ON CLOZAPINE COMPARED TO HALOPERIDOL AT VALKENBERG HOSPITAL

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DECLARATION

This thesis is presented in partial fulfilment of the requirements for the degree of Master of Medicine in Psychiatry at the Department of Psychiatry, Faculty of Health Sciences, University of Cape Town.

I, Dr Shazia Farah Kader Mungly, hereby declare that the work contained in this dissertation is my original work (except where acknowledgements indicate otherwise) and that I have neither previously submitted this whole work, nor in part, at any other university for a degree, neither has it been published prior to registration for this degree.

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23/05/2019

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ABSTRACT

Background: Various studies have shown that people with serious mental illness have an increased risk for metabolic syndrome with prevalence ranging from 28.7% to 60%. Given the amount of evidence suggesting a link between clozapine and metabolic syndrome, several guidelines have recommended regular clinical monitoring of metabolic syndrome in patients on clozapine.

Aim: To determine the screening, prevalence and associated risk factors of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine (study group) compared to patients on haloperidol (control group).

Methods: It is a retrospective, folder review of forensic male adult patients at Valkenberg Hospital, Observatory Cape Town.

Results: There were 45 patients in the study group and 23 patients in the control group. Eight patients (17.8%) in the study group (Clozapine) met criteria for metabolic syndrome according to the NCEP-ATP III criteria and none of the patients in the control group (Haloperidol) did (χ^2 (1) = 4.441, p = .035 V = .257). Patients who had a diagnosis of schizoaffective disorder were also on mood stabilisers in addition to clozapine. Again, while none of the patients on Haloperidol met the criteria for Metabolic syndrome, 6 (24%) of the 25 patients on concurrent Clozapine and sodium valproate did, (χ^2 (1) = 6.051, p = .023 V = .359).

In terms of metabolic disorders, a significantly higher proportion of patients in the study group has hypertension and hyperlipidaemia (p = .003 and p = .021 respectively). Less than 25% of all patients were fully screened for metabolic syndrome. There was a very low rate of

screening of blood tests: fasting glucose, total cholesterol, trigylcerides, High Density Lipoprotein(HDL) or Low-Density Lipoprotein (LDL).

Conclusion: The prevalence of metabolic syndrome was higher in the clozapine group than haloperidol group, which is unsurprising since clozapine is usually associated with a higher risk of metabolic syndrome. However, the prevalence on metabolic syndrome in this study sample was relatively low compared to other studies. This could be due to the low rate of screening of each criteria of metabolic syndrome. Screening for metabolic syndrome should be regularly performed by health professionals in patients with serious mental illness. Further studies are needed to investigate the risk of metabolic syndrome for patients who are on a combination of clozapine and mood stabilisers.

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CHAPTER 1: LITERATURE REVIEW AND INTRODUCTION

LITERATURE REVIEW

A literature review was conducted to critically analyse the screening of metabolic syndrome in severe mental illness. The author has done the review under the headings of 1. Cardiovascular mortality and severe mental illness 2. Definition of metabolic syndrome 3. Mechanisms of metabolic syndrome 4. Prevalence of metabolic syndrome and its associated risk factors 5. Antipsychotic as risk factor for metabolic syndrome 6. Antipsychotic: Clozapine in severe mental illness in forensic setting 7. Antipsychotic: Haloperidol in severe mental illness in forensic setting 8. Severe mental illness as a risk factor for metabolic syndrome 9. Mood disorders and metabolic syndrome 10. Guidelines for screening of metabolic syndrome for second generation antipsychotics 11. Monitoring for detection of metabolic syndrome in severe mental illness on antipsychotics 12. Metabolic monitoring of clozapine in South Africa

The search included key words: Severe mental illness" "schizophrenia" "schizophrenia spectrum disorders" "schizoaffective disorders" "Clozapine" "haloperidol" "sodium valproate" "diabetes mellitus OR "hyperglycaemia" OR "impaired glucose tolerance" OR "fasting glucose" "hypertension OR "high blood pressure", "obesity" OR "overweight" OR "body mass index" OR ""BMI ","Hypercholesterolemia" OR "Hyperlipidaemia" OR "high cholesterol" OR "dyslipidaemia" Metabolic Syndrome" "monitoring" "forensic sciences OR forensic hospitals"

The following databases were searched: Medline, PubMed, and Scopus, EBSCO Host (Africa Wide Information, CINAHL, Psych ARTICLES, and Psych INFO). Other articles were also retrieved by looking at the authors of the references. A limitation was that some of the articles were not in English or they could only be accessed with a fee and therefore only abstracts could be obtained. Studies on paediatric populations were excluded.

INTRODUCTION

1. CARDIOVASCULAR MORTALITY AND SEVERE MENTAL ILLNESS

Cardiovascular mortality is a global priority health concern causing an estimated 17.5 million deaths in 2012 which represents 31% of worldwide deaths (1). A systemic analysis on the Global Burden Disease Study during the period 1990-2013 shows that Sub Saharan Africa has registered one million cardiovascular deaths which contributes to 5.5% of the global cardiovascular deaths(2).

Cardiovascular mortality is a significant cause of premature mortality in patients with severe mental illness compared to the general population (3).Severe mental illness refers to a broad range of major psychiatric disorders such as schizophrenia spectrum disorders, mood disorders and other psychotic disorders which cause impaired functioning at work and socially (4). The literature has shown that patients with severe mental illness have a shorter life expectancy due to cardiovascular events (3,4,5). A review by Azad and colleagues in 2016 showed that patients with schizophrenia have a reduced lifespan by 15-20 years compared to the general population, with cardiovascular deaths as the main cause of death surpassing suicide (3).

According to the World Health Organisation, there are various risk factors associated with cardiovascular deaths, divided as modifiable and non-modifiable factors. Lifestyle modifiable

risk factors include smoking, alcohol abuse, poor physical activity and diet which exist across all the range of psychiatric diagnosis. Patients who are diagnosed with schizophrenia have a higher rates of smoking, poor diet and sedentary lifestyle. They are sedentary for around 11 hours per day, consume 400 calories more than the general population. 1 in 5 patients have or have had alcohol use disorder(5).

2. METABOLIC SYNDROME IN SEVERE MENTAL ILLNESS

Definition of metabolic syndrome

Metabolic syndrome (MS) is a cluster of cardiovascular risk factors which include hyperglycaemia, obesity, dyslipidaemia (hypertriglyceridemia and low high density lipoprotein(HDL) and hypertension leading to cardiovascular deaths (6).It is a worldwide epidemic according to the International Diabetes Federation with a prevalence of 20-25% in the general adult population(7). Metabolic syndrome was first described as Syndrome X. Over the years, metabolic syndrome has been defined in various ways. There are now different diagnostic criteria for metabolic syndrome based on the World Health Organisation (WHO) in 1998, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) in 2001 and modified in 2003 (modified NCEP ATP III), the International Diabetes Federation (IDF) criteria in 2006, and the Joint Interim Statement (JIS) in 2009 (6,7,8).The diagnostic criteria have similar core components with variation on diagnostic cut off values and the requirement of absolute or non- absolute criteria (6). Unfortunately, with the various definitions of metabolic syndrome, it has become more difficult to use a simple screening method to determine the prevalence rates in different population (6).

Table 1 shows the difference in criteria for the widely used definitions of metabolic syndrome (8).

	NCEP-ATPIII, 2001	AHA/NHLBI, 2005	IDF, 2005	JIS, 2009
Criteria required	Any ≥3 of	Any ≥3 of	Mandatory: Waist circumference ≥94 cm (Europid men) or ≥80 cm (Europid women) Plus ≥2 of:	Any ≥3 of
Fasting blood glucose	fasting glucose ≥110 mg/dl (≥6.1 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)
High-density lipoprotein cholesterol	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women
Triglycerides	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)
Waist circumference	≥102 cm (men) ≥88 cm (women)	≥102 cm (men) ≥88 cm (women)		≥94 cm (men) or ≥80 cm (women) for Mediterranean population
Hypertension	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder

NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III, IDF: International Diabetes Federation, AHA: American Heart Association, NHLBI: National Heart Lung and Blood Institute, JIS: Joint Interim Society statement

Table 1. Fully adapted from* Anagnostis P. Metabolic syndrome in the Mediterranean region: Current status. *Indian Journal of Endocrinology and Metabolism*. 2012; 16(1):72-80.

3. Mechanisms of metabolic syndrome

Insulin resistance contributes largely to the pathophysiology of metabolic syndrome. Insulin resistance is defined as high plasma insulin which is unable to maintain normal plasma glucose (9).

Obesity: An increased in free fatty acids is a major contributor to metabolic syndrome. An increase in intra abdominal fat also causes an increase in fatty acids to the liver and can also affect insulin resistance (8).

Dyslipidaemia: Lipid metabolism involves the formation of VLDL (Very Low Density lipoprotein) from the liver. The triglycerides are transported via VLDL and are metabolised to produce IDL (Intermediate Density lipoprotein) which then form LDL (low density lipoprotein). LDL is characterised as the bad lipoprotein (pro atherogenic). HDL is the good lipoprotein(anti atherogenic) which carry fat molecules from the body cells to the liver (8).

Elevated triglycerides is a feature of metabolic syndrome and reflects insulin resistance. The other feature is low high-density lipoprotein (HDL) cholesterol when there is the presence of

hypertriglyceridaemia which is due to a reduction in the cholesteryl ester content of the lipoprotein core. The composition of small dense low-density lipoprotein (LDL) cholesterol is predominant when it is associated with elevated triglyceride and low HDL cholesterol .High LDL level is associated with higher risk of myocardial infarction (8).

