Master of Medicine in Psychiatry: Thesis

Title:

Typical and Atypical Antipsychotic induced weight gain (AIWG) and its metabolic correlates among male forensic inpatients in Cape Town, South Africa

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This dissertation will be submitted as partial fulfilment of a Master in Medicine in

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Declaration page

I, Syed Safwan Nadvi, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Signed by candidate

S. Nadvi

19/6/2021

Abbreviations

AAP – *Atypical antipsychotic*

AHA – *American Heart Association*

AIWG – *Antipsychotic induced weight gain*

ALH – *Alexandra Hospital*

AP – *Antipsychotic*

ARP – *Agouti Related Protein*

BMI – *Body Mass Index*

COVID-19 – *Coronavirus Disease 2019*

EGIR – *European Group for the Study of Insulin Resistance*

EPSE – *Extra-pyramidal Side Effect*

FFA – *Free Fatty Acids*

FRCS – *Framingham Cardiovascular Risk scale*

FTO – *Fat Mass and Obesity Associated (gene)*

GWAS – *Genome Wide Association Study*

HCTZ – *Hydrochlorothiazide*

HREC – *Human Research Ethics Committee*

HDL – *High density lipoprotein*

IDF – *International Diabetes Foundation*

IUGR – *Intra-uterine growth restriction*

LDL, sdLDL – *Low Density Lipoprotein, small dense Low Density Lipoprotein*

LGH – *Lentegeur Hospital*

LMIC – *Lower-middle income countries*

LOA – *Leave of Absence*

MetS – *Metabolic Syndrome*

NCEP *ATP III – National Cholesterol Education Programme Adult Treat Panel III*

NHLBI – *National Heart, Lung and Blood Institute*

NPY – *Neuropeptide Y*

RCT – *Randomised Control Trial*

REDCap® - Research Electronic Data Capture

SMI – *Serious Mental Illness*

SNP – *Single Nucleotide Polymorphism*

SSA – Sub-Saharan Africa

SPSS® - Statistical Package for the Social Sciences

VBH – *Valkenberg Hospital*

UCT-University of Cape Town

WHO – *World Health Organisation*

Study Abstract

Antipsychotic induced weight gain (AIWG) is a well described phenomenon in psychiatric literature. However, there is a dearth of information on its prevalence in patients admitted to forensic units. Forensic inpatients are at heightened risk for weight gain and Metabolic Syndrome (MetS) due to long term exposure to antipsychotic (AP) medications.

Aim: We aimed to describe and compare the weight changes and metabolic profile of male forensic state patients exposed to typical and atypical AP and identify modifiable risk factors, enabling us to determine if there is a significant difference between typical and atypical AP in the development of weight gain and MetS.

Method: The study design was a retrospective folder review. The populations consisted of 75 male forensic state patients, stratified into those prescribed only atypical antipscyhotics (AAP) and those prescribed only typical antipsychotics (AP). The metabolic parameters on admission (From 2017) and at follow up (Up to 2022) were documented. Ethics approval was granted by the University's Human Research Ethics Committee (HREC).

Results: An average increase of 17.7 kg weight from admission to follow-up across both groups, with a 35.1% and 25.1% increase in the atypical and typical groups respectively. There was a 46.2% increase in the incidence of MetS in the AAP group, compared to 40.1% in the typical AP group. Patients on AAP had a significantly larger absolute and % change in weight than those on typical AP (p= 0.01/0.025 respectively).

Conclusion: This study is the first in a forensic unit in South Africa to show that all AP are associated with weight gain and MetS, with AAP having a significantly larger change in weight (p=0.01) . Further studies with larger sample sizes in other forensic state patient populations can be done to confirm associations found in our study.

CHAPTER 1

Introduction

Cardiovascular disease is the leading cause of mortality and premature mortality in persons with severe mental illness (SMI).(1,2) There is further evidence to suggest that long stay or forensic inpatients are at even greater risk of developing cardiovascular disease.(3) There is complex interplay between weight gain and obesity, the development of MetS and its associated cardiovascular complications.

Antipsychotic induced weight gain (AIWG) is well established in psychiatric literature, and dates to the earliest applications of chlorpromazine as an antipsychotic (AP) in the 1950's in the United States. The side effects of AP are almost as well known as the agents themselves.(4) First generation AP are associated to a larger degree with motor side effects, extrapyramidal side effects (EPSE) particularly. This led to the development of clozapine in the 1970's, and the emergence of an array of atypical antipsychotics (AAP) in the 1990's including olanzapine, risperidone and quetiapine. (1)

It soon became clear that these agents are more likely to cause significant metabolic derangements than typical AP. A pivotal study by Allison et al in 1999(1) demonstrated that all AP cause weight gain, but more so with the AAP drugs, with clozapine being the agent most likely to cause metabolic derangements. This may be due to the increased number of receptors with which it binds. (5) Weight gain caused by AAP is evidenced to be sustained by the inhibitory action on serotonin, dopamine and histamine receptors, as well as an

inhibitory effect on melanocortin receptor 4(MCR4); and a stimulatory effect on adrenergic (A2), muscarinic(M3) and serotonergic(5-HT1a/5-HT6) receptors. (5) See table 1 in Appendix B from Fisher et al, which references the relevant receptors.(6)In a recent meta-analysis by Barton et al published in 2020, consisting of 27 Randomised Control Trials, it was reported that, "All AP led to significantly more weight-gain ($p < .001$) and most AP led to a significantly higher risk for a clinically relevant weight-gain of ≥7% compared to placebo (RR = 2.04)."(4)

Metabolic Syndrome has evolved from its earliest characterisation by Reaven as 'Syndrome X' to 'Metabolic Syndrome', described by Grundy in 1999.(7,8) There are several definitions and criteria, which differ in some key areas.(9) Table 1, taken from Huang, highlights four of the commonly used guidelines. These are the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), the World Health Organisation (WHO), the European Group for Study of Insulin Resistance (EGIR) and the International Diabetes Foundation (IDF). The most easily applicable to daily practice is the NCEP ATP III guidelines, as the criteria consist of measurements and lab results that are readily available to clinicians and researchers.(9) According to Saloojee et al metabolic monitoring of persons with SMI in South Africa is poor, with a need for improved health screening. (10)

Table 1: Definitions of Metabolic Syndrome

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia‡ (plasma insulin >75th percentile)	Central obesity (waist circumference§): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below	Hyperinsulinemia, plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m^2	Waist circumference: ≥94 cm (M), ≥80cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx			HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx
Other criteria		Microalbuminuria†		

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.
†Urinary albumin excretion of ≥20 μg/min or albumin-to-creatinine ratio of ≥30 mg/g.
‡Reliable only in patients without T2D.
§Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.
Rx, pharmacologic treatment.

Table copied from Huang, PL, A comprehensive definition for metabolic syndrome. Vol. 2, DMM Disease Models and Mechanisms. 2009. p. 231–7.

Epidemiology of MetS in South Africa: There is a paucity of published literature originating from South Africa that deals with MetS on an ecological scale. However, the South African Demographic and Health Survey was conducted in 1998, and in 2002, Puoane et al published the obesity-related findings from the Survey.(11) It found that 29.2% of males suffered from obesity, with 9.2% having abdominal obesity. Females were found to have a prevalence of 56.6%, with 42% having abdominal obesity. The significant male/female difference was attributed to differences in level of education, access to healthcare and cultural factors such as expectations and perceptions regarding female body shape. In a literature review by Van Der Merwe and Pepper in 2006, data from single studies on obesity in South Africa was collated and discussed. With reference to the MetS, the authors reported significant inter-ethnic variations in prevalence of MetS, with hypertension

being most common among black participants and peripheral insulin resistance and type 2 diabetes most common in Indian-origin participants. (12)

Weight gain and MetS: MetS and its development depends on weight gain and fat deposition, and a tendency to deposit fat in intra-abdominal sites. Abdominal obesity has been found to have a high correlation with insulin resistance, and subsequent development of the MetS.(13,14) Leptin is a peptide hormone responsible for energy homeostasis and food intake through its actions on the hypothalamus with a net effect of weight loss. Levels of leptin have been shown to be increased in patients using AP in the absence of weight loss. (5,15,16) The concept of 'leptin resistance' may account for this. Persistently elevated Leptin levels can dysregulate energy homeostasis resulting in increased appetite, non-adaptive over-eating and weight gain. (15,17)

Forensic psychiatric inpatients, particularly in South Africa, are at risk of weight gain and subsequently developing MetS for several other factors which include a sedentary lifestyle and mandatory long-term adherence to pharmacological agents.(18) The definition of long-stay varies in the literature from 6 months to 5 years.(19) The environment in which the inpatients stay offers limited opportunity for physical exercise- this is due to a combination of a lack of human and recreational resources, the sedating nature of treatment, and the negative symptoms of psychiatric illness. Outpatients often have limited social support and this perpetuates and compounds the already present risk.(20–22)

Literature Review

Introduction

This focussed literature review references a number of criteria related to the profile of male forensic psychiatric patients and their risk of AIWG and MetS. Whilst the broader literature review has been explored in the introduction, this focused review will be looking at specific studies which include long-stay/institutionalised psychiatric patients and their metabolic profile and risk. The type of AP used is of interest, specifically those which have a propensity to cause weight gain. The prevalence of MetS in these populations and the risk factors specific to long-stay forensic patients will be reviewed. Screening and monitoring tools used in the studies will also be summarised. Finally, the interventions and recommendations specific to a forensic or long-term psychiatric population in decreasing the incidence of MetS and AIWG will be highlighted.

Search strategy

We searched the PUBMED database for information related to the topic. Articles relevant to this study were selected and their abstracts scanned. The relevant references were also scanned for inclusion. Those articles and references that met inclusion criteria were read fully.

The PUBMED search was as follows: (("forensic psychiatry"[MeSH Terms] OR ("forensic"[All Fields] AND "psychiatry"[All Fields]) OR "forensic psychiatry"[All Fields]) OR (long[All Fields] AND stay[All Fields]) OR institutionalised[All Fields]) AND ("metabolic

syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields]) AND ("weight gain"[MeSH Terms] OR ("weight"[All Fields] AND "gain"[All Fields]) OR "weight gain"[All Fields])

Literature Review Results

The initial search was for 'antipsychotic induced weight gain', but the search returned a limited number of studies (585) as it excluded studies where the focus was not on pharmacological treatment. 187 records were identified after duplicates were removed. A total of 37 records were screened for relevance.

Inclusion and exclusion criteria: The inclusion criteria were broad, given the paucity of literature on long-stay populations. Any study which included long term inpatient care of at least 1 year, with a focus on cardiovascular or metabolic risk factors was included. The mean age requirement was less than 80 years of age. Local and international data was reviewed. Even with these broad requirements, only 18 studies were eligible for inclusion. These studies included 2 forensic and 16 non-forensic psychiatric patient populations. Only one study from South Africa was found. (23)From these 18 studies, 8 were excluded due to either having a mean population age more than 80, or relating to geriatric conditions not relevant to the study question. Ultimately, 10 studies were chosen for investigation. Table 2 (page 14) summarises the findings from these studies.

Summary of results: There was limited data on long-stay inpatients, forensic and non-forensic. There were only 2 studies looking specifically at metabolic parameters in a purely forensic psychiatric population. (23,24) There were no reviews or meta-analyses in forensic and non-forensic long-stay populations. Two studies performed an intervention, the first analysing the efficacy of a monitoring tool in a medium-secure forensic ward, which appeared to convey benefit. The second analysed the efficacy of annual physical examinations and found that these were of little benefit. (24,25)

Overwhelmingly, 9 of the 10 studies chosen indicated significantly higher prevalence rates of MetS and its components. One study had lower prevalence rates of MetS than the general population, in a population of institutionalised individuals with intellectual disability. (26)Females were universally more affected, with higher prevalence rates of MetS than their male counterparts in all 10 studies. All 10 studies referenced family history/genetics, but pre-existing conditions and family history was a core feature of 7 out of 10 studies.

