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A retrospective review of state sector outpatients (Tara Hospital) prescribed olanzapine: adherence to metabolic and cardiovascular screening and monitoring guidelines

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A retrospective review of state sector outpatients (Tara Hospital) prescribed olanzapine: - adherence to metabolic and cardiovascular screening and monitoring guidelines.

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A research report submitted to the Faculty of Medicine, University of the Witwatersrand Medical School, Johannesburg, in partial fulfilment of the requirements for the degree Masters of Medicine in the branch of Psychiatry.

Johannesburg
2010

Declaration

I, Carina Marsay, declare that this research report is my own work. It is being submitted as partial fulfilment for the degree of Master of Medicine in the branch of Psychiatry, Faculty of Health Sciences, University of Witwatersrand, Johannesburg.

It has not been submitted for any degree or examination at this or any other University.

Signature: C Marsay

Date: 25/10/10

ii

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Abstract

Introduction

Antipsychotics are used for the treatment of psychotic disorders, most commonly schizophrenia, as well as mood disorders e.g. bipolar mood d isorder. The efficacy of the newer second generation (atypical) antipsychotics is equivalent to first generation antipsychotics. The apparent advantage of the second generation antipsychotics is related to their purported reduced side effect profile, thus making them more desirable due to improved compliance and relapse prevention. The limiting factor with this class of drugs, especially in the state sector in South Africa, has been the cost. However, reports of treatment-emergent adverse events such as diabetes mellitus, diabetic ketoacidosis, hyperglycaemia and dyslipidaemia in patients receiving second generation antipsychotics have increased in recent times. This has lead to growing concern about the link between metabolic complications and their use, with consequent reconsideration of the implications of prescribing.

Aims

The study aimed to establish the extent to which metabolic and cardiovascular screening and monitoring has been undertaken on patients who have been prescribed olanzapine, a second generation antipsychotic. Specifically the extent to which the American Diabetes Association Consensus Conference monitoring protocols were being implemented in a specialist psychiatric South African setting i.e.: at Tara: The H. Moross Centre's outpatient department.

Objectives

The study objectives were to describe the demographic profile, clinical diagnosis and risk factors for metabolic complications in a sample of patients receiving olanzapine. Further, to establish the extent to which metabolic and cardiovascular screening and monitoring has been undertaken on patients prescribed olanzapine as well as to what extent the patients's demographics, diagnosis and metabolic risk factors influenced the treating doctor's adherence to screening guidelines.

Method

This study was undertaken at Tara: The H. Moross Centre (outpatient department). A convenience sample of patients prescribed olanzapine were selected as the study group. The study involved a review of case records. It was a retrospective descriptive study. Relevant data was entered on a data sheet, designed for the study in accordance with the objectives and adapted from the American Diabetes Association Consensus Development Conference on Antipsychotic Drugs, Obesity and Diabetes. The data sheet is based on an existing protocol for monitoring metabolic status.

Frequencies for the presence or absence of evidence of screening or monitoring for metabolic complications were established, as per American Diabetes Association monitoring protocol requirements. Although the study involved outpatients, not all patients were intiated on olanzapine as outpatients i.e. some of the prescribing was inpatient initiated.

Results

The sample comprised of 19 females and 20 males. 48.72% female and 51.28% male. The mean age of females in the sample was 52.38 years (SD=16.20) and the mean age of males was 41.28 (SD=17.05) years. The sample were predominantly single (61.54% n=24) with the majority being white (79.49% n=31); most had either tertiarty (43% n=17) or secondary (53.85% n =21) level of education. Only 2.56% (n=1) had only primary level education. With regards to the diagnoses of patients in the sample, 17,95% (n=7) were diagnosed with bipolar 1 disorder, 7.69% (n=3) with major depressive disorder with psychosis, 20,51% (n=8) schizoaffective disorder and 53,84% (n=21) with schizophrenia. The percentage of screening for all the parameters was generally less than 20% and it continued to decline to less than 20% until 4 months. The exception was weight, where frequency increased slightly over time. Comparing inpatient vesus outpatient initiated treatment there were apparent differences in the extent of screening i.e. greater for inpatient initiated treatment, specifically with respect to weight and blood pressure.

Conclusion

The current study was conducted in a very specific setting, but the findings demonstrated an area requiring attention i.e. adherence to acceptable clinical guidelines. Whilst one can only speculate on the basis for non-adherence, having established the status quo, there is a requirement for an appropriate strategy to address the deficit, given the implications of inadequate monitoring.

Table of Contents

Declaration ii
Acknowledgements iii
Abstract iv
Table of Contents vi
Table of Tables viii
Literature Review 1
Introduction 1
Metabolic complications in patients prescribed olanzapine 2
Metabolic syndrome 3
Implications of Metabolic Syndrome 7
Implications for people with mental illness 7
Monitoring for Metabolic Syndrome 8
Implimentation of Guidelines 9
Association between olanzapine and demographics 10
Methods 11
Setting 11
Sample 11
Measures 11
Procedure 12
Analysis 12
Ethics 13
Results 14
Demographic profile 14
Diagnostic profile 16
Risk factors 16
Patient group 17
Screening 18
Number of screenings in each time period 25
Variables associated with screening 25
Discussion 26
Demographic profile 26
Risk factors 27
Patient group 27
Screening 27
Adherence to guidelines 28
Limitations 29
Conclusion 30
References 31
Appendix A 34
Appendix B 37
Appendix C 39

Table of Figures

Figure 1: Frequency of screening – outpatient initiated treatment (n=16)..... 18
Figure 2: Frequency of screening – inpatient initiated treatment (n=23)..... 19
Figure 3: Comparing inpatient versus outpatient initiated treatment screening of blood pressure 20
Figure 4: Comparing inpatient versus outpatient initiated treatment screening of weight 21
Figure 5: Comparing inpatient versus outpatient initiated treatment screening of glucose 22
Figure 6: Comparing inpatient versus outpatient initiated treatment screening of cholesterol 23
Figure 7: Comparing inpatient versus outpatient initiated treatment screening of lipid studies..... 24
Figure 8 : Number of screenings in each time period..... 25

Table of Tables

Table 1: Demographic characteristics of patients in the sample (N = 39) 15
Table 2: Diagnosis of patients in the sample (N= 39)..... 16
Table 3: Risk factors of patients in the sample (N=39)..... 16
Table 4: Patient group in the sample (N= 39) 17
Table 5: Variables associated with screening – p values 25