Hypertension: There is a known risk between insulin resistance and hypertension (8).

4. Prevalence of metabolic syndrome and its associated risk factors

There is progressive evidence in various studies that people with serious mental illness have an increased risk for metabolic syndrome with prevalence ranging from 28.7% to 60% (10-14). One large scale meta-analysis by Mitchel et al. (2013) showed an overall prevalence of 32.5% in schizophrenia patients using any standardised criteria (NCEP ATP III, NCEP ATP III modified, IDF) for metabolic syndrome. Although that study looked at the prevalence among 27 countries, South Africa was not included in the meta-analysis, which limits our data on the prevalence of metabolic syndrome in South Africa. Mitchell et al. also looked at each individual parameter of metabolic syndrome. The proportion of overweight using the NCEP ATP was 49.4% and 44.4% using the IDF criteria. The rate of hyperglycaemia was 19.5% using the NCEP ATP III (Fasting blood sugar >110mg/dl) and 18.8% using NCEP ATP III modified. The prevalence of hypertriglyceridemia was 39.3%, low HDL 42.6%, hypertension was 38.7% and diabetes was 10.9% using any standardised criteria (15). Several studies have reported on different risk factors of metabolic syndrome (16-18). In the meta-analysis by Mitchell et al., older age (>55 years) and longer duration of illness (7.8 years) was associated with increased risk for metabolic syndrome whereas gender was not identified as a risk factor for metabolic syndrome (15). However, there is mixed data on the prevalence rates of metabolic syndrome by gender with evidence from another systematic review by Papanastasiou (2013) showing

an increased prevalence of metabolic syndrome in females (16). A few other studies included in the meta-analysis report increased prevalence in males or no difference (16). There are limited studies looking at ethnicity of patients with metabolic syndrome in high income settings. A few studies showed that Hispanics have higher rates of metabolic syndrome, however no accurate conclusions can be drawn from the limited data (10). Other populations who have a predisposition to increased risk of metabolic syndrome at a lower body mass index and waist circumference are Indians and Asians (19). In South Africa, Indian ethnicity was a significant risk factor for metabolic syndrome in a local psychiatric outpatient setting in Kwazulu Natal (17). In contrast, one other study outside the African context showed that Indians and Asians with mental illness had a lower prevalence of metabolic syndrome, which can be attributable to use of prescribing more typical antipsychotics than atypical antipsychotics with typical antipsychotics known to have less risk for metabolic syndrome (17).

In our resource limited settings in South Africa, there are few studies on metabolic syndrome. There is one cross sectional study which has been done on outpatients with severe mental illness in KwaZulu Natal, South Africa. This study looked at the prevalence of metabolic syndrome in South African patients with severe mental illness of different ethnic groups. Patients with severe mental illness of Indian descent had a higher prevalence of metabolic syndrome (60%) as compared to African patients with a prevalence of 19.4%. The other risk factors apart from Indian ethnicity were female gender. Young patients under 25 years old with serious mental illness also showed an increasing risk for metabolic syndrome. There was significant increased waist circumference (55.1%) and low HDL cholesterol (52.5%) in patients with severe mental illness compared to the control group with no severe mental illness (17).

In another study in South Africa, the prevalence of metabolic syndrome in severe mental illness was higher in Black African females (37.7%) compared to Black African males (10,3%), further supporting the evidence that female gender is a risk factor for metabolic syndrome (20).

A cross sectional study done at Westkoppies Hospital, South Africa looked at the prevalence of metabolic disorders: metabolic syndrome, hypertension, diabetes mellitus, total cholesterol dyslipidaemia, triglyceride dyslipidaemia, Low density lipo-protein (LDL) cholesterol dyslipidaemia, overweight and obesity in 84 long term psychiatric inpatients which excluded forensic patients. The prevalence of metabolic syndrome using the NCEP ATP III criteria was 32%. The prevalence of each metabolic disorder are : hypertension 32% in which 41% of the hypertensive patients were newly diagnosed , diabetes mellitus 8%, cholesterol dyslipidaemia 32%, triglyceride dyslipidaemia 29%, low density lipoprotein (LDL) dyslipidaemia 50%, overweight 37%, and obesity 24%. There were 96% patients newly diagnosed with dyslipidaemia (16).

5. Antipsychotics as risk factor for metabolic syndrome

Antipsychotics form the mainstay of treatment for severe mental illness, referred to as first generation antipsychotics (FGA) or typical antipsychotics and second-generation antipsychotics (SGA) or atypical antipsychotics. Second generation antipsychotics have been associated with greater risk of metabolic syndrome (21). Various studies showed that clozapine and olanzapine are among the second-generation antipsychotics associated with the highest risk of metabolic syndrome (12, 20-22). In one retrospective study, second generation antipsychotics were associated with a threefold increased risk of metabolic syndrome compared to first generation antipsychotics (22). In one of the largest clinical trials,

the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study trial , the prevalence of metabolic syndrome was highest (34.8-43.9%) in patients on olanzapine (12). In the meta-analysis by Mitchel et al, patients who were on clozapine had the highest rate of metabolic syndrome at 51.9%. However the patients on clozapine were older with long duration of illness and had previous exposure to antipsychotics which can contribute to the high rate of metabolic syndrome (15).

First generation antipsychotics which include haloperidol are not without risk for metabolic syndrome. However, there are also no meta analyses comparing the risk of the various first generation antipsychotics associated with metabolic syndrome (15). In the CATIE study the first generation antipsychotic used was perphenazine, which is not being used in South Africa and also showed no significant risk of metabolic syndrome (12). A South African study has demonstrated that patients with schizophrenia who received 12 months of first generation long acting injectable flupenthixol decanoate still reported significant increases in weight and increased in triglycerides (TG) and reductions in HDL with an increase in the TG/HDL ratio which are metabolic parameters predisposing to cardiovascular events (23).

In the study in Kwazulu Natal , South Africa by Saloojee (17), there was no statistical difference in rates of metabolic syndrome between first and second generation antipsychotics, or between monotherapy versus polytherapy (combination of 2 or more antipsychotics and/or sodium valproate and antidepressants). However, a limitation of that study was that there were only 29 patients on clozapine and 13 patients on olanzapine. Both drugs are second generation antipsychotics known to have higher risk of metabolic syndrome, and therefore the results might not be a true reflection of the risk of metabolic syndrome (17). In another

study, clozapine as monotherapy was associated with higher risk of metabolic syndrome than polytherapy with 2 or more first generation antipsychotics (28.6% vs. 70.4%, *p*=0.004) (24).

6. **Antipsychotic: Clozapine in severe mental illness in forensic setting**

Clozapine, a second generation antipsychotic with high risk of metabolic syndrome is the drug of choice used in schizophrenia patients who are resistant to treatment to other antipsychotics (25). Clozapine is therapeutically superior to atypical antipsychotics in patients with better improvement in positive and negative symptoms (38, 40). It is also effective to reduce suicide, self-injurious behaviour and aggressive behaviour (26).

There are only a few studies about metabolic syndrome in forensic patients. Clozapine was widely used in forensic patients in New South Wales to reduce violence and suicide rates. Forensic patients carry a risk of cardiovascular mortality due to limited physical activity in hospital, however there is minimal research on these patients physical health. One study in a 160 bed forensic hospital in Toronto showed that the 22% of the patients met the criteria for metabolic syndrome (43,44).

7. Haloperidol in severe mental illness

Haloperidol, a first-generation antipsychotic is widely used but has an increased risk of extrapyramidal side effects (EPSE). Haloperidol is also commonly used for agitated and violent patients (46). In a Cochrane review, haloperidol was superior to placebo for the treatment of schizophrenia but with high propensity for EPSE. In randomised clinical trial with patients from Veterans medical centres with a diagnosis of treatment resistant schizophrenia were

assigned to either clozapine group or the haloperidol group, it was concluded that clozapine was more effective than haloperidol with fewer EPSE and spent fewer days in hospital (27).

8. Severe mental illness as a risk factor for metabolic syndrome

The risk of metabolic syndrome in severe mental illness is not only associated with antipsychotics, but with the interplay of multifactorial factors ranging from genetic factors to poor lifestyle, to the severe mental illness itself (1, 28, 29). Metabolic abnormalities have been found to be present at the start of psychotic symptoms of schizophrenia, indicating that metabolic disturbances are part of the illness and not due to treatment alone (29). Insulin resistance is present at an early age of 25 in patients with mental illness (30). There is also evidence of impaired fasting glucose in patients with first episode schizophrenia who have not started antipsychotics (31). Further evidence is the presence of Type 2 Diabetes mellitus in 18-30% of first degree relatives of people with schizophrenia (32). However, there are inconsistent results regarding hypertension and lipid abnormalities present in schizophrenia prior to starting antipsychotics (28). The above evidence suggests that the association between metabolic syndrome and schizophrenia is not only due to antipsychotics use. The link between schizophrenia and diabetes mellitus was long established by Maudsley in 1879 prior to the introduction of antipsychotics (30).

Genetic factors play a role in developing metabolic syndrome in schizophrenia. Several genes such as fat mass and obesity associated gene (FTO), leptin and leptin receptor genes (LEP, LEPR), methyl tetrahydrofolate reductase (MHTFR) and serotonin receptor 2 gene (HTR2C) have been hypothesised to be implicated in metabolic syndrome. Schizophrenia and metabolic syndrome has also been hypothesised to share the same pathophysiology of

inflammation which can be another contributing factor (33). Other factors classified as modifiable are poor diet and exercise, alcohol and smoking in patients with severe mental illness. Patients with schizophrenia smoke at least two to three times more than the general population (34).