Most of the studies found that AP worsen the metabolic profile, but 3 out of 10 studies found no significant association.(18,27,28) Out of these 3 studies, only 2 made a distinction between atypical and typical AP in their data analysis. The remaining 7 out of 10 studies did not explicitly compare those with or without antipsychotic use. Length of admission was also a criterion under investigation, and 2 studies found no significant association between admission length and cardiovascular risk.(27,28) One study which found that antipsychotic medication had no significant association, found that admission

length was the biggest indicator of developing MetS. (18) The remainder did not explicitly comment on the link between duration of stay and cardiovascular risk.

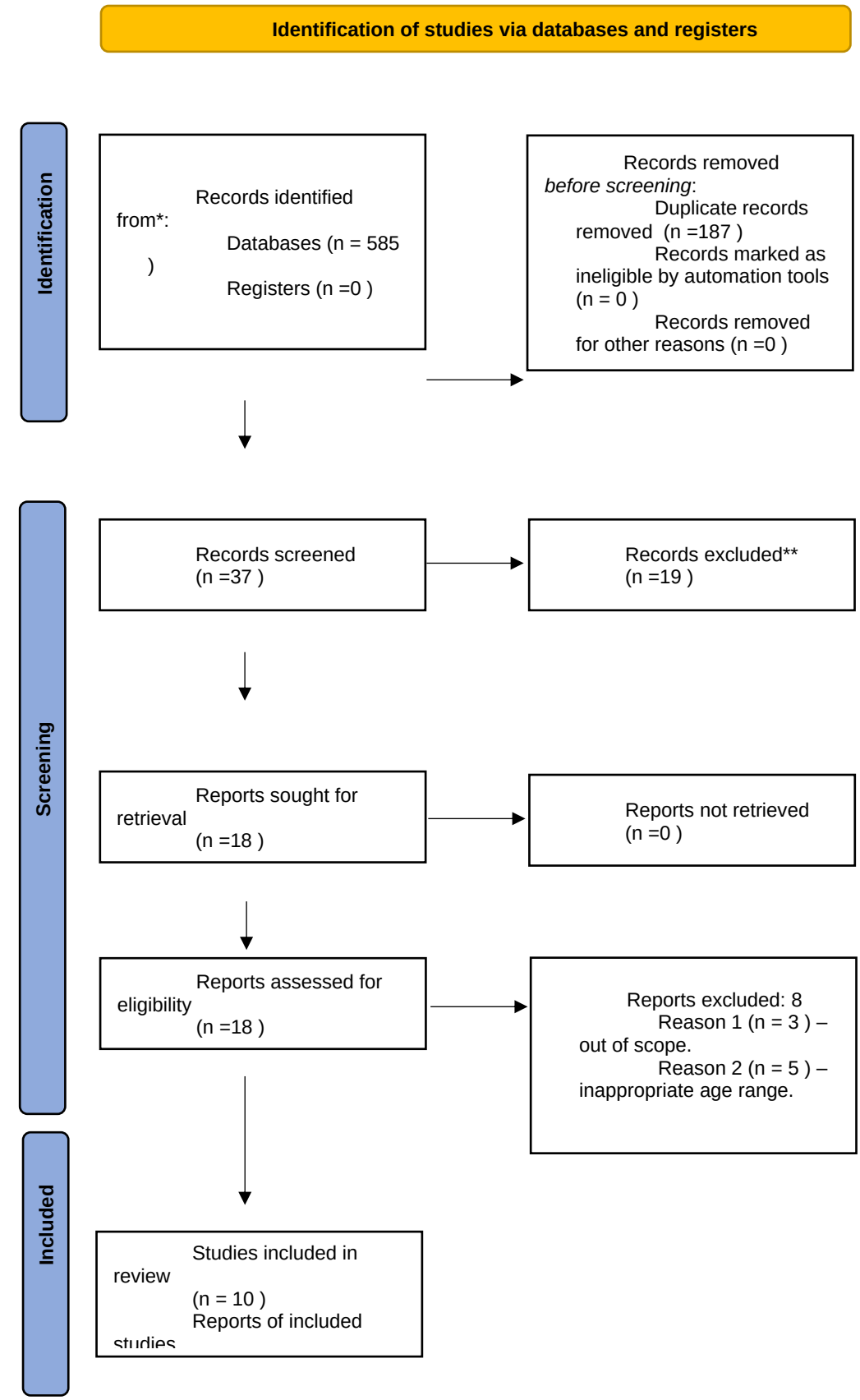

Figure 1. PRISMA Flow Diagram(29)

Table 2: Literature on AIWG/MetS in long-stay populations (Forensic & Non-Forensic)

Study	Study design	Participants	Results	Comments
The prevalence of metabolic syndrome and its associated factors in long-term patients in a specialist psychiatric hospital in South Africa Maaroganye K, Mohapi M, Krüger C, Rheeder P African Journal of Psychiatry (South Africa) (2013) 16(6) 414-423 (23)	Cross-sectional quantitative	Long-term psychiatric patients at a hospital in South Africa	"The prevalence of the metabolic disorders was metabolic syndrome 32%, hypertension 32%,diabetes mellitus 8%, cholesterol dyslipidaemia 32%, triglyceride dyslipidaemia 29%, low density lipoprotein (LDL) dyslipidaemia 50%, overweight 37%, and obesity 24%. Black African and female patients were more likely to have metabolic syndrome. Female patients were more likely to have cholesterol dyslipidaemia and obesity." More exposure to typical AP; 30% on clozapine; general polypharmacy. MetS diagnosed with NCEP ATP III criteria. Family history not reliable due to insufficient records. No interventions recorded.	Concluded that participants are high risk for cardiovascular disease. Did not comment on association between duration of admission and MetS. Did not delineate typical/atypical AP use.
Metabolic syndrome and cardiovascular risk among institutionalized patients with schizophrenia receiving long term tertiary care	Cross sectional	Long-term psychiatric patients at a hospital in Singapore	"Inpatient group had a mean age of 56.1 years and an average length of hospitalization of 8.8 years. The prevalence of MetS in this group was 51.9% and 26.9% based on the AHA/NHLBI and modified NCEP ATP III criteria respectively. Those in the high-risk BMI category and those who had pre-existing diabetes had higher odds of MetS. Their 10-year cardiovascular risk was estimated at 12.8%, indicating intermediate risk based on the Framingham risk function" Study broke	High cardiovascular risk, but independent of antipsychotic medication AND length of stay. No difference between AP used.

Seow L, Chong S, Wang P, Shafie S, Ong H, Subramaniam M Comprehensive Psychiatry (2017) 74 196-203 (28)			down participants into atypical/typical/both antipsychotic use. Used modified NCEP guidelines to diagnose metabolic syndrome, but also made reference to Framingham scores. Disparity in male/female numbers meant it was unclear which sex was at higher risk. Study found that prevalence of MetS was higher when including AHA/NHLBI criterion, suggesting that those with pre-existing conditions were treated for their metabolic risk. As inpatients, their diet was supervised and regular exercise scheduled.	
CanJPsychiatry 2015;60(5):232-238 Weight Gain and Its Correlates Among Forensic Inpatients Hilton Z, Ham E, Lang ;, Grant ;, Harris T(18)	Cross sectional	Forensic psychiatric inpatients over maximum 1 year in Canada	The study looked exclusively at male patients. Most participants were treated with AAP. On admission, 33% were obese and 22% of the 106 patients for whom sufficient data were available met criteria for metabolic syndrome. The 122 forensic inpatients with sufficient information gained an average of 12% of their body weight and 40% increased by at least 1 BMI category, gaining an average of 3.67 kg per month. Weight gain was associated with duration of time and was not attributable to being underweight on admission, diagnosis of schizophrenia, atypical AP treatment, medication adherence, or having been a smoker. The criterion for diagnosis of MetS was not explicitly stated, nor was information on pre-existing conditions or family history.	Higher cardiovascular risk. Was NOT related to antipsychotic treatment but WAS related to time spent as an inpatient. Too few participants on typical AP to draw meaningful comparisons

The risk of metabolic syndrome among institutionalized adults with intellectual disabilities Hsu S, Yen C, Hung W, Lin L, Wu C, Lin J Research in Developmental Disabilities (2012) 33(2) 615-620(26)	Cross sectional	164 adults with intellectual disability over 20 years old in Taiwan	"The prevalence of MS was 11.6% in the study participants (8% in males and 17.2% in females), which is lower than that in the general population of Taiwan. In the logistic regression analysis of the occurrence of MS, we found that gender, TG and HDL-C were variables that could significantly predict MetS after controlling for other potential factors." MetS was diagnosed according to the National Health Institute guidelines. AP were not specifically mentioned in the study. Lifestyle modification was not explicitly implemented.	Lower rates of Metabolic syndrome than general population. No relation to medication or length of stay. Did not delineate AAP/AP use.
High prevalence of risk factors for physical illness in a long-stay psychiatric unit S O, E D, M A, C M Irish journal of psychological medicine (2007) 24(2) 55-58(25)	Cross sectional	Non-forensic psychiatric Inpatients in Ireland	"We found the mean number of comorbid medical diagnosis was 2.7. The prevalence of MetS was 40.7% (44.4% of females and 24.1% of males). The prevalence of obesity was 51%, and 51% also had a total cholesterol in excess of 5.0mmol/l. Prolactin was elevated in two-thirds of female patients." AP were not the focus of the study. A proportion of the patients did have pre-existing conditions that were being treated.	High rates of metabolic syndrome, higher cardiovascular risk. Annual physical examinations did not improve outcomes. Did not comment on length of stay/medication link.
Weight gain and obesity in general adult psychiatric inpatients: a longitudinal and cross-sectional study	Cross sectional longitudinal study	240 non forensic psychiatric inpatients over 1-10 years in the United Kingdom	R2=0.17 (95% CI=0.14-0.20) for males and 0.27 (95% CI=02.0-0.34) for females. Only modest gains in weight; weight gain seems comorbid with psychiatric illness and independent of therapeutic intervention. MetS was not specifically covered, and so no specific criteria was mentioned. Lifestyle was mentioned as a risk factor, including the use of sugar/caffeine containing drinks as	Increased risk of MetS and higher cardiovascular risk, INDEPENDENT of length of stay AND medication use

Lazzari C, Shoka A, Nusair A, Rabottini M (2021) 211-216(27)			a counter to sedation of medication. Only atypical AP were specifically mentioned. The severity of illness was not documented.	
Physical health of patients with severe mental illness: an intervention on medium secure forensic unit K V, PB T, N M International journal of health care quality assurance (2012) 25(4) 363-370 (30)	Cross sectional longitudinal study	15 male forensic psychiatric patients over 1 year in Canada	Only male patients included. Criteria specific to MetS not mentioned. At baseline, 80 per cent of the patients were identified as smokers, 80 per cent had increased body mass index (BMI) and 87 per cent had raised cardiovascular risk over the next ten years. Appropriate interventions were offered to address the risks. At re-audit, the physical health monitoring sheets were up to date in 100 per cent of patients' records. The serum lipids and cardiovascular risk over the next ten years reduced over time. No significant change was noted on the parameters including BMI, central obesity, high blood pressure and smoking status. An intervention of regular monitoring of parameters was completed.	Significantly increased risk of MetS and higher cardiovascular risk. No comment on link between admission length/medication. No difference between AAP/AP use.
Valproic Acid as a Potentiator of Metabolic Syndrome In Institutionalized Residents on Concomitant Antipsychotics: Fat Chance, or Slim to None?(31)	Cross sectional Study	748 patients. 465 on AP, 210 on AP and Valproic Acid in the USA	No significant difference between study groups; increased risk of MetS regardless of treatment choice. NCEP guidelines used for diagnosis of MetS. A range of AP and AAP were looked at. As inpatients, participants were on treatment for comorbidities prior to the study. Severity of illness not stated, but possible proxy was the need for Sodium Valproate as adjuvant treatment.	All patients gained weight, no significant difference in weight gain with comorbid valproate use. Did not specifically delineate between AP/AAP use.