Literature Review

Introduction

Antipsychotics are used for the treatment of psychotic disorders, most commonly schizophrenia, as well as mood disorders such as bipolar mood disorder. Second generation antipsychotics (SGAs) e.g. risperidone and olanzapine are newer drugs whose development has followed that of their predecessors, the typical or first generation antipsychotics e.g. haloperidol, trifluoperazine. The main difference between these 2 classes is that second generation antipsychotics have prominent antagonism at the serotonin 2A receptor as well as dopamine D2 receptor blockade. Thus, these are serotonin-dopamine antagonists. The ratio of serotonin to dopamine blockade is generally higher for these agents and they appear to be more selective for the mesolimbic dopamine pathway, which is thought to be important in mediating antipsychotic action. SGAs have relatively less action on the nigrostriatal pathway thereby minimising extrapyramidal side effects. These drugs have a therapeutic dose range that allows for the antipsychotic effect without inducing significant extrapyramidal side effects. [1]

In essence, the advantage of these drugs lies predominantly in their apparent reduced side effect profile, specifically fewer extrapyramidal side effects, rendering them more desirable and potentially improving compliance and thus contributing to relapse prevention. However it is important to be aware that SGA's cannot be classified as a homogenous class and each drug has a individual side effect profile.[2] Their efficacy is the same as for typical antipsychotics. The limiting factor with this class of drugs, especially in the state sector in South Africa, is the acqusition cost.[3] They are more expensive and therefore are not extensively available due to budget constraints.

Reports of treatment-emergent adverse events such as diabetes mellitus, diabetic ketoacidosis, hyperglycaemia and dyslipidaemia in patients receiving second generation antipsychotic agents have increased in recent times. This has led to growing concern about the link between metabolic complications and SGA use. [4] People with mental illness already have an increased risk of cardiovascular disease.[5] This is due to a higher association of obesity, smoking, diabetes, hypertension and dyslipideaia.[5] Lifestyle factors such as poor diet, sedentary lifestyle and stress also contribute to this higher risk.[6]

It has been recognised that the incidence of metabolic syndrome in psychiatric patients is increasing.[4] It is important for prescribing doctors to be aware and vigilant of this risk in order to prevent and manage it adequately.[7] However, there is a lack of vigilance regarding monitoring and treatment of these patients among the medical community . It is felt that perhaps psychiatrists have a poor understanding of metabolic syndrome and are unsure about monitoring, diagnostic and treatment protocols.[5] Another

factor that could contribute to this problem is that, in general, psychiatric clinics and hospitals are poorly equipped to handle any physical problems. For example limited choices of medication to treat general medical conditions.[8] Psychiatric patients face numerous barriers with regard to access and quality of medical care.[9]

Based on the awareness of metabolic consequences of prescribing SGAs, protocols, such as those arising from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, have been formulated for monitoring metabolic status.[5]

Metabolic complications in patients prescribed olanzapine

Olanzapine

Olanzapine was the third second generation antipsychotic to be developed. It was introduced in 1996 and since then has been a popular choice of antipsychotic. The link between diabetes, hyperglycaemia, lipid dysregulation and olanzapine has been extensively explored.[4]

Olanzapine and weight

Olanzapine has been shown to be responsible for both short term and long term weight gain. According to the manufacturer 29% of patients taking olanzapine for a period of 6 weeks will observe weight gain. A large meta-analysis reported weight gain at an average of 4 kg over 10 weeks in the short term, or in the long term as an average of 10kg over 28 weeks. Most weight gain occurs in the first year of commencing the drug and is due to an increase in fat mass/ body fat.[4] The mechanism of weight gain is insulin resistance, and is not affected by the dose of the drug.[10]

Olanzapine and Diabetes

The FDA MedWatch Drug Surveillance System is one of the main systems responsible for studies and reports that show a significant link between olanzapine and diabetes or hyperglycaemia.[4] There was a relationship between initiation of olanzapine therapy and the development of diabetes/hyperglycaemia. This relationship was reversible on discontinuation of olanzapine treatment. 80% of patients had improved glycaemic control after stopping treatment. About half of the newly diagnosed diabetes occurred within 3 months of starting treatment. 70% occurred within 6 months.[4] The MedWatch study also reported a significant number of cases of diabetic ketoacidosis.[11] 34.6% of the cases of hyperglycaemia reported by the MedWatch study were associated with metabolic acidosis or ketoacidosis. Ketosis or acidosis was reported in 9 of the deaths in the MedWatch study.[11] Therefore >10% of the cases of diabetic ketoacidosis were associated with patient death. An increase in plasma insulin levels is documented with olanzapine. This increase causes a reduction in insulin sensitivity.

This increased risk of diabetes is strongly related to increased adiposity which occurs as a result of the weight gain.[4]

Olanzapine and Hyperlipidaemia

There is consistent evidence that olanzapine has adverse effects on plasma lipids, specifically plasma triglycerides.[4] This correlates with the effects of increasing abdominal fat mass on insulin sensitivity and lipid metabolism. An analysis of data from the UK General Practice Research Database shows a statistically significant increase in the risk of hyperlipidaemia with olanzapine as compared with patients on either typical antipsychotics or no antipsychotic treatment.[12]

There was also a significant increase in triglycerides from pre-treatment levels with olanzapine. Elevated triglyceride levels are an independent risk factor for cardiovascular disease, as well as, appearing to contribute towards diabetes.[13]

There is a statistically significant relationship between weight gain and elevated triglyceride levels. Increased cholesterol levels are also associated with weight gain and BMI in patients treated with olanzapine.[4]

Given the aforementioned data, it is clear that olanzapine is associated with a range of side effects that may impact on physical health. Specifically, that olanzapine may place patients at risk for metabolic syndrome.[4]

Metabolic syndrome

Metabolic syndrome has assumed increasing significance. Whilst a number of definitions exist, there is some consensus on the following constellation of metabolic abnormalities that result in metabolic syndrome:- [14]

- centrally distributed obesity
- decreased high-density lipoprotein cholesterol (HDL-C)
- elevated blood pressure
- hyperglycaemia

These abnormalities are cause for concern as they all contribute to cardiovascular morbidity and mortality.[5] Therefore, it is important to screen for these abnormalities so that effective treatment or preventative measures can be instituted, thus decreasing the risk of cardiovascular disease and thereby improving quality and quantity of life. In an attempt to achieve this, definitions have been formulated by various groups including the World Health Organisation (WHO); European group for the study of insulin resistance (EGIR); National Cholesterol Education Program of the USA and the International Diabetes Federation (IFD).[15]

World Health Organisation (WHO)

This was the first attempt at a global definition for metabolic syndrome. It was published in 1999 and comprised:- [14]

Diabetes or impaired glucose tolerance or insulin resistance.