9. Mood disorders and metabolic syndrome

There are few studies that compared the prevalence of metabolic disorders among various psychotic and mood disorders. A recent meta analysis which included 7616 patients who had a diagnosis of schizoaffective disorder , schizophrenia and other non affective psychosis showed a higher rate of metabolic syndrome in individuals with schizoaffective disorder Odds Ratio 1.41 (95% CI (1.23-1.61) for Metabolic syndrome as compared with schizophrenia and other non affective psychosis (35).

The CLAMORS (The Cardiovascular, Lipid and Metabolic Outcomes Research in Schizophrenia Study) has shown that patients with schizoaffective patients had a higher prevalence of the metabolic syndrome compared with schizophrenia (24.6% in schizophrenia patients vs 25.6% in schizoaffective patients. 43.3% of the schizoaffective patients were on antidepressant treatment in comparison to 25.2% of the patients with schizophrenia. The possible explanation is the presence of affective and psychotic symptoms with use of antidepressants and mood stabilisers which increase the risk of metabolic syndrome.(36)

Antipsychotics are usually prescribed together with mood stabilisers which have an additive effect on metabolic syndrome. The two most common mood stabilisers used are lithium and

sodium valproate. The latter causes a mean weight gain of 6.4 kg over 3 months, increased risk of insulin resistance and type 2 diabetes (5).

10. Guidelines for screening of metabolic syndrome for second generation antipsychotics

There are various guidelines published for the monitoring of metabolic syndrome in patients prescribed antipsychotics. They are the South African Society Treatment Guidelines, Maudsley Guidelines, American Diabetes Association with the American Psychiatric Association and the National Institute of Clinical Excellence (NICE) guidelines (31, 32, 33, and 34).

In 2005 the South African Society Treatment Guidelines recommend a baseline body mass index (BMI) and waist: hip ratio, fasting blood glucose, full blood count , liver function tests and baseline ECG (if cardiovascular risk) before starting antipsychotics.

Table 2 with summary of the guidelines for monitoring metabolic syndrome for patients on antipsychotics

	ADA/APA/2004	Maudsley Guidelines /2012	SASOP Guidelines (South African Guidelines)
Personal/Family History	Baseline and annually		
Weight/BMI	Baseline, 4 weeks, 12 weeks, quarterly	Baseline, 1 month, 3 months, 4-6 months and at 12 months,	Baseline BMI and waist circumference
Waist circumference	Baseline and annually	Baseline, 1 month, 3 months, 4-6 months and at 12 months,	Baseline
Blood pressure	Baseline, 12 weeks and annually	Baseline, frequently during titration	Baseline

Fasting lipids	Baseline, 12 weeks and annually	Baseline, 12 weeks and annually	Baseline
Fasting glucose	Baseline,12 weeks and every 5 years	Baseline, 12 weeks and annually	Baseline

A meta-analysis by Hert et al (2011) looked at all the guidelines on screening for metabolic syndrome and found that 4 of the 18 guidelines identified were recommended. Most of the guidelines did advise for the monitoring of weight, Body Mass Index, waist circumference, blood pressure, fasting lipids and glucose although at different time intervals) with recommendation for monitoring of cardiovascular risk factors usually first at baseline, then 6 weeks, 12 weeks and annually thereafter (37).

11. Monitoring for detection of metabolic syndrome in severe mental illness on antipsychotics

In the CATIE study, 20% of the patients with schizophrenia had hypertension and 11% of patients had diabetes mellitus at baseline. There were high rates of non-detection: 30.2% for diabetes, 62.4 % for hypertension and 88.0% for dyslipidaemia in patients who were not receiving treatment for their chronic disease (12).

Despite the high prevalence of metabolic syndrome, there is low rates of monitoring of metabolic parameters. A meta-analysis across five different countries showed that the screening for metabolic syndrome remained low in patients on second generation antipsychotics, with only 56.1% of patients tested for glucose and 28.9% of patients tested for lipids after implementation of guidelines (38). Similarly after the American Diabetes

Association's Consensus Statement on Antipsychotic Drugs the baseline glucose test was 21.8% and lipid testing was 10.5% in another study in the United States (39).The highest rate of monitoring of risk factors for metabolic syndrome was among the Veteran population, where 80% of veterans with severe mental illness were screened for all the parameters of metabolic syndrome. However Veterans are not a true reflection of the general population as they had greater access to medical health care and strict monitoring programmes (40). There were improved monitoring rates of glucose and lipids in a minority population with schizophrenia who were on medical aid in Kansas, United States (41).

Monitoring across different countries has been poor (38). A study in UK among 106 outpatients with predominant Caucasian population showed that there was poor monitoring across all metabolic parameters with no patient monitored for Body mass index and waist circumference (42).

12. Metabolic monitoring of clozapine in South Africa

There are few studies looking specifically at metabolic syndrome in patients prescribed clozapine. In a study in South Africa, clozapine use was studied in Xhosa patients. It was a very small study of 29 patients that looked at prevalence of metabolic syndrome in outpatients on clozapine. It is the first study on a particular race of patients in South Africa. Metabolic syndrome was present in 45% of patients, with 69% of the patients having a family History of cardiovascular disease which could contribute to the risk of metabolic syndrome. 13% of the patients had undiagnosed diabetes mellitus. The mean waist circumference was 95.6cm which is above the waist circumference according to IDF criteria and showed the presence of obesity in this population (43).

Similarly in an outpatient clinic at Kwazulu Natal looking at screening of individual metabolic parameters of metabolic syndrome for patients prescribed antipsychotics, it was found that only 2 patients out of 331 participants (1%) were screened for all parameters of metabolic syndrome. Antipsychotics was not exclusive to clozapine. The clinic was measuring blood pressure in 99% of patients. There was also poor monitoring of fasting blood glucose (3.9%) and lipids (1.8%) for patients. For patients on clozapine and olanzapine, the medications with the highest metabolic risks, less than 10% were tested for fasting blood glucose and lipids. This was the study with the lowest rate monitoring in the literature, and waist circumference was the least measured variable (0.6%). (44).Waist circumference is a simple screening tool and is a useful predictor for metabolic syndrome with a sensitivity of 79.4% and a specificity of 78.8% (15). Despite waist circumference replacing body mass index in all definitions of metabolic syndrome as it has a better correlation with metabolic syndrome (7), it is poorly documented as evident by several studies both in high income and low income countries (15, 44).

Waist circumference in one study was shown be a good predictor for insulin resistance in schizophrenia patients who were on clozapine (45). In a rural South African community, the waist circumference which could predict the presence of at least two other components of the metabolic syndrome was 86 cm for men (sensitivity 61.2%, specificity 82.9%) and 92 cm for women (sensitivity 45.9%, specificity 81.9%). Elevated waist circumference was highly prevalent in this population with more than 90% of the patients who had elevated waist circumference had metabolic syndrome (46)

AIMS AND OBJECTIVES

The aim of this pilot study is to determine the prevalence of metabolic disorders and investigate the associated risk factors of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine compared to patients on haloperidol.

Objectives:

1) To establish if there is annual screening of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine and haloperidol for at least one year duration.
2) To determine the prevalence of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine compared to haloperidol.
3) To determine the relationship between metabolic disorders and the clinical and demographic risk factors in forensic patients with schizophrenia spectrum disorders who are on clozapine compared to haloperidol.

LIMITATIONS OF LITERATURE AND MOTIVATION FOR STUDY

There is limited research exploring the prevalence and associated risk factors of metabolic disorders in severe mental illness in South Africa with no research done on forensic patients. This sub-population bear exceptional vulnerability to metabolic disorders and cardiovascular mortality and therefore requires metabolic screening.

If there is more screening and detection, there will be improved medical care of forensic patients and reduced burden of cardiovascular mortality and health costs in the midst of an obesity epidemic in Sub Saharan Africa.

Secondly, there are no studies with clear associations of the causative factors of metabolic syndrome in schizophrenia spectrum disorders both in high income settings and low income settings.

To our knowledge this is the first South African study examining the prevalence and associated risk factors of metabolic disorders in schizophrenia spectrum disorders comparing clozapine, widely used antipsychotic in treatment schizophrenia spectrum disorders in forensic patients with high risk of metabolic syndrome to haloperidol which is least associated with metabolic syndrome.

This pilot study will subsequently address the overriding need to assess the prevalence of metabolic syndrome in the forensic population because it is a potentially life-threatening illness that is not being monitored adequately.

CHAPTER 2: METHODS

STUDY DESIGN
The study is a retrospective folder review.

STUDY SETTING
The study was conducted in the Forensic Mental Health Service at Valkenberg Hospital, Cape Town, Western Cape South Africa.

STUDY POPULATION
They are forensic patients who have been recruited from Valkenberg Hospital from ward 11, 12, and ward 20. A sample of 45 participants on clozapine was used for the study group,

and 23 participants who are on haloperidol for the comparison group. The comparison sample was limited by the number of patients who were on haloperidol.