Long-term psychiatric inpatients' perspectives on weight gain, body satisfaction, diet and physical activity: a mixed methods study Every-Palmer S, Huthwaite M, Elmslie J(32)	Mixed Methods with quantitative and qualitative data	51 forensic and non-forensic long-term patients in New Zealand	"Obesity was the norm...Three quarters were obese with a mean BMI of 35.3 (SD 8.1), males 34.2 (SD 7.1), females 39.4 (SD 11.0, $p = 0.07$).The BMIs of our participants differed significantly from the national average. New Zealand has an obesity rate of 31.6% ($\chi^2 = 17.084$, df 1 $p < 0.0001$) and a mean BMI of 28.2 kg/m^2 (observed difference 7.1 kg/m^2, 95% CI 4.9–9.3, $p < 0.00001$).Most participants reported gaining weight since starting antipsychotic medication (mean reported weight gain 33 kg)" No distinction between AP and AAP. MetS criteria not looked at in detail.	Patients had high cardiovascular risk and rates of MetS, worsened by antipsychotic use. Length of admission not assessed. Grouped participants into clozapine and non-clozapine users.
Prevalence of obesity and metabolic syndrome in a long-stay psychiatric unit Udo I, Mooney M, Newman A (2011) 205-208(33)	Cross Sectional	30 non forensic psychiatric inpatients in Ireland	Male and female participants had similar rates of MetS. 66% of residents met criteria for MetS, Irish average is 20.7%. NCEP guidelines used for MetS. Majority of participants were on AAP, rather than AP.	Significantly increased risk of MetS and higher cardiovascular risk, worse in those using antipsychotic medication. Did not specifically delineate between AP/AAP use.

Literature Review Discussion

There were no reviews or randomised control trials in the literature search, and most of the studies were prevalence studies. Given this paucity of data, it would seem difficult to draw any meaningful conclusions – however, there is a wealth of information on persons with SMI (with or without antipsychotic treatment) and their related cardiovascular risk, which appears to be greater than the general population.(33,34) Most of data found in the literature search is from older populations, which may have resulted in an over-estimation of the morbidity from prolonged hospital stays and antipsychotic use.

In this focused literature review, there was no significant difference found between typical AP and AAP use. This contradicts the broader psychiatric literature, which suggests Clozapine and Olanzapine are the most likely antipsychotic agents to contribute to AIWG and MetS.(35,36) Criteria for diagnosis of MetS was primarily with the NCEP ATP III guidelines – other studies either did not specifically comment on criteria or used alternative criteria (NHI/NHLBI/AHA). Females were found to have higher prevalence rates for MetS, and this was postulated to have a multifactorial origin, including higher incidence of mood disorders, increased number of co-morbidities and underlying genetic/epigenetic mechanisms.(26,31,32,37)

There is a consensus that AP, in particular AAP, increase the likelihood of developing MetS.(3,5,34,38–40) There is also emerging evidence that SMI is a risk factor for MetS.(22,33,41,42) Polypharmacy with both AP and non-AP drugs was

highlighted as a risk factor for weight gain and MetS in ALL of the 10 studies. The conditions for which polypharmacy was frequently noted was schizo-affective disorder and comorbid substance use, personality factors and intellectual disability. There were assumptions that the physical inactivity associated with long hospital stays would contribute to worsening cardiovascular risk, however this has not been adequately demonstrated, with a greater number of studies finding no significant difference in length of admission and cardiovascular risk. There was also evidence to suggest that the populations under investigation are at increased risk of MetS/weight gain independent of antipsychotic or other medication use – the implication being an underlying genetic/epigenetic risk.

Literature Review Conclusion

The high prevalence of MetS in persons with SMI has been demonstrated in the absence of medication, and in non-institutionalised individuals. There is also evidence that antipsychotic medication use does have metabolic side effects, and that long hospital stays may exacerbate this risk. Thus, the aetiology of weight gain and MetS in psychiatric long stay/forensic patients is multifactorial. There is evolving evidence that genetic and epigenetic mechanisms underlie the increased risk of developing MetS in persons with SMI, and even in their non-psychiatrically ill siblings. (33)

Several studies from South Africa and SSA have brought light to the inadequate screening and monitoring for metabolic risk in persons with SMI.(43,44)

Whilst some of the interventions are feasible for a developing country, limiting factors include inadequate funding and human resources, poorer patient education and limited access to healthcare facilities. This ultimately results in poorer outcomes, with higher rates of *preventable* morbidity and mortality.(10,45) In the broader literature search, potential interventions and solutions were identified; these interventions included regulated low-calorie diets, ward programmes, patient and provider psychoeducation, nurse-led screening interventions and pharmacological interventions.(30,43,46)However, these may not translate into a health system of a LMIC such as South Africa.

The Maudsley Prescribing Guidelines suggests cessation of the offending agents or switching to an AP with less metabolic side effects. (36) Whilst this is feasible in developed nations, the limited formulary of AP for state patients in South Africa restricts such wholesale changes to treatment.(47,48) Lifestyle interventions such as exercise programmes and nutrition campaigns are more feasible, but also not without drawbacks, such as study attrition bias.(34) Certain drug treatments can be considered such as the blood glucose-lowering drug Metformin, which has been shown to mitigate the progress of MetS.(35,36) In a meta-analysis by Siskind et al, looking at Metformin for augmentation of treatment with clozapine in persons with metabolic derangements, it was found that, '*…metformin was superior to placebo in terms of weight loss (-3.12kg, 95%CI -4.88kg to -1.37kg) and BMI (-1.18kg/m2, 95%CI -)*(49)

CHAPTER 2

Method

Study Aims

To describe and compare the weight changes and metabolic profile of male forensic state patients exposed to typical and atypical AP.

Study Purpose

To determine if there is a significant difference between typical and atypical AP in the development of weight gain and Metabolic Syndrome (MetS).

Study Objectives

Primary:

1. To establish the prevalence of MetS on admission for all participants.
2. To determine possible associations between typical and atypical AP with respect to weight gain and MetS.

Study Design

The study design was a retrospective folder review examining metabolic parameters of 75 forensic psychiatric inpatients with exposure to AP.(51)Data was gathered across a 6-year interval from January 2017- December 2022. The chosen start date of 2017 was based on the availability of hospital and laboratory records, and data was collected up to December 2022.

Study Setting

The study took place in Cape Town, Western Cape, South Africa. The Western Cape is made up of 6 districts; there are 3 facilities in the Western Cape where forensic state patients can be admitted, namely Valkenberg, Lentegeur and Alexandra hospitals. A forensic state patient is an individual who has committed an offence which involved serious violence or injury, but by reason of mental illness was not capable of standing trial, comprehending his/her actions during the offence or not being able to act in accordance with this comprehension.

The study was performed at 3 state psychiatric hospitals. The first was Valkenberg hospital (VBH). The specific forensic wards for male patients are wards 20, 11 and 12. Each ward has between 50 and 65 patients at any time. The second hospital was Lentegeur Psychiatric hospital (LGH). The specific forensic wards that

were utilised were wards 9,10, 11 and 13. Each ward holds between 25-35 patients at any time. Lastly, Alexandra hospital also has a forensic unit for individuals with intellectual disability, with approximately 60 inpatients at any time.

Study population

This study incorporated male forensic state patients at the abovementioned facilities who have been exposed to AP and were admitted between 2017 and 2020 . The chosen date of 2017 is based on the availability of hospital and laboratory records. Patients admitted after 2020 did not have adequate exposure to an AP medication, and were thus excluded. Females were excluded due to the disparity in patient numbers for the male and female state patients. There were fewer than 5 females who would have been eligible for the study and previous studies in South African populations have noted sex differences in metabolic parameters at baseline and in response to antipsychotics. (12)(23) Subjects were between the ages of 18 and 60. The participants were divided into 2 groups, those with exposure to only AAP, and those with exposure only to typical AP. The psychiatric conditions for which patients were receiving AP include psychotic disorders, mood disorders, substance-related disorders and neurocognitive disorders or intellectual developmental disorder with behavioural disturbance. The definition of long-stay varies in the literature from 6 months to 5 years, with some studies further subdividing into categories of short (weeks to months), medium (months to years), and long (5 years and beyond) term stays. (19) For the purposes of this study, long

stay is defined as more than 2 years for reasons of convenience, as it pairs with the inclusion criterion of a minimum of 2 years of exposure to an AP medication.

Sampling

The population in question was male forensic state patients admitted between 2017 and 2020. A non-probability convenience sampling approach was utilised, as there are a limited number of facilities within each province in South Africa to accommodate forensic state patients. VBH, ALH and LGH are the three forensic psychiatric hospitals in the Western Cape. These facilities represent the entirety of the forensic inpatient services in the Western Cape.

Inclusion Criteria

1. Forensic State Patients at VBH/LGH/ALH
2. Male
3. Between the ages of 18-60
4. Admitted between the years 2017 and 2020
5. Exposure to an antipsychotic medication for at least 2 years
6. Any diagnosis or comorbidities
7. Any combination of medications, if there is evidence of treatment with an antipsychotic

Exclusion Criteria

1. Female
2. Non-forensic patients
3. Below the age of 18, or above the age of 60
4. Admitted before 2017, or after 2020.
5. Non-users of AP
6. Participants with missing folders/data

Recruitment and Informed Consent

Information on Participants was sourced from the three forensic units in the Western Cape – namely VBH, ALH and LGH hospitals. This study is a folder review without patient contact, and data was stored without identifying details, with participants' folder number being used to differentiate them. As a result, informed consent was not individually sought from study participants. As it was a folder review, participants were excluded due to transfer out of the province, death, abscondment, discharge or missing folders.

Data Collection

(See Appendix A)

The process of data collection for this study had several steps. Whilst it is a folder review, the information from the file spanned several years:

1. We used Clinicom to identify a list of patients admitted to the forensic service between 2017 and 2020. Clinicom is an electronic patient referencing and booking system managed by the Western Cape Government Department of Health.

2. This list was cross referenced with a ward location function, in order to determine participant location and/or status – VBH/ALH/LGH/LOA/Discharged/Demised.

3. With this information, the relevant folders were requested for review.

4. Those participants who did not meet inclusion criteria were excluded

5. The study participants were separated into 2 groups – those with AAP exposure only (Group 1) and those with exposure only to typical AP. (Group 2). For the purposes of this study, antipsychotic exposure is defined as treatment with an antipsychotic for a minimum duration of 2 years across the study period. Prior exposure to AP did not count toward these 2 years, due to uncertainty about adherence. Adequate exposure was defined as 2 years for reasons of convenience, as it would become challenging to

acquire older records.

6. From these folders, the demographic data, prior history and metabolic profile of the both groups on admission as state patients (2017-2020) was documented with the aid of the Research Electronic Database Capture (REDCap) programme. An example of the data capture tables outlining the variables being tested can be found below (See Appendix A).