Plus 2 of the following

- Obesity: BMI >30kg/m2 or
    - WHR>0.9 (male) or >0.85(female)
- Dyslipidaemia
    - Triglycerides >= 150mg/dl (1.7mmol/l)
    - or HDL-C <35mg/dl (0.9mmol/l)-male <39mg/dl(1.0mmol/m)-female
- Hypertension
    - BP >= 140/90 mmHg or on medication
- Microalbuminuria
    - albumin excretion >= 20Ug/min or albumin:creatinine ratio >= 30mg/g

The limitation of this definition is the need to use a of euglycaemic clamp to measure insulin sensitivity, thus making it difficult to use in clinical practice and epidemiological studies.[14]

European group for the study of insulin resistance (EGIR)

EGIR modified the WHO definition to use fasting glucose instead of microalbuminia. Whilst they felt that insulin resistance was the underlying cause of metabolic syndrome, they restricted the definition and only included those in whom insulin resistance could easily be measured.[14]

Insulin resistance or hyperinsulineamia (only in non-diabetic subjects)

Plus 2 or more of the following

- Central obesity:
    - Waist circumference >= 94cm (male); >= 80cm (female)
- Dyslipidaemia
    - Triglycerides > 177mg/dl (2.0mmol/l) or HDL-C < 39mg/dl (1.0mmol/l)
- Hypertension:
    - BP >= 140/90 mmHg or on medication
- Fasting blood glucose:

- >= 110mg/dl (6.1mmol/l)

The problem with this definition (EGIR) is that people with diabetes were excluded from the definition. The reason being that beta-cell dysfunction in type 2 diabetes makes the estimates of insulin sensitivity unreliable.[14]

National Cholesterol Education Program of the USA (Adult Treatment Panel III definition; ATP III)

Two years later, in 2001, the National Cholesterol Education Program of the USA introduced the ATP III definition. This definition was designed to be more useful for clinical practice. It does not measure insulin resistance and treats all components with equal importance. This has been the most popular definition because all of the components are easily measured in both clinical and research settings.[14] The definition is:-

Three or more of the following:-

- Central obesity:
    - Waist circumferences>102cm(male); >88cm (female)
- Hypertriglyceridaemia
    - Triglycerides >= 150mg/dl (1.7mmol/l)
    - Low HDL-C <40mg/dl (1.03mmol/l)-male, <50mg/dl (1.29mmol/l)-female
- Hypertension
    - BP>=130/85mmHg or on medication
- Fasting plasma glucose
    - >= 110mg/dl (6.1mmol/l)

As opposed to the WHO and EGIR definitions there is no threshold of criteria required to qualify for a diagnosis.

International Diabetes Federation (IDF)

In 2005 the IFD developed an even more practical definition. They felt that a globally applicable solution was needed to identify people at high risk for cardiovascular disease and diabetes. A consensus group was formed including representatives from organisations who had contributed to previous definitions. Their approach emphasized central obesity as a critical component.[14] The following criteria were proposed:-

- Central obesity
    - waist circumference - ethnicity specific *

- plus any 2 of the following
- Raised Triglycerides
    - >= 150mg/dl (1.7mmol/l) or specific treatment for lipid abnormalities
- Reduced HDL-Cholesterol
    - < 40mg/dl (1.03mmol/l) in males
    - <50mg/dl (1.29mmol/l) in females
    - or specific treatment for this lipid abnormality
- Raised blood pressure
    - systolic >= 130mmHg
    - diastolic >= 85mmHg
    - or treatment of previously diagnosed hypertension.
- Raised fasting plasma glucose
    - fasting plasma glucose >=mg/dl (5.6mmol/l) or previously diagnosed type 2 diabetes
    - if above 5.6mmol/l or 100mg/dl, Oral Glucose Tolerance Test is strongly recommended but is not necessary to define presence of the syndrome.

- Ethnic group Waist circumference
    - Europids male>=94cm; female>=80cm
    - South Asians male>=90cm; female>=80cm
    - Chinese male>=90cm; female>=80cm
    - Japanese male>=85cm; female>=90cm

(Sub-Saharan Africans; South and Central Americans; Eastern Mediterranean and Middle East - use European data until more specific data is available.) [14]

The prevalence rates of metabolic syndrome vary using the different diagnostic criteria as follows :-[15]
IDF: 22.3%
ATP III: 22.6%
WHO: 15.4%

Whilst it can be expected that in the general population 22.3% of people will have metabolic syndrome,[14] this will differ from population to population. For example, the prevalence rate in the US is estimated at 20-30%; 30-40% among urbanised Indians. 30% of Iranians, 20% of Greeks and 17% in Italians.[5]

Implications of Metabolic Syndrome

Metabolic syndrome increases the risk of developing diabetes and cardiovascular disease which can result in myocardial infarction and stroke. Even the presence of one of the defined metabolic abnormalities, increases the risk of cardiovascular disease. The risk increases proportionately with increased number of metabolic abnormalities. In a recent study of patients with existing vascular disease, the presence of metabolic syndrome was associated with advanced vascular damage measured by: carotid intima media thickness, ankle-brachial pressure index and albuminuria. A higher number of abnormal metabolic components were also associated with an increase in the advanced vascular damage indicators.[5]

Implications for people with mental illness

The prevalence of obesity and diabetes in individuals with schizophrenia and affective disorders is about 1.5-2 times higher than the general population.[5] Therefore one should consider it an independent risk factor for metabolic syndrome. People with mental illness already have an increased risk of cardiovascular disease. This is due to a higher prevalence of obesity, smoking, diabetes, hypertension and dyslipidaemia. Lifestyle factors also contributed to this higher risk.[5]

Other factors that may predispose to metabolic syndrome in the mentally ill include[16,17] :

- poor diet
- lack of exercise
- smoking
- substance abuse
- stress
- medication that causes weight gain
- adherence to prescribed medication
- financial hardship
- symptoms resulting in poor self esteem and lack of motivation
- limited availability and co-ordination of medical care

Psychiatric disease itself can lead to changes in energy intake and expenditure. This is as a result of changes in sleeping and eating patterns as well as a change in day to day activities.[18] Individuals with schizophrenia are more likely to have an unhealthy lifestyle than the general population. There is some evidence to suggest that patients with schizophrenia have more visceral adiposity than healthy individuals. However, this is not a universal observation. It is a well supported theory that visceral fat deposition is linked to insulin resistance. Another contributing factor is smoking. It is very common in

patients with schizophrenia and effectively increases insulin resistance.[18] It is estimated that 75% of patients with schizophrenia are smokers.[4]