Inclusion criteria:

1) Participants are forensic patients at Valkenberg Hospital.
2) All participants are males.
3) All Participants are adults >18 years.
4) Participants have a clinically documented primary diagnosis within the schizophrenia spectrum disorders which include either brief psychotic episode, schizophreniform, schizophrenia , schizoaffective disorders or delusional disorder.
5) Participants can have comorbid psychiatric diagnosis of substance use disorder or personality disorder.
6) In the study group, participants have been on clozapine for at least one year as at 30th April 2017 as monotherapy or combined with another psychotropic or chronic medications except haloperidol.
7) In the comparison group, participants have been on haloperidol for least one year as at 30th April 2017 or combined with another psychotropic or chronic medications except clozapine.
8) The use of any concurrent medications which include other antipsychotics, mood stabilisers, antidepressants, anti cholinergics and benzodiazepines are included in both study and comparison group
9) Participants can have any comorbid medical condition.
10) The use of any comorbid chronic medications for chronic disease are included in both study and comparison group.

Exclusion criteria:

1) Participants who are on both clozapine and haloperidol.(This is not common practice).
2) Female patients (There are only male patients in the forensic setting at Valkenberg Hospital)
3) Participants who can't give informed consent.
4) Participants who refuse to participate in study.

DATA COLLECTION

The folders numbers of forensic patients who are on clozapine (study group) and haloperidol (comparison group) were obtained from the pharmacy at Valkenberg Hospital.

- Baseline data on demographics (age, marital status, ethnicity, level of education, employment and grant status), psychiatric diagnosis, medical comorbidities, past family history, and criminal offenses was obtained from patients folders.
- Baseline data on Blood pressure, weight, Body mass index, waist circumference was extracted from the nursing folders and patients folders.
- Baseline data on fasting lipids and fasting glucose were obtained from the National Health Laboratory Service (NHLS) on the website www.trackcarelabwebview.nhls.ac.za or the patient's folder.
- Baseline data on medications was obtained from prescription charts and the patient's folder.
- The data on blood pressure, weight, body mass index, waist circumference, fasting lipids and glucose was obtained as from 30th April 2016 to 30th April 2017 over a one-year period. The latest data was collected from the relevant folders.

The following variables was obtained from the relevant folders using a data collection form (Appendix 1):

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1) **Demographic data:**

- Age
- Marital status
- Ethnicity
- Level of education
- Employment status and grant status

2) **History of smoking**

3) **Psychiatric Diagnosis:**

- Schizophrenia spectrum disorders: schizophrenia, schizoaffective Disorder, schizophreniform disorders, delusional disorder, brief psychotic Disorder.
- Age at diagnosis
- Duration of illness

3) **Psychiatric Treatment**

- *Study group:* Duration of clozapine use, dosage of clozapine.
- *Comparison group:* Duration of haloperidol, dosage of haloperidol.

- *Other antipsychotics in combination:*

First generation antipsychotics
Depot antipsychotics
Second generation antipsychotics

- *Other medications in combination:*

Mood stabilisers
Antidepressants
Benzodiazepines
Anticholinergics
Other medications

4) **Medical treatment**

- Antihypertensive
- Hypoglycaemics or insulin therapy
- Statins
- Antiretrovirals
- Other medical treatment

5) **Comorbidities**

- Diabetes mellitus
- Hypertension
- Hyperlipidaemia
- HIV disease
- Other comorbidities

6) **Family history of medical/psychiatric illness**

7) **Offense**

Murder
Physical assault
Sexual assault
Others

8) **Metabolic parameters:**

The latest data that has been documented will be taken for this study over a one year period from 30th April 2016 to 30th April 2017.

- Weight in kg
- Body Mass index (kg/m2)
- Waist circumference (cm)
- Blood pressure (mm/Hg)
- Fasting blood glucose(mmol/l)
- Fasting lipids (mmol/l)
  - Total cholesterol
  - Triglycerides
  - HDL cholesterol
  - LDL cholesterol

DEFINITION CRITERIA

For the purpose of this study, the following was defined for metabolic disorders. Patients are defined as having a metabolic disorder if they had a documented diagnosis and treatment for one of the disorders and/or met criteria for one of the definitions of the disorder(Table 3).

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Table 3: Fully Adapted from Maaroganye K, Mohapi M, Kruger C, Rheeder P. The prevalence of metabolic syndrome and its associated factors in long-term patients in a specialist psychiatric hospital in South Africa: original. African journal of psychiatry. 2013; 16(6):414-23.

Metabolic syndrome NCEP-ATP III	Three or more of the following five risk factors: fasting blood glucose ≥5.6 mmol/l (100 mg/dl), BP ≥130/85 mmHg, fasting triglyceride ≥1.7 mmol/l (150 mg/dl), high-density lipoprotein cholesterol <40 mg/dL (<1.03 mmol/L) in men and <50 mg/dL (<1.29 mmol/L) in women, waist circumference> 102 cm in men and waist circumference >88 cm in women
Hypertension 2003 European Society of Hypertension (ESH)	Systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg.
Diabetes mellitus The 1998-1999 European Diabetes Policy Group's	Confirmed fasting venous plasma glucose level above or equal to 7,0 mmol/l (>125 mg/dl)
Total cholesterol dyslipidaemia	Total cholesterol >5.2 mmol/l
Triglyceride dyslipidaemia	Triglycerides >1.7 mmol
Low density lipo-protein (LDL) cholesterol dyslipidaemia	LDL cholesterol >3.4 mmol/l
Overweight WHO definition	Body mass index (mass/height^2) ≥ 25
Obesity WHO definition	Body mass index (mass/height^2) ≥ 30

DATA ANALYSIS

All analyses were performed using SPSS version 24. It stands for Stastical Package for Social Sciences used for statistical analysis. Unless noted otherwise, the threshold for statistical significance (α) will be set at .05. For each of the analyses described below, we calculated the appropriate effect size estimate, and interpreted these estimates following convention. Where assumptions underlying inferential statistical tests are violated, we will use the appropriate non-parametric tests.

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Descriptive statistics were used to describe continuous variables (mean, standard deviation, median) and categorical variables (counts). Normally distributed continuous data was analysed using student's *t*- tests. Non-normally distributed data was analysed using the Kruskal Wallis tests or Wilcoxon rank sum test. Categorical variables were analysed using the Chi Square or Fischers test.

The specific analyses used to answer our research questions were:

(1) An independent sample's *t*-test compared the prevalence of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine versus those on haloperidol.

(2) Linear regressions were run to determine the relationship between clinical and demographic risk factors and the prevalence of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine compared to haloperidol.

ETHICAL CONSIDERATIONS

1) A written informed consent was obtained from each participant to access their medical data. (*Informed consent as attached in Appendix 2)*

2) Each participant was anonymous.

3) There was no coercion or financial incentive for participation.

4) Participants had the right to refuse to participate in the study.

5) Confidentiality was respected by assigning each patient a number on the data collection sheet. A separate file was kept with the patient's name and folder number and stored in locked cabinet.

6) All data were kept in a secured protected password computer for which only the investigator had access.

7) The study involved minimal harm to the participants.

8) This study was approved by the University of Cape Town, Human Research Ethics Committee, the National Department of Health and Valkenberg Hospital Research Committee.

CHAPTER 3: RESULTS

The mean age of participants in the Study group was 42.69±11.78 years, and 39.96±10.29 years in the Control group ($t(66) = -0.943$, $p = .349$). Table 4 describes the demographic characteristics of both groups, and illustrates no significant between-group differences (all $ps > .222$).

Table 4
Demographic profile of patients in the Study and Control group

	Study Group $N = 45$		Control Group $N = 23$				
Variable	*n*	%	*N*	%	χ^2	*p*	*V*
Ethnicity					2.039	.361	.173
Black	17	37.8	12	52.2			
Coloured	26	57.8	11	47.8			
White	2	4.4	0	0			
Employment					Fischer's	.316	.173
Unemployed	43	95.6	18	85.7			
Employed	2	4.4	3	14.3			
Education					0.509	.775	.091
Primary	13	32.5	7	33.3			
Secondary	23	57.5	13	61.9			
Tertiary	4	10.0	1	4.8			
Marital Status					Fischer's	.162	.279
Single	36	81.8	20	90.9			
Married	2	4.5	1	4.5			
Divorced	6	13.6	0	0			
Widowed	0	0	1	4.5			
Smoker					Fischer's	.222	.171
Yes	44	97.8	18	90.0			
No	1	2.2	2	10.0			

Patients in both groups had a range of psychiatric conditions, and were taking a range of medications (see Table 5). Of note is that 95.7% of the Control group had schizophrenia

compared to 48.9% of the Study group, and 48.9% of the Study group had Schizoaffective Disorder compared to only 4.3% of the Control group (both *p*s <.001). Cannabis use was relatively high in both the Control and Study group (69.6% and 73.3% respectively). The most common medication used in the Control group was anticholinergics (30.4%), whereas the most common medication used by participants in the Study group was mood stabilizers (60%). 4 controls (33.3%) and 9 in the study group (42.9%) had a family history of a medical or psychiatric condition (χ^2 (1) = 0.290, p = .719 V = .094).

Patients in both groups had a similar number of psychiatric diagnoses, and the duration of psychiatric illness was not significantly different between the two groups (see Table 6). There were no significant differences in the duration of antipsychotic treatment between the Study group (who were all on Clozapine) and the Control group (who were all on Haloperidol).

Table 7 represents the physiological profile of patients. There were no significant between-group differences (all *p*s > .088), except that the Study group had a significantly higher weight compared to the Control group (p =.023).