7. Thereafter, using the same programme, the same information from up to December 2022 was documented . This ensured that study participants were inpatients for at least 2 years when data was collected, as the cut-off for admission in inclusion criteria is December 2020. The purpose of a minimum 2-year interval between admission and current parameters was to ensure adequate exposure to antipsychotic medication and to demonstrate the effect of a long inpatient stay on metabolic parameters.

8. The data was proof checked to ensure accuracy.

Statistical Analysis

Sample size

There were anecdotally approximately 180 males admitted as forensic state patients in the Western Cape between 2017 and 2020. Using a standardised online sample size calculator, the following was determined(52):

Population:180

Confidence level: 95%

Margin of error: 5%

Appropriate sample size: 123

Our original Aim: 150

Actual Sample Size: 75

Reasons for Discrepancy

The primary reason for the gross discrepancy in intended participants and actual participants was the discrepancy between the number of state patient admissions and the number of inpatients. A number of folders had missing information, however these belonged to patients who were not currently inpatients in the wards, without exception. This was due to leave of absence, abscondment, death or , rarely, discharge. Outpatient status was not an exclusion criterion, but

often meant information was not recorded as comprehensively as with inpatient notations.

The reason for discrepancy between the sample size and the eventual number of participants included in the analysis was the infrequency of patients prescribed only typical antipsychotics. This has a negative effect on the validity of the study and is addressed in the limitations.

Distribution of Data

Descriptive Data Analysis

Data was captured on the Research Electronic Database Capture (REDCap®) programme. Thereafter, the Statistical Package for Social Sciences (SPSS®) Version 27 statistical programme was used for data analysis, with the aid of the biostatistics department. For each of the analyses described below, appropriate effect size estimate was calculated. Where assumptions underlying inferential statistical tests were violated, the appropriate non-parametric tests were used. Non-normally distributed data was analysed using dependent sample t-test and Mc Nemar test. Descriptive statistics were used to describe continuous variables (mean, standard deviation, median) and categorical variables (counts and proportions).

The findings that were of particular interest to us:

1. The prevalence of MetS <u>on admission</u>

2. The incidence of weight gain and MetS during inpatient admission in atypical and typical AP groups. (minimum 2 years).

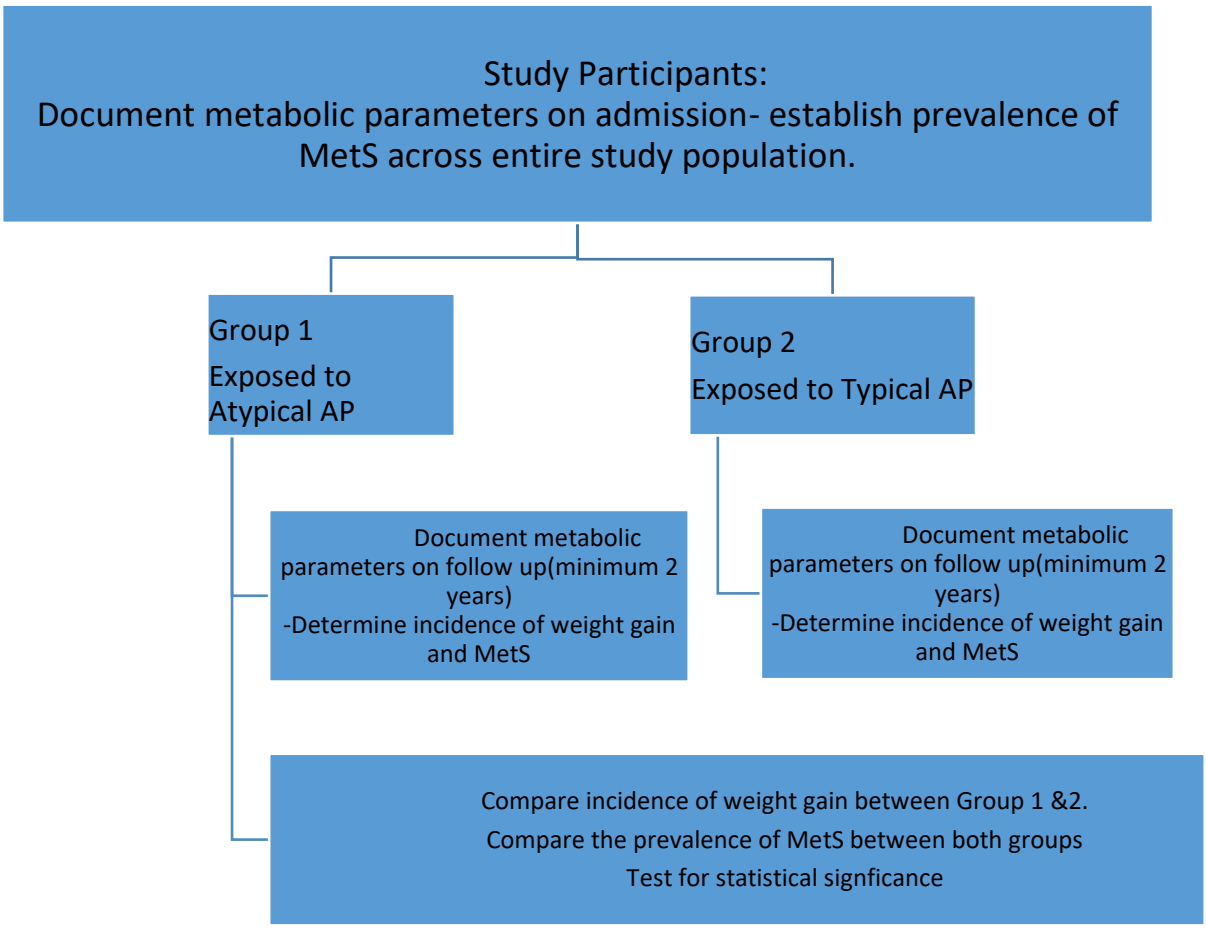

Figure 2- Summary of Study Design

Differentiating between general weight gain and AIWG is a challenge, especially in the setting of a long-term admission; however, in the case of this study, all of the participants have similar diets, living conditions and level of physical exercise, and the primary differences in their **care** relate to pharmacological management, whilst remaining cognisant of underlying genetic

and epigenetic differences.

Statistical Analysis

1. Comparisons between metabolic parameters of participants exposed to AAP only (Group 1) and those exposed to typical AP only (Group 2).

Normally distributed continuous data was analysed using student's t- tests. Non-normally distributed data was analysed using dependent sample t-test and Mc Nemar test. The means, range, variance and standard deviation of these values was calculated and compared across the minimum 2-year admission. The mean follow-up time was also calculated.

The Modified NCEP-ATP III and Limitations of Body Mass Index (BMI) values

Obesity is defined as a Body Mass Index (BMI) in excess of 30kg/m^2. The criterion for increased abdominal girth differs between guidelines. The EGIR and IDF define increased abdominal girth as more than or equal to 94cm in males and 80cm in females, whereas the NCEP ATP III guidelines require an abdominal circumference of more than 40in (101cm) in males and 35in(89cm) in females. Due to the lack of data on abdominal circumference in the study population, we decided to use a proxy to determine obesity, rather than leave out the variable. The proxy in this case is BMI.(53) The NCEP ATP III scoring method is simple, more generalisable and requires fewer investigations than other scoring systems. Abdominal

circumference is part of the criteria of all the accepted definitions of MetS. The exception is the WHO guidelines which has an alternative criterion of waist to hip ratio OR Body Mass Index (BMI) of more than or equal to 30.(54) This provides an alternative in a resource limited setting where metabolic monitoring is inadequate.(55)

There are limitations to the use of BMI as a proxy for abdominal circumference, particularly in a setting dominated by people of non-European origin. The origin of BMI as a measure of health has its origins in centuries old ideas, and is based on norms in a European population. This would not necessarily translate to non-European origin study participants, and thus may under or overestimate the burden of MetS, for example. BMI as a health measure is further flawed in assessing person's with higher than average muscle bulk – since muscle is heavier than fat, a physically healthy individual with an increased muscle mass may have a BMI that shows as overweight or obese, but this is not an accurate reflection of that individuals health status.

Measures of Association

Weight gain and the development of MetS were the outcomes that were being investigated. The effects of typical compared to atypical AP use on weight gain and MetS is of primary interest to us. However, given that this is a folder review, causation cannot be established. An association however, between typical/atypical AP and corresponding metabolic derangements has previously been

demonstrated in the literature, but not in a resource limited setting such as in this study.

Ethical considerations

Approval

Ethical approval was granted by the University of Cape Town (UCT) Human Research Ethics Committee (HREC) on 02/06/2022, with Reference 293/2022. Facility approval for Valkenberg, Alexandra and Lentegeur Hospitals was acquired on the 31st of August 2022, with Reference WC_202204_038.

Potential Risks and Benefits

The harm or risk to the participants is minimal and was monitored and mitigated as the study progressed. This study abides by both the UCT HREC regulations, as well as the Helsinki Declaration – the rights of the participants were not infringed upon in the pursuit of knowledge.

Approval of the study was dependant on approval from the individual facilities where the study took place i.e. Valkenberg, Alexandra and Lentegeur hospitals. An application was made via the National Health Research Database to conduct a folder review at these sites, which was granted. This was a retrospective

folder review. There was no intervention applied to the participants, and no distinct study/control groups.

The primary utility of this study is to influence policy change regarding standard treatment guidelines. For example, in psychiatric literature several agents have been associated with minimal metabolic derangements, such as Aripiprazole. (54)

Privacy and Confidentiality

The privacy and confidentiality of the participants was maintained throughout the research process with folder numbers being the only identifiable measure. This data was only available to the principal investigator (PI), the supervisors and the statistician and was stored in an encrypted database using REDCap. In addition, each participant/folder was deidentified using a unique participant identification number (PIN).

Reimbursement for Participation

As this was a folder review with no participant contact, participants were not reimbursed.

Emergency Care and Insurance for Research Related Injuries

As this was a folder review, there was no insurance required.

CHAPTER 3

Results

Demographic characteristics of patients (See Table 3)

The patient's ages clustered between the ages of 18 and 35, with 69.3% of participants below the age of 35 at commencement of study (see Figure 3). The majority of patients had either a Grade 1-7 or 8-12 education (38.7% each) and had their illness for more than 5 years (66.7%). Just over a quarter (26.7%) had no prior antipsychotic exposure, and just over one-third (34.7%) had been on AP for more than 5 years. The majority of the patients (74.7%) had never had a cardiac event on admission. Only 4 patients (5.3%) had a family history of MetS (one component) and 3 (4%) had a strong family history of MetS (two components). However, a family history of MetS was unknown for most patients (77.3%).