It has become clear that psychiatric patients are at increased risk of developing metabolic syndrome. It is important that this risk is agknowledged and managed by medical professionals. Psychiatric patients face numerous barriers with regard to access and quality of medical care.[9] They especially receive poorer care for chronic conditions such as heart disease and diabetes.[19] This leads to an increased risk of premature death.[19] The key issue of adressing mentally ill patient's physical needs needs to be given priority.[20]

Monitoring for Metabolic Syndrome

Visceral adiposity has a direct association with dyslipidaemia and glucose intolerance. Therefore weight gain seems to be the root cause of the metabolic complications associated with the use of second generation antipsychotics. Knowing this, we can appreciate the importance of regular charting of weight as an important tool in the monitoring of patients on second generation antipsychotics.

At the consensus development conference on antipsychotic drugs and obesity and diabetes, the panel recommended that both baseline and follow-up monitoring should be done at baseline and then reassessed at 4, 8 and 12 weeks after the commencement of the second generation antipsychotics. They considered the following parameters to be most important for screening.

- Personal and family history of obesity, diabetes, dyslipidaemia, hypertension, or cardiovascular disease.
- BMI, which requires weight and height.
- Waist circumference
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile [21]

If weight gain is > 5% of the patient's initial weight at any point during the treatment; it is recommend that treatment be changed to another appropriate antipsychotic even if they have become apsychotic and are well on treatment. Blood pressure, fasting glucose and fasting lipid profile should be reassessed at 12 weeks. At one year the personal history, waist circumference, blood pressure, fasting plasma glucose should be reassessed. The lipid profile should be done every 5 years.[21]

If any abnormalities are noted, the panel recommends that appropriate treatment, for metabolic syndrome is initiated. Psychiatrists must also not hesitate to refer patients to specialist physicians. The panel also emphasised the importance of good nutrition and physical activity to help combat any metabolic complications.[21]

Implimentation of Guidelines

Sernyak, noted that the main conclusion of the Consensus Development Conference, which led to the relevent guidelines, was that psychiatrists need to pay more attention to patients' physical needs and monitor for the metabolic effects of second generation antipsychotics.[22] A study to evaluate the implementation of the guidelines was undertaken. Before the guidelines were released 7.8% of patients had their lipids tested at baseline. After the guidelines were released only 8.5% had lipids tested at baseline.[23] In the international setting, guideline publication appears not to have influenced clinical practice. Guidelines do have many benefits. They inform doctors of evidence based practices thereby striving to minimise inadequate practices as well as standardise practices. They can be useful in enabling the professional to evaluate what they are doing.[23] Clearly they do not always succeed.

It has been proposed that in order to improve patient care clinicians should:-[22]

- Encourage a culture of healthy lifestyle in patients with mental illness. This may include visits to a dietician, or even healthy eating groups run by dietician.

- Implement exercise programs

- Routinely monitor weight

- Build awareness of guidelines among patients and professionals

- Implement electronic record keeping with automated prompts regarding monitoring of key indicators of health.

- Establish who is going to be responsible for the monitoring, as opposed to just co-ordinating patient care.

Association between olanzapine and demographics

A study by Wang et al identified factors associated with being prescribed one of the newer generation antipsychotics like olanzapine to include being elderly, having more education and being white.[24] Socioeconomic status and access to prescription benefits did not significantly alter the findings of Wang et al regarding the lower likelihood of non-white patients and patients of lower education levels to be given newer generation antipsychotics.[24]
This suggests that the demographic profile of patients influences the prescribing patterns of doctors. The question must therefore be asked if the demographic profile influences the adherence of doctors to monitoring guidelines for cardiovascular and metabolic side effects.

In summary, olanzapine is a widely prescribed second generation antipsychotic that can lead to metabolic syndrome which has serious implications for the patient. Second generation antipsychotic drugs are not a homogeneous class, and differ from each other in many ways.[2] The risk for metabolic syndrome is significantly higher with olanzapine than other second generation antipsychotics.[4] It is neccessary for prescribing doctors to be aware of this risk in order to prevent it; and/or manage it appropriately.[7] Guidelines such as those arising from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, have been formulated for monitoring metabolic status.[21] The current study aimed to establish the extent to which metabolic and cardiovascular screening and monitoring has been undertaken on patients who have been prescribed olanzapine in a specific setting. The hypothesis was that screening was suboptimal (i.e. less than 100%).

The study objectives were:-

- To describe the demographic profile, clinical diagnosis and risk factors for metabolic complications in a sample of patients receiving olanzapine.
- To establish the extent to which metabolic and cardiovascular screening and monitoring has been undertaken on patients prescribed olanzapine.
- To determine to what extent the patients's demographics, diagnosis and metabolic risk factors influence the treating doctor's adherence to screening guidelines.

Methods

Setting

The study was a cross sectional, retrospective descriptive study involving review of case records. It was undertaken in the outpatient department of Tara: The H. Moross Centre, a specialist psychiatric hospital, located in the greater Johannesburg area and affiliated to the Division of Psychiatry in the Faculty of Health Sciences at the University of the Witwatersrand. A convenience sample of all patients who had been prescribed olanzapine during 2008 between January and March were selected. Olanzapine was chosen not only as it is one of the most widely prescribed second generation antipsychotic drugs in this setting, but also because it is associated with increased weight gain, insulin resistance, hyperglycaemia and diabetes mellitus. These risks are significantly higher for olanzapine than for any other second generation antipsychotic.[4] It has been suggested that the metabolic consequences of olanzapine should be considered by clinicians before prescribing it.[7]

Sample

The initial acquisition of the sample commenced in the outpatient department. There were two groups of patients, those who commenced olanzapine as outpatients (n=16), and those who commenced as inpatients (n=23).

Once the latter group (those commenced on olanzapine as inpatients) had been identified, it was necessary to review their inpatient files. This was necessary in order to establish the exact date of starting olanzapine and also to document any screening that may have occured as an inpatient. The data was collected using the same data capture sheet for either group. It was decided to compare and separate these groups as to get a more accurate account of the screening process, that was free from confouding variables.