Table 5

Clinical profile of patients in the Study and Control group

Variable	Study Group N = 45		Control Group N = 23				
	N	%	*N*	%	χ^2	*P*	*V*
Psychiatric Diagnosis							
Schizophrenia	22	48.9	22	95.7	14.575	<.001*	.463
Alcohol use disorder	17	37.8	8	34.8	0.059	.809	.029
Cannabis use disorder	33	73.3	16	69.6	0.107	.743	.040
Methamphetamine use disorder	15	33.3	6	26.1	0.374	.541	.074
Methaqualone use disorder	6	13.3	3	13.0	0.001	.973	.004
Schizoaffective disorder	22	48.9	1	4.3	13.491	<.001*	.445
Antisocial Personality disorder	6	13.3	0	0	Fischer's	.089	.222
Other diagnoses[a]	2	4.4	3	13.0	Fischer's	.327	.156
Medication use							
Mood stabilizers	27	60.0	3	13.6	12.845	<.001*	.438
Antidepressants	3	6.7	1	4.3	Fischer's	1.00	.047
Benzodiazepines	1	2.2	0	0	Fischer's	1.00	.086
Anticholinergics	3	6.7	7	30.4	6.855	.009*	.318

Note. [a]2 participants in the Control group had intellectual disability, and 1 participant had psychosis due to HIV. 1 participant in the Study group had intellectual disability and another used Glue.

Table 6

Clinical and treatment profile of participants

	Study Group N = 45		Control Group N = 23				
Variable	Mean (SD)	Range	Mean (SD)	Range	*t*	*p*	*d*
Number psychiatric diagnoses	2.67 (1.55)	0-6	2.52 (1.08)	1-5	-0.40	.690	0.11
Duration of psychiatric illness(years)	14.11 (9.36)[b]	1-37	11.33 (8.48)	0.5-31	-1.20	.237	0.31
Clozapine treatment	319.33 (118.99)	100-500	-	-	-	-	-
Haloperidol treatment	-	-	2.78 (1.46)	0.5-5	-	-	-
Duration antipsychotic treatment (years)	4.59 (3.24)[b]	1-17	7.52 (5.46)[c]	1-18	331	.064	0.23

[a]Mann-Whitney *U* test performed. [b]Data based on 44 participants. [c]Data based on 21 participants.

Table 7

Physiological measurements of patients in the Study and Control group

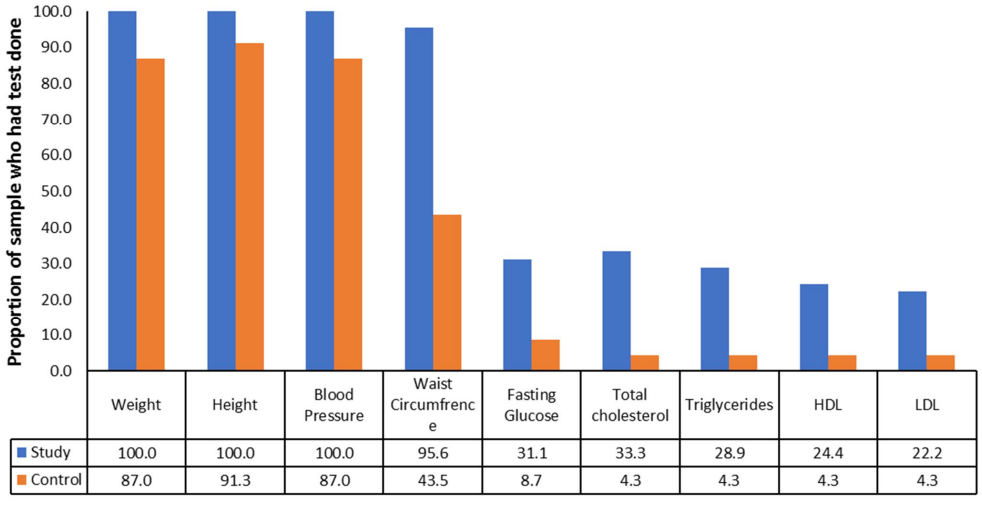
	Study Group N = 45		Control Group N = 23				
Variable	Mean (SD)	Range	Mean (SD)	Range	*t*	*p*	*D*
Systolic blood pressure (mmHg)	119.67 (14.57)	86-150	123.25 (12.94)[g]	95-143	0.95	.348	0.25
Diastolic blood pressure (mmHg)	77.24 (11.18)	51-98	77.80 (12.87)[g]	50-97	0.18	.860	0.05
Waist circumference (cm)	91.85 (12.80)[a]	70-121	85.85 (14.40)[d]	65-111	-1.31	.198	0.46
Height (cm)	1.74 (0.07)	1.57-1.9	1.71 (0.07)[h]	1.59-1.85	-1.68	.097	0.43
Weight (kg)	74.71 (15.41)	51-109.79	65.69 (11.91)[g]	52-95	-2.32	.023*	0.62
Body mass index	24.67 (4.62)	16.4-36.3	22.60 (4.00)[g]	16.4-30.3	-1.74	.088	0.47
Fasting blood glucose (mmol/l)	5.70 (3.48)[b]	3.8-17.5	4.55 (0.07)[i]	4.5-4.6	-0.45	.657	0.34
Fasting HDL (mmol/l)	0.94 (0.26)[c]	0.62-1.46	0.74[j]	-	-	-	-
Fasting LDL (mmol/l)	2.47 (0.53)[d]	1.64-3.41	2.62[j]	-	-	-	-
Fasting total cholesterol (mmol/l)	4.33 (1.27)[e]	2.76-8.01	4.16[j]	-	-	-	-
Fasting triglycerides (mmol/l)	2.47 (1.45)[f]	1-6.34	1.75[j]	-	-	-	-

Note. [a]Data based on 43 participants. [b]Data based on 14 participants. [c]Data based on 11 participants. [d]Data based on 10 participants. [e]Data based on 15 participants. [f]Data based on 13 participants. [g]Data based on 20 participants. [h]Data based on 21 participants. [i]Data based on 2 participants. [j]Data based on 1 participant.

There were no significant between-group differences in terms of features of Metabolic Syndrome (see Table 8). However, although none of the Control group met the criteria for Metabolic Syndrome, 8 patients in the Study group did (χ^2 (1) = 4.441, p = .035 V = .257)[1].

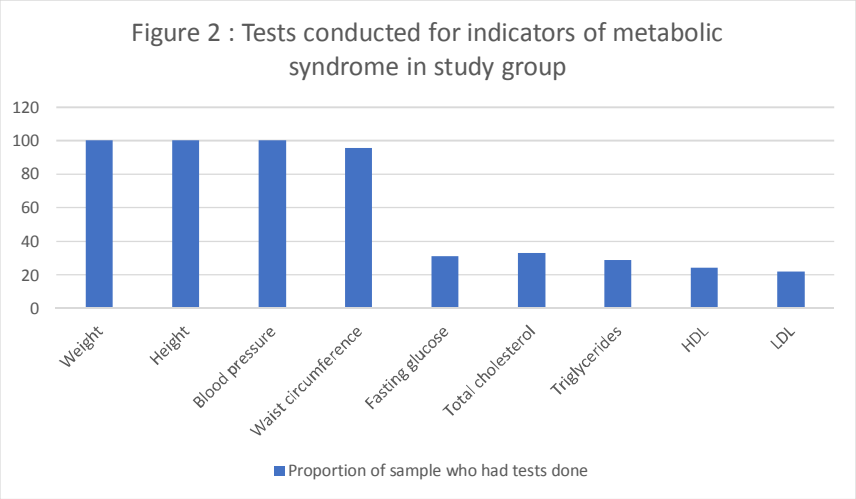
Patients on concurrent Clozapine and sodium valproate were compared to patients on Haloperidol. Again, while none of the patients on Haloperidol met the criteria for Metabolic syndrome, 6 (24%) of the 25 patients on concurrent Clozapine and sodium valproate did, (χ^2 (1) = 6.051, p = .023 V = .359).

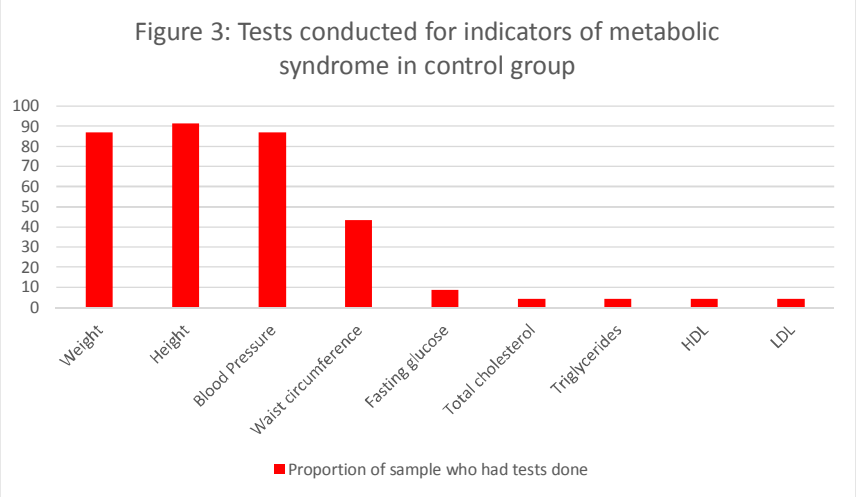
Figure 1: Tests conducted for indicators of Metabolic Syndrome



	Weight	Height	Blood Pressure	Waist Circumfrence	Fasting Glucose	Total cholesterol	Triglycerides	HDL	LDL
Study	100.0	100.0	100.0	95.6	31.1	33.3	28.9	24.4	22.2
Control	87.0	91.3	87.0	43.5	8.7	4.3	4.3	4.3	4.3

In terms of metabolic disorders, a significantly higher proportion of patients in the study group has hypertension and hyperlipidaemia (p = .003 and p = .021 respectively).