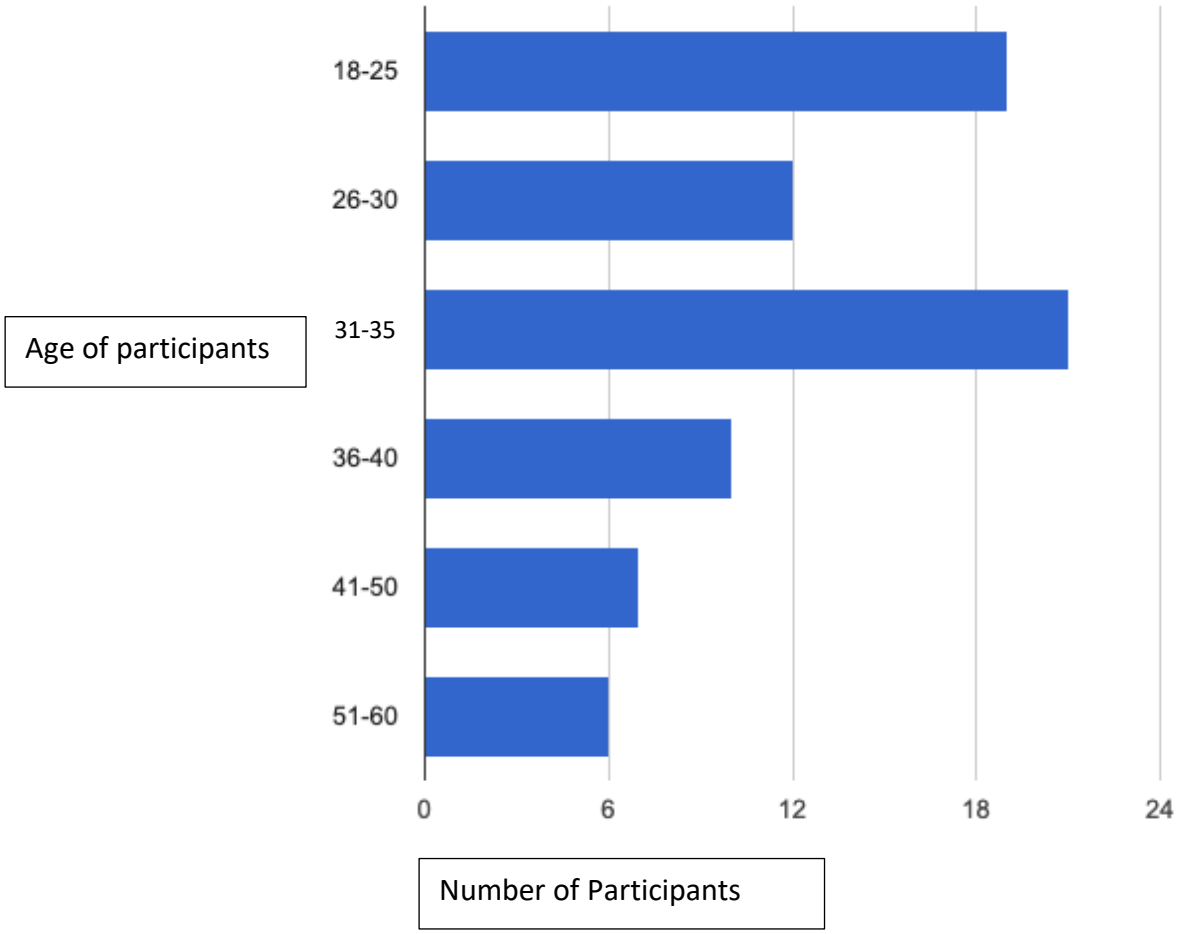

Figure 3 – Participants grouped by age

Table 3. Baseline demographics

	n	%
Education		
None	7	9.3
Special needs	7	9.3

Grade 1-7	29	38.7
Grade 8-12	29	38.7
Tertiary	3	4.0
Illness Duration		
1st presentation	5	6.7
1-3 years	13	17.3
4-5 years	7	9.3
>5 years	50	66.7
Pre-admission antipsychotic exposure		
None	20	26.7
< 1 years	11	14.7
1-3 years	14	18.7
4-5 years	4	5.3
> 5 years	26	34.7
Cardiac Event		
No	56	74.7
Unknown	19	25.3
Family History of MetS		
No	10	13.3
Unknown	58	77.3
1 component	4	5.3
2 or > components	3	4.0

Medication and Treatment

Of the 67 patients on a sedative hypnotic, the majority were on Lorazepam (n = 65; 86.7%). It should be noted that Lorazepam is routinely prescribed on an 'as needed' basis for agitation. It is almost never prescribed as a regular or chronic treatment. Relatively few patients were on drugs with mood stabilising proprieties, the most popular being Sodium Valproate (n = 19; 25.3%). The most commonly prescribed antipsychotic was Risperidone (n = 31; 41.3%), followed by Haloperidol (n = 13; 17.3%) and Olanzapine (n = 10; 13.3%). Few patients were on antidepressants or co-prescriptions (see Table 4).

Very few patients were on anti-diabetic/lipid treatment (n = 5) or anti HPT/platelet treatment (n = 4). 39 patients were on antiretroviral treatment (see Table 5).

Table 4. Psychiatric Medication Use

	Admission		**Follow-up**	
	n	**%**	**n**	**%**
Sedative Hypnotic				
Lorazepam	65	86.7	37	49.3

Diazepam	2	2.7	0	0
Clonazepam	0	0	0	0
Other	0	0	0	0
Drugs with Mood Stabilising Properties				
Sodium Valproate	19	25.3	33	44.0
Lithium	1	1.3	3	4.0
Carbamazepine	1	1.3	0	0
Lamotrigine	0	0	0	0
Other	0	0	1	1.3
Antipsychotics				
Clozapine	4	5.3	27	36.0
Olanzapine	10	13.3	22	29.3
Quetiapine	0	0	0	0
Risperidone	31	41.3	19	25.3
Chlorpromazine	7	9.3	6	8.0
Amisulpiride	1	1.3	12	16.0
Haloperidol	13	17.3	4	5.3
Zuclopenthixol decanoate	8	10.7	17	22.7
Flupentixol decanoate	7	9.3	7	9.3

Risperdal consta	1	1.3	0	0
Antidepressants				
Fluoxetine	5	6.7	14	18.7
Citalopram	3	4.0	1	1.3
Amitryptilline	1	1.3	1	1.3
Venlafaxine	0	0	1	1.3
Mirtazepine	0	0	0	0
Other	0	0	0	0
Common co-prescriptions				
Orphenadrine	7	9.3	15	20.0
Lactulose	1	1.3	5	6.7
Promethazine	0	0	5	6.7
Hyoscine	0	0	0	0
Depot Medroxyprogesterone	0	0	3	4.0
Cryptocerone acetate	2	2.7	1	1.3
Propranolol	0	0	5	6.7

Table 5. Non Psychiatric Medication Use

	Admission		**Follow-up**	
	n	**%**	**n**	**%**

Anti-diabetic/Lipid Treatment				
Metformin	2	2.7	13	17.3
Glimepiride	1	1.3	4	5.3
Insulin	0	0	2	2.7
Simvastatin	2	2.7	23	30.7
Atorvastatin	0	0	1	1.3
Rosuvastatin	0	0	0	0
Bezafibrate	0	0	0	0
Other	0	0	0	0
Anti-HPT/anti-platelet				
HCTZ	2	2.7	4	5.3
Enalapril	2	2.7	7	9.3
Atenolol	0	0	12	16.0
Amlodipine	1	1.3	5	6.7
Furosemide	0	0	0	0
Aspirin	0	0	1	1.3
Clopidogrel	0	0	0	0
Other	0	0	1	1.3
Anti-retroviral treatment				
TDF/3TC/DTG	1	1.3	2	2.7
TDF/FTC/EFV	2	2.7	0	0
LPR/RTV+TDF/FT	0	0	0	0

OTHER	1	1.3	3	4.0

Psychiatric and Medical diagnoses

The most common primary psychiatric diagnoses on admission were Schizophrenia (48%), schizoaffective disorder (28%) and Intellectual Disability (18.7%). In terms of comorbid psychiatric diagnoses, 62 patients (82.7%) had substance use disorder, and 15 (20%) had personality disorders (See Table 6). Four patients had ischemic heart disease, three had HIV, epilepsy or diabetes Type 2, and two had hypertension or obesity on admission.

Table 6. Psychiatric and Medical diagnoses

	Admission		Follow-up	
	n	**%**	**n**	**%**
Primary psychiatric diagnosis				
Schizophrenia	36	48.0	36	48.0
Bipolar d/o	3	4.0	3	4.0
Schizoaffective d/o	16	21.3	21	28.0
Intellectual disability	12	16.0	14	18.7
Substance induced d/o	4	5.3	0	0
Mood/psychotic d/o 2° another medical condition/TBI	8	10.7	8	10.7
Neurocognitive d/o	7	9.3	8	10.7
Other	0	0	0	0
Comorbid psychiatric diagnosis				
Substance (including alcohol) use d/o	65	86.7	62	82.7
Personality d/o	9	12.0	15	20.0
Intellectual disability*	4	5.3	10	13.3
Neurocognitive d/o	3	4.0	4	5.3
Anxiety d/o	0	0	0	0
Obsessive compulsive d/o	0	0	0	0
Medical comorbidities				

Hypertension	7	9.3	19	25.3
Obesity	2	2.7	16	21.3
Diabetes mellitus type2	2	2.7	14	18.7
Dyslipidaemia	3	4.0	31	41.3
Asthma/COPD	0	0	0	0
Ischaemic heart disease	0	0	0	0
HIV	4	5.3	4	5.3
Epilepsy	3	4.0	3	4.0
Familial medical history				
Hypertension	3	4.0	2	2.7
Obesity	1	1.3	1	1.3
Diabetes mellitus type2	2	2.7	2	2.7
Dyslipidaemia	4	5.3	5	6.7
Asthma/COPD	0	0	0	0
Ischaemic heart disease	0	0	0	0
HIV	0	0	0	0

*Some participants with suspected intellectual disability were given a secondary diagnosis of intellectual disability on admission

Metabolic Parameters

The mean time to follow up was 3.125 years, with a minimum of 2 years to ensure adequate antipsychotic exposure. The average weight upon admission was

61.7kg (SD = 11.1kg), ranging from 43 to 91kg. The average weight at follow-up was 79.3kg (SD = 13.7kg), ranging from 51 to 121kg (see Table 7). There was an average increase of 17.7kg (increase of 30.6%) in weight from admission to follow-up. Upon admission, very few patients had MetS (n = 6; 8%), whereas at follow-up, just over half had MetS (n = 41; 55.4%).

Table 7. Weight and MetS

	Mean	**SD**	**Range**	**Median**	**IQR**
Admission weight (kg's)	61.7	11.1	43-91	60	54-68
Follow-up weight (kg's)	79.3	13.7	51-121	80	69-86
Change in weight (kg's)	17.7	12.3	8-45	17	7-27
% Change in weight	30.6	22.6	9.1-88.2	29.7	9.4-45.7
Time to follow-up (years)	3.1	1.1	2-5	3	2-4
	n	**%**			
MetS at admission	6	8			
MetS at follow-up	41	55.4			
Weight gain	60	80			

Of the 6 patients who had MetS upon admission, 5 continued to have this diagnosis at follow-up, whereas 1 patient no longer had MetS at follow-up. 36 patients who did not have MetS at admission, later had it at follow-up – an incidence of 0.49 (36/74). 32 patients did not have MetS at admission and remained so at follow-up. 80% of patients gained weight (an increase of 7kg or greater) from admission to follow-up, with only 3 patients (represented by <0) losing weight, (see Table 7 and Figure 4).