Measures

The data capturing sheet (Appendix A) was based on the metabolic and cardiovascular screening instrument developed by Pfizer for patients receiving second generation antipsychotics and is used to determine the extent to which metabolic status is being monitored (Appendix B). This screening and monitoring instrument was adapted from the American Diabetes Association Consensus Development Conference on Antipsychotic Drugs, Obesity and Diabetes. It is based on an existing protocol for monitoring metabolic status.[21] Included in the data capture sheet was information about the patients demographic details (gender/age/educational level/socioeconomic status), diagnosis, risk factors for metabolic syndrome and any existing, contributing medical problems as well as which patient group

they belonged to (inpatient initiated or outpatient initiated)

Procedure

The screening variables of *body mass index*, *waist circumference* and *finger prick glucose test (HGT),* were not included in the results as there was no data for these variables. The screening variables; *blood pressure; formal glucose; weight; cholesterol and lipids* were grouped into time periods. i.e. up to 4 months (initial), 4 months to 1 year (intermediate) and more than one year (long term). These time frames were chosen as they reflect the frequency at which screening should occur i.e. up to 4 months, screening is done monthly; from 4 months to 1 year screening is done 4 monthly; and after 1 year, screening is done annually. If the guideline was being accurately followed the percentage of screening would be 100%. After the 4 month time period (initial), the paucity of data made it unhelpful to continue to calculate the percentage screening for each variable. However the number of times any screening test was done in the specific time period (initial, intermediate, long term) was determined. Other descriptive variables such as family history of medical illness, date of diagnosis of medical illness were not included in the analysis as the data collection revealled no information for these variables.

Analysis

Descriptive statistics were used to describe the sample in terms of: *age*; *gender; race; marital status; highest level of education; hospital classification; diagnosis; risk factors and patient group.* Frequencies for these variables were calculated.

The frequency of screening for each variable during the initial time period was noted as per the guideline and reflected as a percentage of screening for each variable at each time point. i.e. total number of patients screened/total number of patients. Inpatient and outpatient initiated treatment data was then compared for the initial time peroid only. The number of times a screening test was done in each specific time period (initial, intermediate, long term) was also determined.

Using Statisica, a computerised statisical program the following variables *(gender; race; marital status; highest level of education; hospital classification; diagnosis; gender and patient group)* were analysed for normal distribution. Only *diagnosis, gender* and *patient group* were normally distributed. Screenings in each time period were studied in relation to the diagnosis, gender and patient group (inpatient or outpatient initiated) using the Fisher exact test, to ascertian whether any of these descriptive variables influenced the treating doctor's adherence to screening guidelines.

Ethics

The protocol for this study was approved by the Human Research Ethics Committee at the University of the Witwaterand (protocol number M 070446). No identifying information appeared on the data capture sheet. Each entry of data was coded with a number that was cross referenced to the patient's hospital number. The researcher was the only one with access to this list. This ensured that data could be checked should the need have arisen. (Appendix C)

Results

Demographic profile

The sample comprised of 19 females and 20 males. (48.72% female and 51.28% male). The mean age of females in the sample was 52.38 years (SD=16.20) and the mean age of males was 41.28 (SD=17.05) years. The sample were predominantly single (61.54% n=24) with the majority being white (79.49% n=31); most had either tertiary (43% n=17) or secondary (53.85% n =21) level of education. Only 2.56% (n=1) had only primary level education. The majority of patients (84.62% n=33) in this sample were classified as H1 patients. H1 refers to patients with an individual income of less than R36 000 per annum or a household income of less than R50 000 per annum. It is also used as a default classification for those patients without any income. Patients classified as H2 have an indivdual income of less than R72 000 per annum or a household income of less than R100 000 per annum. H3 patients have an indivdual income greater than R72 000 per annum or a household income of greater than R100 000 per annum. Patients classified as P, are patients who are externally funded or are being treated by a private practioner in a public hospital. This catergory also includes certain foreign nationals. These classifications are stipulated by the National Depaertment of Health. (Table 1)

Table 1: Demographic characteristics of patients in the sample (N = 39)

Gender	N	%
Female	19	48.72
Male	20	51.28
Race		
Black	5	12.82
Coloured	2	5.13
Indian	1	2.56
White	31	79.49
Marital status		
Divorced	4	10.26
Married	8	20.51
Single	24	61.54
Widowed	3	7.69
Highest level of education		
Primary	1	2.56
Secondary	21	53.85
Tertiary	17	43.59
Hospital classification		
H1	33	84.62
H2	2	5.13
H3	1	2.56
P	3	7.69

Diagnostic profile

With regards to the diagnoses of patients in the sample, 17,95% (n=7) were diagnosed with bipolar 1 disorder, 7,69% (n=3) with major depressive disorder with psychosis, 20,51% (n=8) schizoaffective disorder and 53,84% (n=21) with schizophrenia. (Table 2)

Table 2: Diagnosis of patients in the sample (N= 39)

Diagnosis	N	%
Bipolar 1 disorder	7	17.95
MDD with Psychosis	3	7.69
Schizoaffective	8	20.51
Schizophrenia	21	53.84

Risk factors

In 35.9%; (n=14) of the sample, no risk factors were documented. 15.38% (n=6) were documented as having no risk factors. Specific risk factors were as follows; 10,26% (n=4) with hypertension, 5,13% (n=2) with diabetes, 2,56% (n=1) with hyperlipidaemia, 5,13% (n=2) with obesity, 20,51% (n=8) were smokers. 5.13% (n=2) had multiple risk factors documented. None of the sample had cardiovascular disease as a risk factor. (Table 3). There was no information as to the date of diagnosis of non-psychiatric illness.

Table 3: Risk factors of patients in the sample (N=39)

Risk factors	N	%
Hypertension	4	10.26
Diabetes	2	5.13
Hyperlipidaemia	1	2.56
CVS disease	0	0
Obesity	2	5.13
Smoking	8	20.51
Not documented	14	35.90
Nil	6	15.38
Multiple*	2	5.13

* one patient with hypertension and hyperlipideamia
the other with hypertention, hyperlipideamia and smoking

Patient group

The total number of patients in the sample was 39. Of this; 41% (n=16) were initiated on olazapine as outpatients and 59% (n=23) were initiated on olanzapine as inpatients. (Table 4)

Table 4: Patient group in the sample (N= 39)