A very low percentage of patients in both groups had tests conducted for fasting glucose, cholesterol, triglycerides, HLD and LDL (see Figure 1). Waist circumference was measured in 95.6% of the study group compared to 43% of the control group. The measurements of weight, height and blood pressure is done in almost 100 % of the patients in the study group.

Table 8

Features of Metabolic Syndrome and metabolic disorders in the Study and Control group

	Study Group N = 45		Control Group N = 23				
	N	%	*N*	%	χ^2	*P*	*V*
Metabolic Syndrome	8	17.8	0[e]	0	4.441	.035*	.257
Features of Metabolic Syndrome							
Elevated Triglycerides	6[a]	54.5	1[h]	100.0	-	-	-
Elevated Waist circumference	14[b]	32.6	2[g]	20.0	0.607	.436	.107
Elevated Blood pressure	9	20.0	4[f]	20.0	0	1.00	.00
Decreased High Density low protein	7[a]	63.6	1[h]	100.0	Fischer's	1.00	.460
Elevated Fasting Glucose	2[j]	14.3	0[k]	0	Fischer's	1.00	.143
Metabolic disorders							
Overweight	10	22.2	3[f]	15.0	0.451	.502	.083
Obese	7	15.6	2[f]	10.0	0.358	.549	.074
Diabetes	6	13.3	0[i]	0	Fischer's	.089	.222
Hypertension	14	31.3	0[i]	0	9.011	.003*	.364
Hyperlipidaemia	9	20.0	0[i]	0	5.302	.021*	.279
Hypertriglyceridemia	1	2.2	0[i]	0	Fischer's	1.00	.087
TG dyslipidaemia	7[c]	53.8	1[h]	100.0	-	-	-
Cholesterol dyslipidaemia	2[d]	13.3	0[h]	0	-	-	-
LDL dyslipidaemia	12[d]	80.0	1[h]	100.0	-	-	-
Number elevated features of MetS					8.718	.069	.361
0	17		16	72.7			
1	14		4	18.2			
2	6		2	9.1			
3	5		0	0			
4	3		0	0			

Note. 72.8% of the Control group had no features of MetS, 18.2% had 1 feature, and 2.6% had 2 features. In contrast, 37.8% of the Study group had no features of MetS, 31.1% had 1 feature, 13.3% had 2 features, 11.1% had 3 features, and 6.7% had 4 features.
[a]Data based on 11 participants. [b]Data based on 43 participants. [c]Data based on 13 participants. [d]Data based on 15 participants. [e]Data based on 22 participants. [f]Data based on 20 participants. [g]Data based on 10 participants. [h]Data based on 1 participant. [i]Data based on 23 participants. [j]Data based on 14 participants. [k]Data based on 2 participants.

Associations between metabolic features/disorders and demographic/clinical variables

There were no significant associations within the Control group. Within the Study group, being on mood stabilizers meant patients were less likely to be overweight and more likely to be obese. Patients with schizophrenia were less likely to be obese, whereas patients with schizoaffective disorder were more likely to be obese (see Table 9).

Table 9

Associations (chi-square) between metabolic features/disorders and demographic/clinical variables

Metabolic features and disorders	Variable tested	Odds ratio (95% CI)	*p*	Interpretation
Overweight	Mood stabilizer	0.196	.028	Those on mood stabilizers less likely to be overweight
Obesity	Schizophrenia	Cannot be calculated – zero cell frequency	.009	Patients with schizophrenia less likely to be obese
Obesity	Schizoaffective	Cannot be calculated – zero cell frequency	.004	Patients with schizoaffective disorder more likely to be obese
Obesity	Mood stabilizer	Cannot be calculated – zero cell frequency	.031	Those on mood stabilizers more likely to be obese

Correlational analyses

Within both groups, there were significant positive correlations between age and duration of antipsychotic treatment (see Table 10).

Within in the Control group only, there was a significant positive correlation between age and dosage of Haloperidol treatment. There was also a significant negative association between number of psychiatric diagnoses and duration of antipsychotic treatment (see Table 10).

Within the Study group only, there was a significant negative association between age and number of psychiatric diagnoses (see Table 10).

Table 10
Significant correlations between demographic and clinical variables

		Study Group		**Control Group**	
Variable 1	**Variable 2**	*R*	*p*	*r*	*P*
Age	Number psychiatric diagnoses	-.315	.035	-	-
Age	Dosage of Haloperidol treatment	-	-	.423	.044
Age	Duration of antipsychotic treatment	.350	.020	.679	.001
Number psychiatric diagnoses	Duration antipsychotic treatment	-	-	-.445	.043

CHAPTER 4: DISCUSSION

This was the first South African study that investigated the prevalence of metabolic disorders and associated risk factors in forensic patients with schizophrenia spectrum disorders at Valkenberg Hospital. The primary aims were to determine (1) if there is annual screening of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine and haloperidol, (2) the prevalence of metabolic disorders and investigate the associated risk factors of metabolic disorders in forensic patients with schizophrenia spectrum disorders who are on clozapine compared to patients on

haloperidol, and (3) the relationship between metabolic disorders and the clinical and demographic risk factors in these patients.

SCREENING OF METABOLIC SYNDROME

A meta-analysis across five different high-income countries (United States of America (USA), United Kingdom (UK), Australia, Canada and Spain) showed a low screening rate for metabolic syndrome in patients taking antipsychotics with only 56.1% of patients tested for glucose and 28.9% of patients tested for lipids after implantation of guidelines (33). In South Africa, we have even a lower rate of screening of metabolic syndrome compared to high income countries. The screening of metabolic syndrome for patients with severe mental illness on antipsychotics in a South African outpatient clinic showed only 2 subjects (0.6%) out of 331 were screened for all five components of Metabolic syndrome. There was also reported low rates of testing with only 1.8% of patients tested for cholesterol and 3.9% for fasting glucose in patients (39).

In the current study, the rates of screening in patients on Clozapine was higher for each metabolic component as compared to patients on Haloperidol (Figure 1). This may be because patients on Clozapine have a higher risk of developing metabolic syndrome, and therefore monitoring of metabolic parameters is especially important in this patient group. There also clear guidelines recommending monitoring of metabolic syndrome in patients on clozapine. The rates of screening for each metabolic component in the current study was higher than the Saloojee (2014) South African study. However, screening rates in current study are still low compared to higher income countries.

Overall a high proportion of patients in both groups had their weight, height and blood pressure measured, which is usually done on each admission of a patient. Although waist circumference is not routinely done, a high proportion of patients on Clozapine had this measurement (95%) compared to only 42% of patients on Haloperidol. Across both groups there as a very low rate of screening of blood tests: fasting glucose, cholesterol, trigylcerides, HDL or LDL (generally under 25% of patients had these measurements done). In summary, there is suboptimal screening of metabolic syndrome both in high income and low-income settings. In the current study less than 25% of all patients were fully screened for metabolic syndrome. Therefore, proper diagnoses and management of this syndrome cannot be established, and these tests should be routinely performed.

The American Diabetes Association (ADA) and American Psychiatric Association (APA) guidelines need to be followed for monitoring patients on antipsychotics.

Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history[b]	X					X
Weight (body mass index)	X	X	X	X	X	
Waist circumference	X					X
Blood pressure	X			X		X
Fasting plasma glucose	X			X		X
Fasting lipid profile	X			X		X

a

Lifestyle modifiable risk factors should be addressed using the Diabetes Prevention Program as a guideline which recommends maintaining body weight or decrease by 5-7% of total

body weight, reducing calorie intake, more physical activity of 150 minutes of moderate to vigorous physical activity and light intensity activity and cessation of smoking (5).

PREVALENCE OF METABOLIC SYNDROME AND METABOLIC DISORDERS

Eight patients (17.8%) in the study group (Clozapine) met criteria for metabolic syndrome according to the NCEP-ATP III criteria and none of the patients in the control group (Haloperidol) did.

The prevalence of metabolic syndrome in the current study is lower than the meta-analysis conducted by Mitchel et al. 2013 in which there was a 32.5% prevalence of metabolic syndrome in patients with schizophrenia who were on a range of antipsychotics. In the same meta-analysis, patients on clozapine had the highest rate of metabolic syndrome at 51.9%. In a very small study that looked at prevalence of metabolic syndrome in outpatients on clozapine in Xhosa patients in South Africa, metabolic syndrome was present in 45% of patients (38). The prevalence of metabolic syndrome in the current study is lower than both of these studies in Pretoria with a prevalence of 32% in long terms psychiatric patients (15) and in Durban with a prevalence of 23.2% outpatients respectively (14).

The lower prevalence of metabolic syndrome in the current study could be due to the inadequate screening of the syndrome, as we had very limited data on fasting glucose and cholesterol, both of which are key criteria for the diagnosis of metabolic syndrome. We would have expected a higher prevalence of metabolic syndrome on patients on clozapine compared to previous studies which looked at a range of antipsychotics as it is associated

with the highest risk of metabolic syndrome. However, our population of forensic patients is also a distinct group compared to other patients with mental illness as they are long term inpatients on a hospital diet and a routine schedule in ward. This may be an important factor since a bad dietary lifestyle is known to play a role in increasing the risk of metabolic syndrome (1). Our patients strict hospital diet may contribute to the lower prevalence of metabolic syndrome seen in our sample.

In terms of metabolic disorders, a significantly higher proportion of patients in the study group had hypertension and hyperlipidaemia. Similarly, the CATIE study (9) also had 20% of patients with hypertension at baseline, and in the meta-anaylsis by Mitchel et al. (2013), the prevalence of hypertriglyceraemia was 39.3% and hypertension 38.7%.