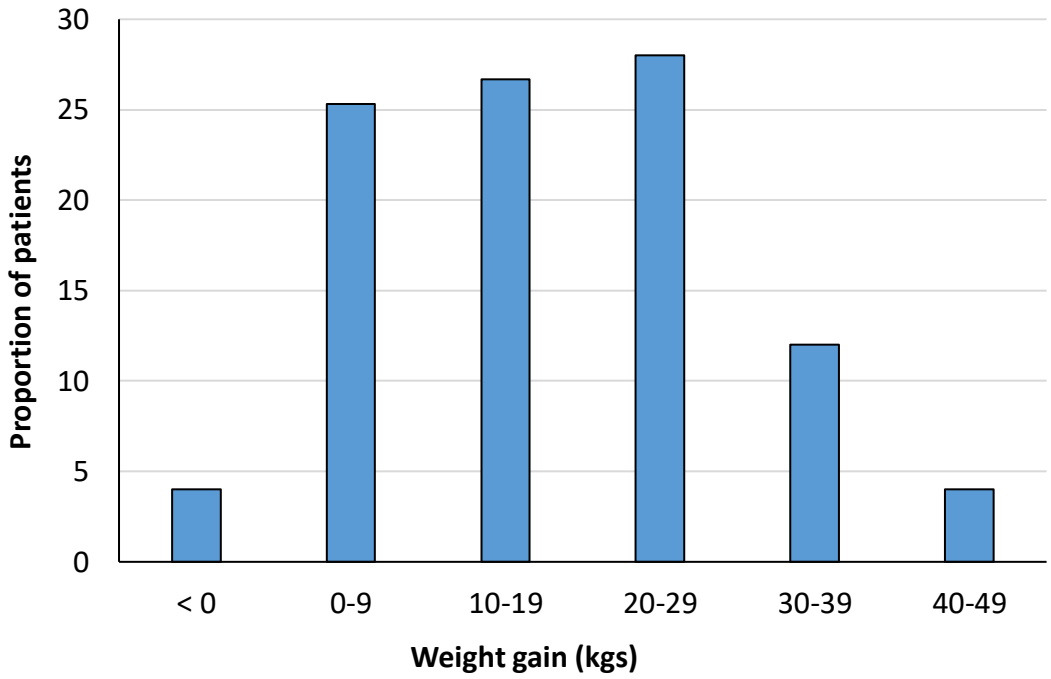

Figure 4. Change in weight from admission to follow-up.

Comparisons of metabolic parameters between participants exposed to AAP and those exposed to typical AP only

The second objective was to compare the relative metabolic effects of typical and atypical AP. The total number of participants that were on typical AP only (14) and those on AAP only (26) was 40, as shown in Table 8. This is substantially less than the total of 75 participants, as this analysis excluded those with exposure to both types of AP. Whilst this reduces the power of the analysis, it was necessary to answer the question of how AAP compared to AP affected weight gain and MetS. A power analysis was performed, which demonstrated this reduced power.

Table 8. Summary of findings for changes in weight and MetS

	Atypical antipsychotics	Typical antipsychotics	t/χ^2	*p*	*d/V*	*Power*
	n = 26	n = 14				
Admission weight mean	60.9	64.9	1.23	0.112	0.41	0.33
Follow-up weight mean	81.5	77.9	-0.84	0.204	0.28	0.21
Change in weight mean	20.5	13.1	-1.93	0.031*	0.64	0.60

% Change in weight	35.1	21.4	-2.03	0.025*	0.67	0.63
MetS at admission	1 (3.8%)	3 (21.4%)	-	0.115	0.28	0.43
MetS at follow-up	13 (50%)	8 (61.5%)	0.46	0.496	0.11	0.11
Weight gain	23 (88.5%)	9 (64.3%)	3.32	0.068	0.29	0.45

There was no statistically significant difference in weight upon admission or at follow-up between patients on atypical versus typical AP, nor the proportion with MetS upon admission or at follow-up. However, within both the typical and atypical group, the change in weight from baseline to follow-up increased significantly (p value < .001 for both`). Within both the typical and atypical group, the proportion of patients with MetS increased significantly from baseline to follow-up (p value < .001 for both). Patients on AAP had a significantly larger absolute and percentage change in weight compared to patients on typical AP (p = 0.031 and 0.025 respectively). There was also a trend towards a larger proportion of patients on AAP having gained weight compared to patients on typical AP (p = 0.068) (see Table 8).

CHAPTER 4

Discussion

This is the first study investigating the effect of all typical and atypical AP on the development of MetS in male forensic state patients in South Africa; a previous study looked at Haloperidol and clozapine specifically, but did not look at other AP**.** The objectives of the study were to determine the prevalence of MetS on admission and follow up, and the comparative effects of typical and atypical AP on metabolic profiles.

Weight gain and MetS on Antipsychotics

Only 6 (8%) of the participants had MetS on admission; this increased to 42(55.4%) on follow up. This dramatic increase is one that has been frequently reproduced internationally. There is evidence of weight gain on both types of AP, however more so with AAP. (1,4,39,40)

Out of 75 participants, **80%** gained clinically significant weight (more than 7kg) and **55%** of participants met criteria for MetS on follow up. Whilst these figures do align with other studies including long-stay patients, their mean time to follow up ranged from 8.80 years to 21.62 years, far greater than the 3.125 years in this study. (28,33) The relatively large effect size may be explained by the small

sample size or other confounders such as the impact of the Coronavirus Disease 2019 (COVID-19) pandemic on patient movement and activities of a physical nature, which were suspended.

In the 40 participants with exposure to only a single type of antipsychotic, there was no statistically significant difference between atypical and typical AP, and this too is due to the limited power of the study (small sample sizes). In spite of the limitations of this study, it was shown that patients on AAP had a significantly larger absolute and percentage change in weight ($p = 0.01$ and 0.025 respectively) across the study period. There was also a trend towards a larger proportion of patients on AAP having gained weight ($p = 0.068$).

The relevance of AP causing MetS lies in the increased risk of cardiovascular disease and type 2 diabetes mellitus associated with this condition. Individuals with MetS are at higher risk of developing heart disease, strokes, and other metabolic derangements. (1) In this study, there were no significant cardiovascular events such as a heart attack or stroke recorded during the study period, and this is likely due to the younger age of the participant population (69.3% under the age of 35), the relatively short mean follow-up time of 3.25 years and again, a small sample size.

Future studies in forensic psychiatric populations should be better resourced to ensure sufficient sample sizes which would yield better validity.

Long-term inpatients

Long-term inpatient stays have been associated with an increased risk of developing MetS in forensic psychiatric patients. (33) Prolonged hospitalization can lead to a sedentary lifestyle and limited access to healthy food choices, which both contribute to the development of MetS. In this study, roughly half of the study period was affected by limitations of the COVID-19 Pandemic; patient movement was limited, and most recreational activities curtailed or halted. This strengthens the internal validity of this study by confirming adherence to antipsychotic and other treatments by participants during the study period.

Importance of screening, monitoring

Given the significant metabolic side effects associated with antipsychotic medications as evidenced above, it is important to screen and monitor metabolic parameters in long-stay patients using these medications. Screening can help identify patients who are at increased risk of developing metabolic disorders, while monitoring can help detect early signs of metabolic disorders and allow for timely intervention. Some of the metabolic parameters that should be screened and monitored in long-stay patients using antipsychotic medications include body weight, waist circumference, blood pressure, fasting blood glucose and lipid levels. (56)

Whilst most of these parameters were readily available in the folder records, certain parameters were not routinely measured e.g., waist circumference. Though a proxy of BMI was used in this study, it departs from the accepted international criteria for MetS which uses waist circumference, as BMI is prone to error. (9)

Body weight and waist circumference are important measures of adiposity and should be measured at baseline and annually thereafter.(36) Fasting blood glucose and lipid levels should be measured at baseline and 6 monthly thereafter, as these were the parameters most significantly affected by administration of AP.(36) The benefit of early detection is that it informs prescribing practice and would potentially prevent the development of MetS in long stay patients. The cost associated with management of treatment related side-effects increases exponentially the longer an individual is on treatment; this can be mitigated by effective screening and monitoring. (57)

Interventions/Preventative measures

There are several interventions that can be used to manage metabolic side effects in patients using antipsychotic medications, including lifestyle modifications, medication changes, and pharmacological interventions. (43)

Lifestyle modifications, including diet and exercise, are the first-line interventions for managing metabolic side effects in patients using antipsychotic medications. This does require several additional resources for long-stay inpatients. A healthy diet (ideally overseen by a dietician or dietetics department) rich in fruits, vegetables, whole grains, and lean protein, can help manage weight gain and dyslipidaemia. Regular exercise, including both aerobic and resistance training, can help manage weight gain, improve insulin sensitivity, and reduce the risk of developing diabetes mellitus. Allied mental health services (such as dieticians, physiotherapists, and occupational therapists) could be consulted to assist with the development of exercise and weight loss programmes.

Antipsychotic changes, including switching to a different antipsychotic medication or reducing the dose of the current antipsychotic is currently the most cost-effective method in managing metabolic side effects. Switching to a lower-risk medication may be effective in reducing metabolic side effects, but this is not always a possibility with the limited range of AP currently available in the state sector.

There are several pharmacological interventions that can be used to manage metabolic side effects in patients using antipsychotic medications, including metformin, AAP medications, and lipid-lowering agents. Metformin is an oral antidiabetic medication that has been shown to improve insulin sensitivity and reduce weight gain in patients using antipsychotic medications. (58) The co-prescription of Metformin with clozapine is a directive undertaken by several mental healthcare institutions locally and internationally due to the burden of

metabolic disease caused by clozapine.(59) Lipid-lowering agents, such as statins, can be effective in managing dyslipidaemia and should be started early if there is evidence of abnormality in lipid levels. (36)

Certain atypical antipsychotic medications, such as aripiprazole and ziprasidone, are associated with a lower risk of metabolic side effects compared to other second-generation antipsychotic medications - these however are not available in the state sector in most provinces of South Africa and must be privately purchased by patients or their families, making it inaccessible to most patients. Availability of these medications in the state sector could significantly reduce the burden of MetS in forensic state patients and the greater population exposed to AP. Whilst AAP's have a greater propensity for AIWG, Aripiprazole in particular has evidence as monotherapy or adjunctive treatment in patients with established MetS or are at risk for MetS.(36)

There is a growing interest in the genetic basis for response to antipsychotic treatment, as well as the adverse effects which include metabolic derangements. A better understanding of who is at highest risk of adverse effects can assist clinicians in predicting and managing these effects.(38)

Study Limitations

Time

This MMED forms a part of the psychiatry registrar training. As such it is one of multiple responsibilities and requirements that a registrar has over the 4 years of training.

Cost

There is a research grant offered by UCT, to the Value of R4000, to aid in producing a research project. Additional funding can be applied for. The cost limitations of the study affected the breadth and scope of the study. With more financial resources a research assistant could be hired to collect data.

Sample Size

Due to the time and cost limitations noted above, there were challenges in recruiting enough participants to strengthen the validity of the results.

Cross Sectional Study design limitations

Due to the snapshot nature of the data collection, it is not possible to make causal inferences between exposures and outcomes. In addition, the study population is large and heterogenous, which results in several confounders.

Data Capturing Quality Control

As the data was collected from folders, the information contained within may have inaccuracies. For example, weight is recorded but there is no means to confirm that the scale used was properly calibrated. This is a limitation that we are aware of,

but not explicitly able to address, as the specific measuring instruments used may have changed from one weight reading to the next.

Confounders

- Age:

  Participants over the age of 50 are at significantly higher risk of developing MetS. With a heterogenous sample, this confounder was minimised but not excluded.

- Diagnosis:

  There is evidence that SMI itself is a risk factor for MetS. This study does not exclude those with mood disorders. This may confound data as those who are manic or depressed may have significant weight fluctuation.

- Lifestyle:

  Inpatient use of Patients who have been on LOA will no longer be following the ward routine, and so adherence and diet are no longer controlled. In addition, whilst most patients smoke, they will have access to illicit substances and alcohol when outside the hospital, which could further alter their adherence and diet. The general use of tobacco within and outside the hospital also contributes to the burden of risk for cardiovascular illnesses

and events.(60)

- Pre-existing metabolic conditions:

  The prevalence of MetS on admission to the forensic services is also of interest to us. However, if many participants have MetS on admission, it will be difficult to draw meaningful conclusions from the data after a 6-year period.