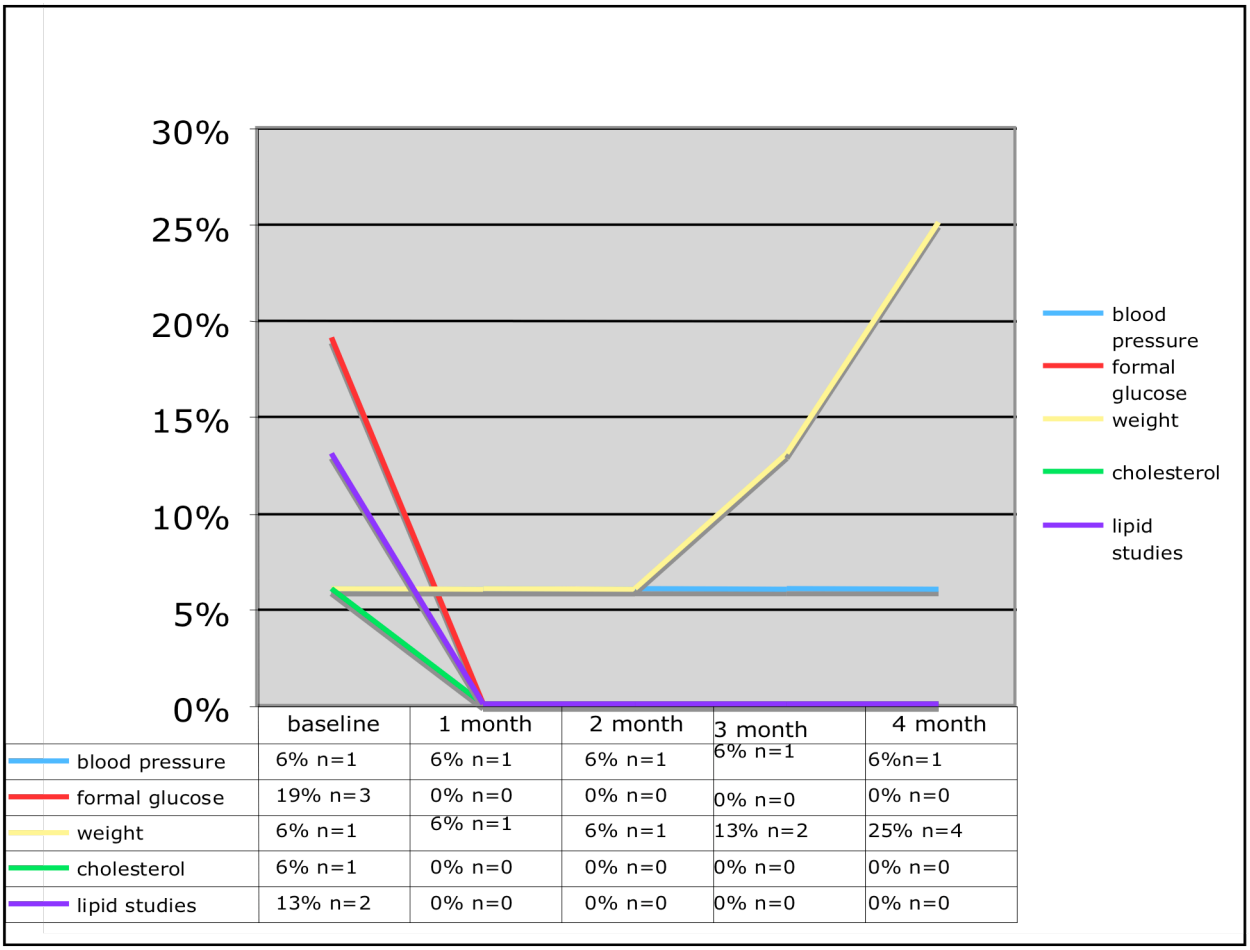
Patient group	N	%
Inpatient initiated	23	58.97
Outpatient initiated	16	41.03

Screening

The screening variables of *body mass index*, *waist circumference* and *finger prick glucose test (HGT),* were not included in the results as there was no data for these variables. This means that screening using these variables either was not undertaken or undertaken but not recorded.

At baseline, all screening variables for outpatient initiated treatment were less than 20% of the expected i.e. 100%. Gluocose testing was most frequently done at 19%, followed by lipid studies at 13% and weight, cholesterol and blood pressure at 6%. Formal glucose, lipid studies and cholesterol were not recorded again after 1 month. At 2 months only blood pressure (6%) and weight (6%) were recorded. Between 2 and 4 months the screening of weight increased to 25%, but that of blood pressure remained constant at 6%. (Figure 1)

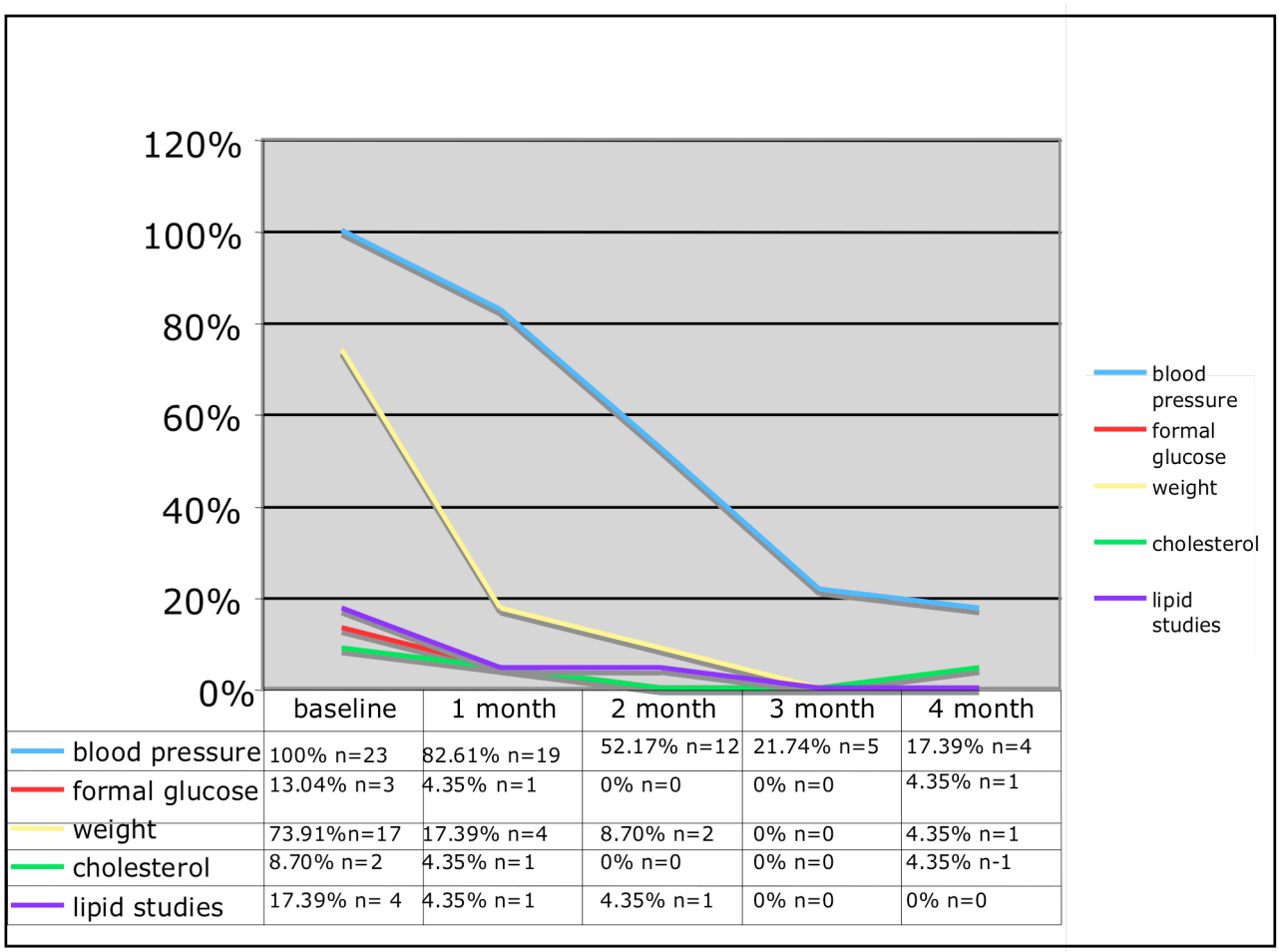
Figure 1: Frequency of screening – outpatient initiated treatment (n=16)