DEMOGRAPHIC RISK FACTORS FOR METABOLIC SYNDROME

There are several risk factors for metabolic syndrome that were not investigated in the current study.

First, our study population consisted of only male forensic patients at Valkenberg Hospital with schizophrenia spectrum disorders. Although it is the first study in South Africa to look at metabolic syndrome in forensic patients, other studies have found a significant association between female gender and having Metabolic syndrome (13,14).

Second, the mean age of participants in the Study group was 42.69±11.78 years, and 39.96±10.29 years in the Control group. However, it was shown that individuals with severe mental illness who older than 55 years have higher odds of having metabolic syndrome (15).

Third, our sample consisted of mainly Black and African male patients. In one study, it was shown that South Africans of Indian descent was a risk factor for metabolic syndrome among individuals with severe mental illness on antipsychotics (15). Furthermore, black females with severe mental illness have a higher prevalence of metabolic syndrome compared to black males(47). Since this study consisted of only male participants, such comparisons could not be made.

Fourth, a family history of cardiovascular disease is a risk factor for cardiovascular deaths (1). However, this variable was poorly documented in the current study, and therefore we cannot comment on how this variable may play a role in the risk for developing metabolic syndrome.

THE CLINICAL RISK FACTORS ASSOCIATED WITH METABOLIC SYNDROME

This study looked at forensic patients with a diagnosis of schizophrenia spectrum disorders at Valkenberg Hospital.

In this study, the most common diagnosis within the schizophrenia spectrum disorders was schizophrenia and schizoaffective disorders. Patients with a diagnosis of schizoaffective disorder were more likely to be on both a mood stabiliser and clozapine in the study group with a higher risk of metabolic syndrome.

There is little research on mood stabilisers as a risk for metabolic syndrome compared to clozapine which is known to be associated with the risk of metabolic syndrome (13).

This study had similar results to the CLAMORS (The Cardiovascular, Lipid and Metabolic Outcomes Research in Schizophrenia Study) which shown that patients with schizoaffective patients had a higher prevalence of the metabolic syndrome compared with schizophrenia

with the probable explanation that schizoaffective patients are on antipsychotics and also on mood stabilisers with increased risk of metabolic syndrome (36) . Sodium valproate used as a mood stabiliser in psychiatric disorders and in epilepsy has been associated with weight gain, obesity, hyperinsulinaemia and dyslipidaemia(48) .

A first recent meta-analysis also showed that metabolic syndrome was higher in schizoaffective disorder than schizophrenia and other non-affective psychosis with an odds ratio of 1.41 95% CI (1.23-1.61) (35). Previous meta-analysis haven't looked at the differences in metabolic syndrome between different disorders in the schizophrenia spectrum disorders. In this meta-analysis, it is hypothesised that the increased risk of metabolic syndrome in schizoaffective disorder can be due to different combination of antidepressants, mood stabilisers and antipsychotics which further increase the risk of metabolic abnormalities. However, there is no clear causal association between the diagnosis of schizoaffective disorder and the higher risk of metabolic syndrome which will require further research (43).

LIMITATIONS

It was a pilot study with a small sample size with retrospective study design.

There were no female participants and the findings only apply to male patients.

It was an underpowered study and intended only as a pilot study.

CONCLUSION

This study comprised only male forensic patients with schizophrenia spectrum disorders, using either clozapine or haloperidol. The prevalence of metabolic syndrome was higher in

the clozapine group than haloperidol group, which is unsurprising since clozapine is usually associated with a higher risk of metabolic syndrome. However, the prevalence on metabolic syndrome in this study sample was relatively low compared to other studies. This could be due to the low rate of screening of each criteria of metabolic syndrome.

There is a need for better screening of metabolic syndrome in forensic patients on antipsychotic treatment in South Africa. Further studies are needed to investigate the risk of metabolic syndrome for patients who are on a combination of clozapine and mood stabilisers as it represents a higher risk for metabolic syndrome.

REFERENCES

1. Deaton C, Froelicher ES, Wu LH, Ho C, Shishani K, Jaarsma T. The global burden of cardiovascular disease. European Journal of Cardiovascular Nursing. 2011;10(2 suppl):S5-S13.
2. Mensah GA, Sampson UK, Roth GA, Forouzanfar MH, Naghavi M, Murray CJ, et al. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990-2013: a systematic analysis of data from the Global Burden of Disease Study 2013: cardiovascular topic. Cardiovascular journal of Africa. 2015;26(Supplement 1):6-10.
3. Azad MC, Shoesmith WD, Al Mamun M, Abdullah AF, Naing DKS, Phanindranath M, et al. Cardiovascular diseases among patients with schizophrenia. Asian journal of psychiatry. 2016;19:28-36.
4. Ruggeri M, Leese M, Thornicroft G, Bisoffi G, Tansella M. Definition and prevalence of severe and persistent mental illness. The British Journal of Psychiatry. 2000;177(2):149-55.
5. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. The Lancet Psychiatry. 2019;6(8):675-712.
6. Huang PL. A comprehensive definition for metabolic syndrome. Disease models & mechanisms. 2009;2(5-6):231-7.
7. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. Diabetic medicine. 2006;23(5):469-80.
8. Anagnostis P. Metabolic syndrome in the Mediterranean region: Current status. Indian journal of endocrinology and metabolism. 2012;16(1):72.
9. Han TS, Lean ME. Metabolic syndrome. Medicine. 2015;43(2):80-7.
10. Kato MM, Currier MB, Gomez CM, Hall L, Gonzalez-Blanco M. Prevalence of metabolic syndrome in Hispanic and non-Hispanic patients with schizophrenia. Prim Care Companion J Clin Psychiatry. 2004;6(2):74-7.
11. John AP, Koloth R, Dragovic M, Lim S. Prevalence of metabolic syndrome among Australians with severe mental illness. Med J Aust. 2009;190(4):176-9.
12. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophrenia research. 2005;80(1):19-32.
13. Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS Study. Schizophrenia research. 2007;90(1):162-73.
14. Ho CS, Zhang MW, Mak A, Ho RC. Metabolic syndrome in psychiatry: advances in understanding and management. Advances in psychiatric treatment. 2014;20(2):101-12.
15. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. Schizophrenia bulletin. 2013;39(2):306-18.
16. Papanastasiou E. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Therapeutic advances in psychopharmacology. 2013;3(1):33-51.
17. Saloojee S, Burns JK, Motala AA. Metabolic Syndrome in South African Patients with Severe Mental Illness: Prevalence and Associated Risk Factors. PloS one. 2016;11(2):e0149209.
18. Maaroganye K, Mohapi M, Kruger C, Rheeder P. The prevalence of metabolic syndrome and its associated factors in long-term patients in a specialist psychiatric hospital in South Africa: original. African journal of psychiatry. 2013;16(6):414-23.
19. Nag T, Ghosh A. Cardiovascular disease risk factors in Asian Indian population: A systematic review. Journal of cardiovascular disease research. 2013;4(4):222-8.

20. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects. CNS drugs. 2005;19(1):1-93.
21. Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: a drug safety review. Expert opinion on drug safety. 2015;14(1):73-96.
22. De Hert M, Schreurs V, Sweers K, Van Eyck D, Hanssens L, Šinko S, et al. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. Schizophrenia research. 2008;101(1):295-303.
23. Chiliza B, Asmal L, Oosthuizen P, Van Niekerk E, Erasmus R, Kidd M, et al. Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic. European Psychiatry. 2015;30(2):277-83.
24. Softic R, Sutovic A, Avdibegovic E, Osmanović E, Bećirović E, Mirković Hajdukov M. Metabolic syndrome in schizophrenia-who is more to blame: FGA polypharmacy or clozapine monotherapy? Psychiatria Danubina. 2015;27(4):0-384.
25. Solanki R, Singh P, Munshi D. Current perspectives in the treatment of resistant schizophrenia. Indian journal of psychiatry. 2009;51(4):254.
26. Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Archives of General Psychiatry. 2006;63(6):622-9.
27. Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. New England Journal of Medicine. 1997;337(12):809-15.
28. Chadda RK, Ramshankar P, Deb KS, Sood M. Metabolic syndrome in schizophrenia: differences between antipsychotic-naïve and treated patients. Journal of pharmacology and pharmacotherapeutics. 2013;4(3):176.
29. Darcin AE, Cavus SY, Dilbaz N, Kaya H, Dogan E. Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. Schizophrenia research. 2015;166(1):201-6.
30. Foley DL, Mackinnon A, Watts GF, Shaw JE, Magliano DJ, Castle DJ, et al. Cardiometabolic risk indicators that distinguish adults with psychosis from the general population, by age and gender. PLoS One. 2013;8(12):e82606.
31. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. American Journal of Psychiatry. 2003;160(2):284-9.
32. Koro CE, Fedder DO, Gilbert JL, Weiss S, Magder L, Kreyenbuhl J, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. Bmj. 2002;325(7358):243.
33. Malan-Müller S, Kilian S, van den Heuvel LL, Bardien S, Asmal L, Warnich L, et al. A systematic review of genetic variants associated with metabolic syndrome in patients with schizophrenia. Schizophrenia research. 2016;170(1):1-17.
34. Addington J, El-Guebaly N, Campbell W, Hodgins DC, Addington D. Smoking cessation treatment for patients with schizophrenia. American Journal of Psychiatry. 1998;155(7):974-5.
35. Bartoli F, Crocamo C, Caslini M, Clerici M, Carra G. Schizoaffective disorder and metabolic syndrome: A meta-analytic comparison with schizophrenia and other non-affective psychoses. Journal of psychiatric research. 2015;66:127-34.
36. . !!! INVALID CITATION !!! {}.
37. De Hert M, Vancampfort D, Correll C, Mercken V, Peuskens J, Sweers K, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. The British Journal of Psychiatry. 2011;199(2):99-105.
38. Mitchell A, Delaffon V, Vancampfort D, Correll C, De Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. Psychological medicine. 2012;42(01):125-47.

39. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. Diabetes Care. 2009;32(6):1037-42.
40. Khatana SAM, Kane J, Taveira TH, Bauer MS, Wu W-C. Monitoring and prevalence rates of metabolic syndrome in military veterans with serious mental illness. PLoS One. 2011;6(4):e19298.
41. Moeller KE, Rigler SK, Mayorga A, Nazir N, Shireman TI. Quality of monitoring for metabolic effects associated with second generation antipsychotics in patients with schizophrenia on public insurance. Schizophrenia research. 2011;126(1):117-23.
42. Mackin P, Bishop DR, Watkinson HM. A prospective study of monitoring practices for metabolic disease in antipsychotic-treated community psychiatric patients. BMC psychiatry. 2007;7(1):28.
43. Faasen N, Niehaus DJ, Koen L, Jordaan E. Undiagnosed metabolic syndrome and other adverse effects among clozapine users of Xhosa descent. South African Journal of Psychiatry. 2014;20(2):54-7.
44. Saloojee S, Burns JK, Motala AA. Very low rates of screening for metabolic syndrome among patients with severe mental illness in Durban, South Africa. BMC psychiatry. 2014;14(1):228.
45. Henderson DC, Fan X, Sharma B, Copeland PM, Borba CP, Freudenreich O, et al. Waist circumference is the best anthropometric predictor for insulin resistance in nondiabetic patients with schizophrenia treated with clozapine but not olanzapine. Journal of psychiatric practice. 2009;15(4):251.
46. Motala AA, Esterhuizen T, Pirie FJ, Omar MA. The prevalence of metabolic syndrome and determination of the optimal waist circumference cutoff points in a rural South African community. Diabetes care. 2011;34(4):1032-7.
47. Saloojee S, Burns JK, Motala AA. High risk of metabolic syndrome among black South African women with severe mental illness. South African Journal of Psychiatry. 2017;23(1).
48. Belcastro V, D'Egidio C, Striano P, Verrotti A. Metabolic and endocrine effects of valproic acid chronic treatment. Epilepsy research. 2013;107(1-2):1-8.

APPENDIX 1
DATA COLLECTION CAPTURE FORM (STUDY GROUP)

Date	
Patient number	
Ward	

DEMOGRAPHICS

1. **Sex**

Male		Female	

2. **Age**

18-25	
26-35	
36-50	
51-60	
>60	

3. **Ethnicity**

White/Caucasian	
Black	
Indian/Asian	
Coloured	
Other	
Unknown/Missing	

4. **Marital status**

Single	
Married	
Divorced	
Widowed	
Co habiting	
Unknown/Missing	

5. **Educational level**

No school	
Primary school	
Secondary school	
Tertiary school	

6. **Employment status**

Employed				
Unemployed	**On grant**		**Not on grant**	

7. SMOKING

SMOKING	YES	NO

8. PSYCHIATRIC DIAGNOSIS

Brief psychotic episode	
Delusional disorder	
Schizophreniform disorder	
Schizophrenia disorder	
Schizoaffective disorder	
Cormorbid psychiatric diagnosis	
Substance use disorder	
Personality disorder	

9. COMORBID MEDICAL CONDITIONS

Diabetes mellitus	
Hypertension	
Hyperlipidaemia	
HIV disease	
Other medical comorbidities	

10. FAMILY HISTORY OF MEDICAL CONDITION/PSYCHIATRIC CONDITION

Diabetes	
Hypertension	
Hyperlipidaemia	
Psychiatric condition	
Others(SPECIFY)	

11. TREATMENT (STUDY GROUP)

DRUG	Dosage	Duration of treatment
CLOZAPINE		

12. TREATMENT

OTHER DRUG	DOSAGE
CHLORPROMAZINE	
RISPERIDONE	
OLANZAPINE	
AMISULPIRIDE	
FLUPENTHIXOL DEPOT	
ZUCLOPENTHIXOL DECANOATE	

FLUPHENAZINE DECANOATE	
OTHERS(specify)	

13. COMORBID MOOD STABILISERS

LITHIUM	
SODIUM VALPROATE	
LAMOTRIGINE	
CARBAMAZEPINE	
Other mood stabilisers	

14. COMORBID ANTIDEPRESSANTS

CITALOPRAM	
FLUOXETINE	
AMITRYPTILINE	
VENLAFAXINE	
OTHER ANTIDEPRESSANTS	

15. COMORBID BENZODIAZEPINES

LORAZEPAM	
DIAZEPAM	
CLONAZEPAM	

16. COMORBID ANTICHOLINERGICS

Orphenadrine	

17. OTHER CHRONIC MEDICATIONS

18. OFFENSE

MURDER	
PHYSICAL ASSAULT	
SEXUAL ASSAULT	
OTHERS(SPECIFY)	

19. METABOLIC PARAMETERS

	SCREENED(YES/NO)	VALUE
Weight(kg)		
Height(cm)		
Body Mass index(BMI) (kg/m2)		
Blood pressure(mm/Hg)		
Waist circumference (cm)		
Fasting glucose(mmol/l)		
Fasting lipids(mmol/l) **Total Cholesterol** **Triglycerides** **High Density protein(HDL)**		

DATA COLLECTION CAPTURE FORM (COMPARISON GROUP)

Date	
Patient number	
Ward	

DEMOGRAPHICS

1. Sex

Male		Female	

2. Age

18-25	
26-35	
36-50	
51-60	
>60	

3. Ethnicity

White/Caucasian	
Black	
Indian/Asian	
Coloured	
Other	
Unknown/Missing	

4. Marital status

Single	
Married	

Divorced	
Widowed	
Co habiting	
Unknown/Missing	

5. Educational level

No school	
Primary school	
Secondary school	
Tertiary school	

6. Employment status

Employed				
Unemployed	**On grant**		**Not on grant**	

7. SMOKING

SMOKING	**YES**	**NO**

8. PSYCHIATRIC DIAGNOSIS

Brief psychotic episode	
Delusional disorder	
Schizophreniform disorder	
Schizophrenia	
Schizoaffective disorder	
Comorbid psychiatric diagnosis	
Substance use disorder	
Personality disorder	

9. COMORBID MEDICAL CONDITIONS

Diabetes mellitus	
Hypertension	
Hyperlipidaemia	
HIV disease	
Other medical comorbidities	

10. FAMILY HISTORY OF MEDICAL CONDITION/PSYCHIATRIC CONDITION

Diabetes	
Hypertension	

Hyperlipidaemia	
Psychiatric condition	
Others(SPECIFY)	

11. TREATMENT (COMPARISON GROUP)

DRUG	Dosage	Duration of treatment
HALOPERIDOL		

DRUG	DOSAGE
CHLORPROMAZINE	
RISPERIDONE	
OLANZAPINE	
AMISULPIRIDE	
FLUPENTHIXOL DEPOT	
ZUCLOPENTHIXOL DECANOATE	
FLUPHENAZINE DECANOATE	
OTHERS(specify)	

12. COMORBID MOOD STABILISERS

LITHIUM	
SODIUM VALPROATE	
LAMOTRIGINE	
CARBAMAZEPINE	
Other mood stabilisers	

13. COMORBID ANTIDEPRESSANTS

CITALOPRAM	
FLUOXETINE	
AMITRYPTILINE	
VENLAFAXINE	
OTHER ANTIDEPRESSANTS	

14. COMORBID BENZODIAZEPINES

LORAZEPAM	
DIAZEPAM	

CLONAZEPAM	

15. COMORBID ANTICHOLINERGICS

Orphenadrine	

16. OTHER CHRONIC MEDICATIONS

17. OFFENSE

MURDER	
PHYSICAL ASSAULT	
SEXUAL ASSAULT*	
OTHERS(SPECIFY)	

18. METABOLIC PARAMETERS

	SCREENED(YES/NO)	**VALUE**
Weight(kg)		
Height(cm)		
Body Mass index(BMI) (kg/m2)		
Waist circumference(cm)		
Blood pressure(mm/Hg)		
Fasting glucose(mmol/l)		
Fasting lipids(mmol/l) **Total Cholesterol** **Triglycerides** **High Density protein(HDL)**		

APPENDIX 2

INFORMED CONSENT

RESEARCH PROJECT FOR MMED PSYCHIATRY

I, Dr Shazia Mungly will be looking at the physical effects of your medication: metabolic syndrome (a condition characterised by cluster of high sugar level, high blood pressure, obesity and high fat level in blood). You have already had the blood tests and treatment for your condition.

I will be taking the information out of your folders but I will not be taking your name.

Your information will remain confidential.

You have the right to refuse participation in the study.

I have read the above information, or it has been read to me.

I consent voluntarily to participate in this research.

*Name of participant:*_____ **Thumb print of participant(if unable to sign)**

Signature of Participant _____

Principle Investigator : Dr Shazia Mungly

Signature : ……..

Witness name : ……..

Witness signature:……

Date:……

Appendix 3 : Ethics approval letter

Appendix 4 : University of Cape Town Approval Letter

Appendix 5: Department of Health Western Cape Approval Letter

Appendix 6: Valkenberg Hospital Approval Letter