- Pharmacological Treatment prior to Admission and Polypharmacy:

  The inclusion criteria for the exposure group is at least 3 months of exposure to an AAP as an inpatient. Pre-admission exposure to AP/other treatment wasn't considered as AAP exposure due to adherence uncertainty. However, treatment with mood stabilisers, especially Sodium Valproate which is commonly co-prescribed with clozapine and is known to cause weight gain, can confound the data.(31) Antidepressants and hormonal treatment (such as medroxyprogesterone) can also contribute to weight gain.(20,61,62)

- Sampling

  The study design utilised a convenience sampling approach, over a limited period of time, so this may have influenced the results

- COVID-19 Pandemic

  The pandemic affected many aspects of healthcare from its onset to present. Specific to the participants (forensic inpatients), there was limited movement between wards and no LOA's from the hospital. In addition, many physical and recreational activities that would require human contact were suspended for 12-16 months. . This contributed to the sedentary nature of the prevailing lifestyle among participants. The study design utilised a convenience sampling approach, over a limited period of time, so this may have influenced the results

Publication Policy

We intend on publishing in an African Journal.

Conclusion

There is a dearth of local data on MetS in forensic state patients. This study relating to AIWG and MetS is the third in a forensic unit (or any psychiatric unit) in South Africa. There were three main findings from the study. Firstly, almost all participants (80%) gained clinically significant weight (>7kg's) across the follow up period (mean 3.1 years). Secondly, there was a 47.3% increase in participants meeting criteria for MetS over this period. Thirdly, patients on AAP had a

significantly larger absolute and percentage change in weight (p = 0.01 and 0.025 respectively) than patients on typical AP – this finding is noteworthy given the relatively small sample size.

This is also the first study from South Africa that aligns with international data both in terms of the high (>60%) proportion of participants who met criteria for MetS on follow up, and the significantly greater tendency for atypical AP to contribute to MetS than typical AP. A possible reason for the size of the effect seen is the fact that the study was affected by the COVID-19 pandemic, which severely restricted patient movement and activity between 2020 and 2022. This may have exaggerated the severity of weight gain and development of MetS.

The deleterious effect of long-term (>1year) inpatient stays on metabolic profiles was by default evident in this study, and is also in line with international data. Reasons highlighted in the literature include a sedentary lifestyle due to the sedating nature of treatment and the negative symptoms of psychiatric illness, and increased caloric intake due to appetite inducing side effects of treatment.(21,63)

Whilst there is clear evidence that AP cause weight gain and contribute to MetS, this study had a limited number of participants to derive statistically significant data. Future studies with broader inclusion criteria (such as including female participants), with larger sample sizes and adequate controls will strengthen the validity of the findings and possibly inform interventions that would be suitable/applicable to low-and middle-income country (LMIC) settings like SA. Recommendations applicable to LMICs include the availability of AP with less propensity to cause MetS in the state/public sector

Recommendations applicable to a local setting include the availability, in state, of AP with less propensity to cause MetS, such as Aripiprazole and Ziprasidone. Less resource-dependant measures can be instituted as an interim measure, such as health education, screening for MetS annually and monitoring of metabolic parameters. The prescription of readily available anti-diabetic/lipid treatments both for therapeutic and prophylactic use has a growing evidence base, and is a cost-effective measure. With greater access to resources, infrastructure changes with a larger focus on physical wellbeing can be instituted. These include the building of gymnasiums/pools and the development of exercise and nutrition programmes with input from allied health professionals such as physiotherapists, occupational therapists and dieticians. The development of AP with less propensity to cause MetS, as well as genetic testing to predict metabolic response to AP is an area of growing interest and research.(38)

Timeline of Thesis Development

	4. 21	5. 21	6. 21	7. 21	8. 21	9. 21	10. 21	11. 21	12. 21	1. 22	2. 22	3. 22	4. 22	5. 22	6. 22	7. 22	8. 22	9. 22	10. 22	11. 22	12. 22	01 23	9. 23	10. 23	11 23
Protocol Writing																									
Develop Protocol																									
Present protocol and edits																									
Ethics submission and edits																									
Data Collection																									
Data Analysis																									
Collate results																									
Statistical Analysis																									
Dissertation Writing																									

Complete literature review																									
Write Dissertation																									
Submit dissertation																									
Edits and final submission																									

References

1. Allison DB, Mentore JLE, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis. Vol. 156, Am J Psychiatry. 1999.
2. 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. Vol. 39, Schizophrenia Bulletin. 2013. p. 306–18.
3. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. Schizophr Res. 2010 Nov;123(2–3):225–33.
4. Barton BB, Segger F, Fischer K, Obermeier M, Musil R. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. Vol. 19, Expert Opinion on Drug Safety. Taylor and Francis Ltd; 2020. p. 295–314.
5. McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic-induced weight gain. J Clin Psychiatry. 2001;62 Suppl 23.
6. Fisher JE, Swingen DN, Harsin CM. Agitated and Aggressive Behavior. Comprehensive Clinical Psychology. 1998;413–31.
7. Reaven GM. Role of Insulin Resistance in Human Disease. Diabetes. 1988 Dec 1;37(12).
8. Grundy SM. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. Am J Cardiol. 1999 May;83(9).
9. Huang PL. A comprehensive definition for metabolic syndrome. Vol. 2, DMM Disease Models and Mechanisms. 2009. p. 231–7.
10. 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 Aug 12;14(1).
11. Puoane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, et al. Obesity in South Africa: The South African Demographic and Health Survey. Vol. 10, Obes Res. 2002.
12. Van Der Merwe MT, Pepper MS. National Prevalence of Obesity Obesity in South Africa. Blackwell Science. 2006;
13. Dulloo AG, Montani JP. Pathways from dieting to weight regain, to obesity and to the metabolic syndrome: An overview. Vol. 16, Obesity Reviews. Blackwell Publishing Ltd; 2015. p. 1–6.
14. M V, P V, E K, P H, J T. Relation between obesity from childhood to adulthood and the metabolic syndrome: population based study. BMJ [Internet]. 1998 Aug 1 [cited 2021 Sep 3];317(7154):319. Available from: https://pubmed.ncbi.nlm.nih.gov/9685277/
15. Lee AK, Bishop JR. Pharmacogenetics of leptin in antipsychotic-associated weight gain and obesity-related complications. Vol. 12, Pharmacogenomics. 2011. p. 999–1016.
16. Jin H, Meyer JM, Mudaliar S, Jeste D v. Impact of atypical antipsychotic therapy on leptin, ghrelin, and adiponectin. Vol. 100, Schizophrenia Research. 2008. p. 70–85.

17. Endomba FT, Tankeu AT, Nkeck JR, Tochie JN. Leptin and psychiatric illnesses: Does leptin play a role in antipsychotic-induced weight gain? Vol. 19, Lipids in Health and Disease. BioMed Central Ltd.; 2020.
18. Hilton Z, Ham E, Lang ; Carol, Grant ;, Harris T. CanJPsychiatry 2015;60(5):232-238 Weight Gain and Its Correlates Among Forensic Inpatients [Internet]. Available from: www.TheCJP.ca
19. Taiwo H, Ladapo O, Aina OF, Lawal RA, Adebiyi OP, Olomu SO, et al. Long stay patients in a psychiatric hospital in Lagos, Nigeria. Afr J Psychiatry (Johannesbg) [Internet]. 2008 [cited 2022 Mar 27];11(2):128–32. Available from: https://pubmed.ncbi.nlm.nih.gov/19582331/
20. Schwartz TL, Nihalani N, Jindal S, Virk S, Jones N. Psychiatric medication-induced obesity: a review. Blackwell Science. 2004.
21. P H, AS D, R K, S PE, SO J, HØ S, et al. Improving the physical health of long-term psychiatric inpatients. Aust N Z J Psychiatry [Internet]. 2014 [cited 2021 Sep 10];48(9):861–70. Available from: https://pubmed.ncbi.nlm.nih.gov/24810873/
22. Penninx BWJH, Sjors ;, Lange MM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications [Internet]. 2018. Available from: www.dialogues-cns.org
23. Maaroganye K, Mohapi M, Krüger C, Rheeder P. The prevalence of metabolic syndrome and its associated factors in long-term patients in a specialist psychiatric hospital in south africa. African Journal of Psychiatry (South Africa). 2013;16(6):414–23.
24. K V, PB T, N M. Physical health of patients with severe mental illness: an intervention on medium secure forensic unit. Int J Health Care Qual Assur [Internet]. 2012 Apr [cited 2021 Sep 9];25(4):363–70. Available from: https://pubmed.ncbi.nlm.nih.gov/22755485/
25. S O, E D, M A, C M. High prevalence of risk factors for physical illness in a long-stay psychiatric unit. Ir J Psychol Med [Internet]. 2007 [cited 2021 Sep 9];24(2):55–8. Available from: https://pubmed.ncbi.nlm.nih.gov/30290551/
26. Hsu SW, Yen CF, Hung WJ, Lin LP, Wu CL, Lin JD. The risk of metabolic syndrome among institutionalized adults with intellectual disabilities. Res Dev Disabil. 2012 Mar;33(2):615–20.
27. Lazzari C, Shoka A, Nusair A, Rabottini M. Weight gain and obesity in general adult psychiatric inpatients: a longitudinal and cross-sectional study [Internet]. Vol. 56, Riv Psichiatr. 2021. Available from: www.danielsoper.com
28. Seow LSE, Chong SA, Wang P, Shafie S, Ong HL, Subramaniam M. Metabolic syndrome and cardiovascular risk among institutionalized patients with schizophrenia receiving long term tertiary care. Compr Psychiatry. 2017 Apr 1;74:196–203.
29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;n71.
30. Vasudev K, Thakkar PB, Mitcheson N. Physical health of patients with severe mental illness: An intervention on medium secure forensic unit. Int J Health Care Qual Assur. 2012 Apr;25(4):363–70.
31. Valproic Acid as a Potentiator of Metabolic Syndrome In Institutionalized Residents on Concomitant Antipsychotics: Fat Chance, or Slim to None?