	baseline	1 month	2 month	3 month	4 month
blood pressure	6% n=1	6% n=1	6% n=1	6% n=1	6%n=1
formal glucose	19% n=3	0% n=0	0% n=0	0% n=0	0% n=0
weight	6% n=1	6% n=1	6% n=1	13% n=2	25% n=4
cholesterol	6% n=1	0% n=0	0% n=0	0% n=0	0% n=0
lipid studies	13% n=2	0% n=0	0% n=0	0% n=0	0% n=0

The range of screening for inpatient initiated treatment for the relevant screening variables differed to those for outpatient initiated treatment. In general there was a higher level of screening, although it declined over time. Blood pressure (100%), then weight (73.91%) were most frequently assessed at baseline followed by lipid studies (21,74%), glucose (13,04%) and cholestrol (8,7%) levels. For all varaibles measured, the trend was for screening to decline over time. At 2 months only 3 parameters, blood pressure (52,17%), weight (8,70%) and lipid studies (4,35%) were screened. At 3 months only blood pressure (21,74%) was screened. At 4 months there was an increase in screening of weight, glucose and cholesterol, all having a frequency of 4,35%. Blood pressure screening continued to decline to 17,39%. (Figure 2)

Figure 2: Frequency of screening – inpatient initiated treatment (n=23)



	baseline	1 month	2 month	3 month	4 month
blood pressure	100% n=23	82.61% n=19	52.17% n=12	21.74% n=5	17.39% n=4
formal glucose	13.04% n=3	4.35% n=1	0% n=0	0% n=0	4.35% n=1
weight	73.91%n=17	17.39% n=4	8.70% n=2	0% n=0	4.35% n=1
cholesterol	8.70% n=2	4.35% n=1	0% n=0	0% n=0	4.35% n-1
lipid studies	17.39% n= 4	4.35% n=1	4.35% n=1	0% n=0	0% n=0

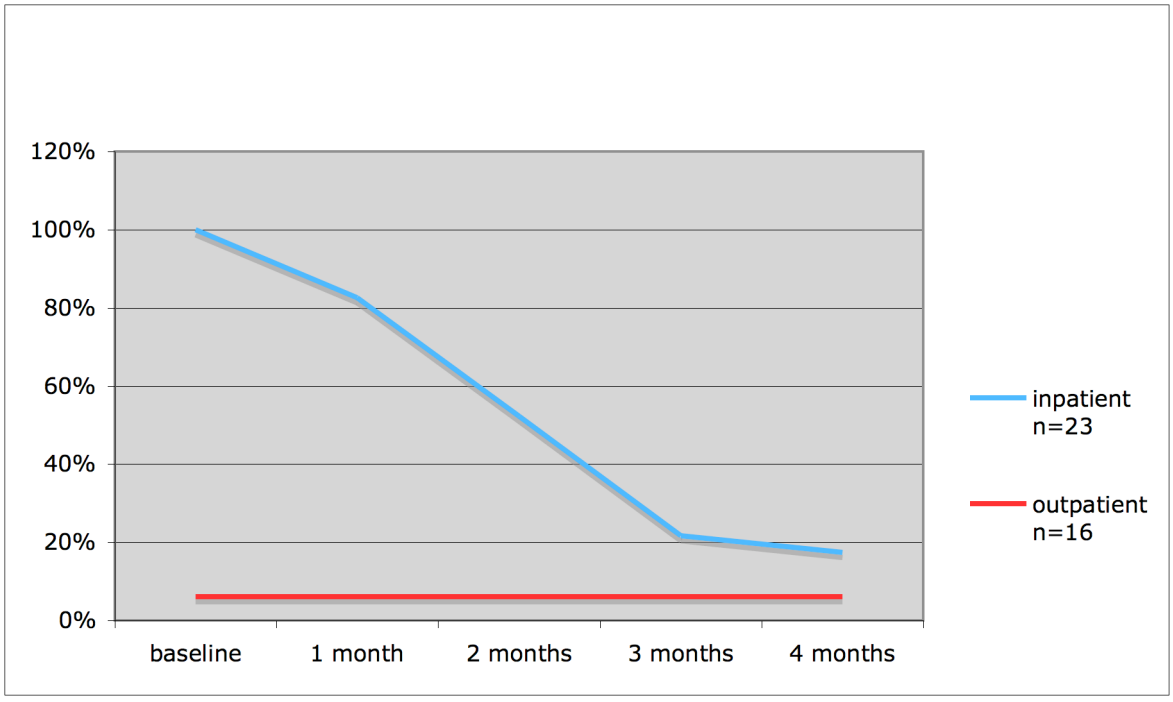
Comparing inpatient versus outpatient initiated treatment for each variable (Figures 3-7) there were apparent differences in the extent of screening. In general, screening was greater for inpatient initiated treatment then outpatient initiated treatment. It must be noted that inpatients follow-up as outpatients after discharge, thus over time screening is underaken as an outpatient, but for the purposes of this study such screening was not noted separately.