32. Every-Palmer S, Huthwaite MA, Elmslie JL, Grant E, Romans SE. Long-term psychiatric inpatients' perspectives on weight gain, body satisfaction, diet and physical activity: a mixed methods study. Available from: https://doi.org/10.1186/s12888-018-1878-5
33. Udo I, Mooney M, Newman A. Prevalence of obesity and metabolic syndrome in a long-stay psychiatric unit. Vol. 28, Ir J Psych Med. 2011.
34. Chadda R, Ramshankar P, Deb K, Sood M. Metabolic syndrome in schizophrenia: Differences between antipsychotic-naïve and treated patients. Vol. 4, Journal of Pharmacology and Pharmacotherapeutics. 2013. p. 174–84.
35. Kendall T, Hollis C, Stafford M, Taylor C. Recognition and management of psychosis and schizophrenia in children and young people: summary of NICE guidance. BMJ. 2013 Jan 23;346(jan23 1).
36. Taylor DM, TREB and AHYoung. The Maudsley Prescribing Guidelines, 13th Edition, 2018. 13th ed. 2018.
37. Jeon SW, Kim YK. Unresolved issues for utilization of atypical antipsychotics in schizophrenia: Antipsychotic polypharmacy and metabolic syndrome. Vol. 18, International Journal of Molecular Sciences. MDPI AG; 2017.
38. Shams TA, Müller DJ. Antipsychotic Induced Weight Gain: Genetics, Epigenetics, and Biomarkers Reviewed. Vol. 16, Current Psychiatry Reports. Current Medicine Group LLC 1; 2014.
39. Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: A drug safety review. Vol. 14, Expert Opinion on Drug Safety. Informa Healthcare; 2015. p. 73–96.
40. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry. 2001;62 Suppl 7.
41. Enez Darcin A, Yalcin Cavus S, Dilbaz N, Kaya H, Dogan E. Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. Schizophr Res. 2014 Aug 8;166(1–3):201–6.
42. Correll CU, Malhotra AK. Pharmacogenetics of antipsychotic-induced weight gain. Psychopharmacology (Berl). 2004;174(4):477–89.
43. Gurusamy J, Gandhi S, Damodharan D, Ganesan V, Palaniappan M. Exercise, diet and educational interventions for metabolic syndrome in persons with schizophrenia: A systematic review. Vol. 36, Asian Journal of Psychiatry. Elsevier B.V.; 2018. p. 73–85.
44. Qiao Q, Gao W, Zhang L, Nyamdorj R, Tuomilehto J. Metabolic syndrome and cardiovascular disease. Vol. 44, Ann Clin Biochem. 2007.
45. Saloojee S, Burns JK, Motala AA. Metabolic syndrome in South African patients with severe mental illness: Prevalence and associated risk factors. PLoS One. 2016 Feb 1;11(2).
46. Marteene W, Winckel K, Hollingworth S, Kisely S, Gallagher E, Hahn M, et al. Strategies to counter antipsychotic-associated weight gain in patients with schizophrenia. Vol. 18, Expert Opinion on Drug Safety. Taylor and Francis Ltd; 2019. p. 1149–60.
47. Jaspers Faijer-Westerink H, Kengne AP, Meeks KAC, Agyemang C. Prevalence of metabolic syndrome in sub-Saharan Africa: A systematic review and meta-analysis. Nutrition, Metabolism and Cardiovascular Diseases. 2020 Apr 12;30(4):547–65.

48. Dalal S, Beunza JJ, Volmink J, Adebamowo C, Bajunirwe F, Njelekela M, et al. NON-COMMUNICABLE DISEASES Non-communicable diseases in sub-Saharan Africa: what we know now. Int J Epidemiol [Internet]. 2011;40:885–901. Available from: https://academic.oup.com/ije/article/40/4/885/682926
49. Siskind DJ, Leung J, Russell AW, Wysoczanski D, Kisely S. Metformin for clozapine associated obesity: A systematic review and meta-analysis. PLoS One. 2016 Jun 1;11(6).
50. de Boer N, Guloksuz S, van Baal C, Willebrands L, Deenik J, Vinkers CH, et al. Study protocol of a randomized, double-blind, placebo-controlled, multi-center trial to treat antipsychotic-induced weight gain: the Metformin-Lifestyle in antipsychotic users (MELIA) trial. BMC Psychiatry 2021 21:1 [Internet]. 2021 Jan 5 [cited 2021 Sep 10];21(1):1–11. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-020-02992-4
51. Thiese MS. Observational and interventional study design types; an overview. Biochem Med (Zagreb). 2014;24(2):199–210.
52. https://www.calculator.net/sample-size-calculator.html. Sample Size Calculator.
53. Gierach M, Gierach J, Ewertowska M, Arndt A, Junik R. Correlation between Body Mass Index and Waist Circumference in Patients with Metabolic Syndrome. ISRN Endocrinol [Internet]. 2014 Mar 4 [cited 2021 Oct 1];2014:1–6. Available from: /pmc/articles/PMC3960736/
54. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-Defined Metabolic Syndrome, Diabetes, and Prevalence of Coronary Heart Disease Among NHANES III Participants Age 50 Years and Older. 2003.
55. Seloka MA, Matshipi M, Mphekgwana PM, Monyeki KD. Obesity indices to use for identifying metabolic syndrome among rural adults in south africa. Int J Environ Res Public Health. 2020 Nov 2;17(22):1–10.
56. Brunero S, Lamont S. Systematic screening for metabolic syndrome in consumers with severe mental illness. 2009;
57. Sales MC, Oliveira LP, Liberalino LCP, Cunha ATO, Sousa SES, Lemos TMAM, et al. Frequency of metabolic syndrome and associated factors in institutionalized elderly individuals. Clin Interv Aging. 2018;13:2453–64.
58. de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry [Internet]. 2016 Oct 3 [cited 2022 Apr 19];16(1). Available from: /pmc/articles/PMC5048618/
59. Zheng W, Li X bin, Tang YL, Xiang YQ, Wang CY, de Leon J. Metformin for Weight Gain and Metabolic Abnormalities Associated With Antipsychotic Treatment: Meta-Analysis of Randomized Placebo-Controlled Trials. J Clin Psychopharmacol [Internet]. 2015 Oct 12 [cited 2022 Apr 19];35(5):499–509. Available from: https://pubmed.ncbi.nlm.nih.gov/26280837/
60. Freund KM, Belanger AJ, D'Agostino RB, Kannel WB. The health risks of smoking. The Framingham Study: 34 years of follow-up. Ann Epidemiol. 1993 Jul;3(4):417–24.

61. Alswat KA, Alnemari AK, Alghamdi I, Almalki AA, Al-Thomali B, Mahfouz T. Prevalence of Metabolic Syndrome in the Hospitalized Psychiatric Patients. Med Arch. 2017 Dec 1;71(6):412–6.
62. Moreira FP, Jansen K, Cardoso TDA, Mondin TC, Magalhães P v., Kapczinski F, et al. Metabolic syndrome and psychiatric disorders: A population-based study. Revista Brasileira de Psiquiatria. 2019 Jan 1;41(1):38–43.
63. De Hert M, Schreurs V, Sweers K, Eyck D Van, 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. Vol. 101. 2008.

Appendices

Appendix A
Data Collection Tools

DEMOGRAPHICS						
Age	18-25	26-30	31-35	36-40	41-50	51-60
Marital Status	SINGLE	MARRIED	DIVORCED	WIDOWED	LONG-TERM PARTNER	UNKNOWN
Level of Education	NONE	SPECIAL NEEDS	GRADE 1-7	GRADE 8-12	TERTIARY	OTHER

DATE OF *ADMISSION:*						

LONGITUDINAL&FAMILY HISTORY					
Duration of Illness	First presentation	Less than 1 year	1-3 years	4-5 years	>5 years
Pre-admission AP exposure	Nil	Less than 1 year	1-3 years	4-5 years	>5 years
Cardiac Event (Myocardial infarct/Cerebrovascular accident CVA)	Yes	No	Unknown		
Family History of MetS	No	Yes, 1 component	Yes, 2 components	Yes, 3 components	More than 3 components

PHARMACOLOGICAL

TREATMENT

PSYCHIATRIC:							
ANTIPSYCHOTICS - ORAL	CLOZAPINE	OLANZAPINE	QUETIAPINE	RISPERIDONE	CHLORPROMAZINE	AMISULPIRIDE	HALOPERIDOL
ANTIPSYCHOTICS - DEPOT	ZUCLOPENTHIXOL DECANOATE	FLUPHENAZINE DECANOATE	RISPERDAL CONSTA	OTHER			
HORMONAL DEPOT	CRYPTOCERONE ACETATE	MEDROXY-PROGESTERONE ACETATE	OTHER				
DRUGS WITH MOOD STABILISING PROPERTIES	NA VALPRAOTE	LITHIUM	CARBAMAZEPINE	LAMOTRIGIENE	OTHER		
ANTIDEPRESSANTS	FLUOXETINE	CITALOPRAM	VENLAFAXINE	AMITRYPTILLINE	MIRTAZEPINE	OTHER	
SEDATIVE HYPNOTICS	DIAZEPAM	CLONAZEPAM	LORAZEPAM	OTHER			

COMMON CO-PRESCRIPTIONS	ORPHENADRINE	LACTULOSE	PROMETHAZINE	HYOSCINE			

NON-PSYCHIATRIC:						
HYPERTENSIVE	HCTZ	ENALAPRIL	ATENOLOL	AMLODIPINE	FUROSEMIDE	OTHER
DIABETIC	METFORMIN	GLIMEPIRIDE	INSULIN	OTHER		
LIPID-LOWERING	SIMVASTATIN	ATORVASTATIN	BEZAFIBRATE	OTHER		
ANTIPLATELET	ASPIRIN	CLOPIDOGREL	OTHER			
ARV TREATMENT	TDF/3TC/DTG	TDF/FTC/EFV	LPR/RTV+TDF/FTC	OTHER		
OTHER-SPECIFY						

DIAGNOSED CONDITIONS			
MEDICAL COMORBIDITIES	***FAMILIAL MEDICAL HX***	***PRIMARY PSYCHIATRIC DIAGNOSIS***	***COMORBID PSYCHIATRIC DIAGNOSIS***
HYPERTENSION	HYPERTENSION	SCHIZOPHRENIA	SUBSTANCE USE D/O
OBESITY	OBESITY	BIPOLAR D/O	PERSONALITY D/O
DIABETES MELLITUS TYPE2	DIABETES MELLITUS TYPE2	SCHIZOAFFECTIVE D/O	INTELLECTUAL DISABILITY
DYSLIPIDAEMIA	DYSLIPIDAEMIA	INTELLECTUAL DISABILITY	NEUROCOGNITIVE D/O
ASTHMA/COPD	ASTHMA/COPD	SUBSTANCE INDUCED D/O	ANXIETY D/O
ISCHAEMIC HEART DISEASE	ISCHAEMIC HEART DISEASE	MOOD/PSYCHOTIC D/O [2] ANOTHER MEDICAL CONDITION	OBSESSIVE COMPULSIVE D/O
HIV	HIV(VERTICAL	PERSONALITY D/O	

GOUT		OTHER MOOD D/O	
		NEUROCOGNITIVE D/O	

METABOLIC PARAMETERS			
WEIGHT (kg)		VALUE	
HEIGHT (cm)		VALUE	
BMI(CALCULATED) (kg/m2)		VALUE	NORMAL/OVERWEIGHT/OBESE
ABDOMINAL CIRC.(cm)		VALUE	NORMAL/ABNORMAL/NA
TOT CHOL(mmol/L)		VALUE	NORMAL/ABNORMAL/NA
HDL (mmol/L)		VALUE	NORMAL/ABNORMAL/NA
LDL (mmol/L)		VALUE	NORMAL/ABNORMAL/NA
TRIGLYCERDIDES (mmol/L)		VALUE	NORMAL/ABNORMAL/NA
FASTING GLUCOSE (mmol/L)		VALUE	NORMAL/ABNORMAL/NA
BLOOD PRESSURE (mm/Hg)		VALUE	NORMAL/ABNORMAL/NA
METABOLIC SYNDROME?		YES/NO	

Appendix B

Drug	Class	Sedation	Receptor/Tranporter								
			H_1	$5HT_{2A}$	$5HT_{2C}$	α_1	M	D_1	D_2	5HTT	NET
aripiprazole	atypical	+									
asenapine	atypical	+++									
chlorpromazine	typical	++++									
clozapine	atypical	++++									
fluphenazine	typical	+									
haloperidol	typical	++									
iloperidone	atypical	++									
loxapine	typical	++++									
lurasidone	atypical	++									
olanzapine	atypical	+++									
paliperidone	atypical	+									
perphenazine	typical	+++									
pimozide	typical	++									
quetiapine	atypical	+++									
risperidone	atypical	+++									
thioridazine	typical	++++									
thiothixene	typical	++									
trifluoperazine	typical	+									
ziprasidone	atypical	++									

Affinity

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