Specific parameters

(i)Blood pressure

Figure 3 shows a much greater frequency of screening for blood pressure among inpatient initiated treatment. At baseline 100% of patients were screened, however screening then decreased to 17.39% by 4 months. Outpatient initiaited screening of blood pressure remains constant at 6%

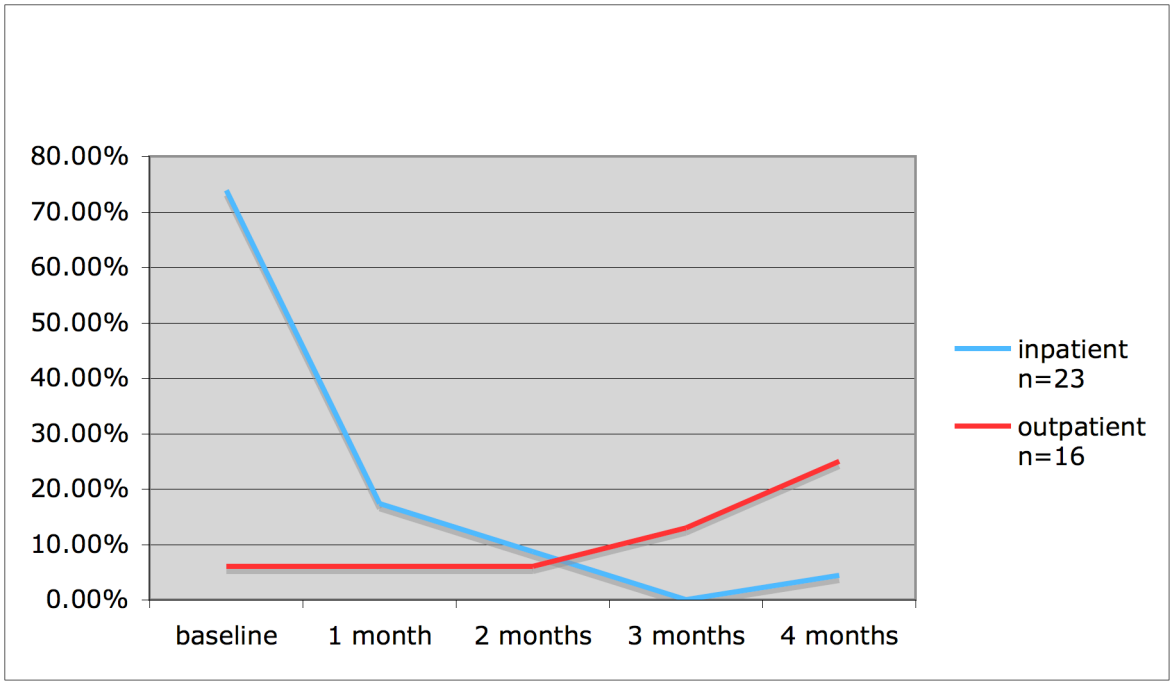
Figure 3: Comparing inpatient versus outpatient initiated treatment screening of blood pressure



(ii) Weight

In Figure 4 inpatient initiated screening of weight at baseline is 73.91%. It then shows a downward trend to 3 months where no screening is done. By 4 months screening improves again to 6 %. The frequency of outpatient initiated screening starts off at 6 % and gradually increases after 3 months to 25% at 4 months.

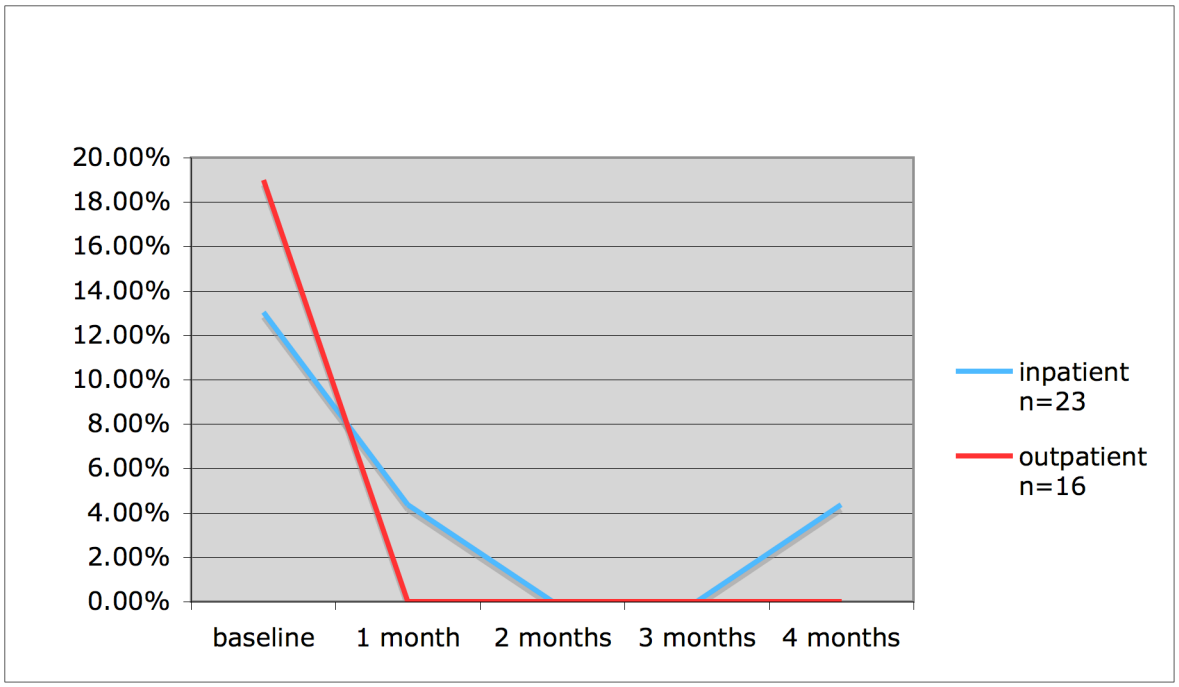
Figure 4: Comparing inpatient versus outpatient initiated treatment screening of weight



(iii) Glucose

The frequency of glucose screening (Figure 5) is greater at baseline in outpatient initiated treatment, than inpatient initiated treatment (19% vs 13.4%). By 4 months inpatient initiated treatment shows slightly more screening, than outpatient initiated treatment (4.35% vs 0%).

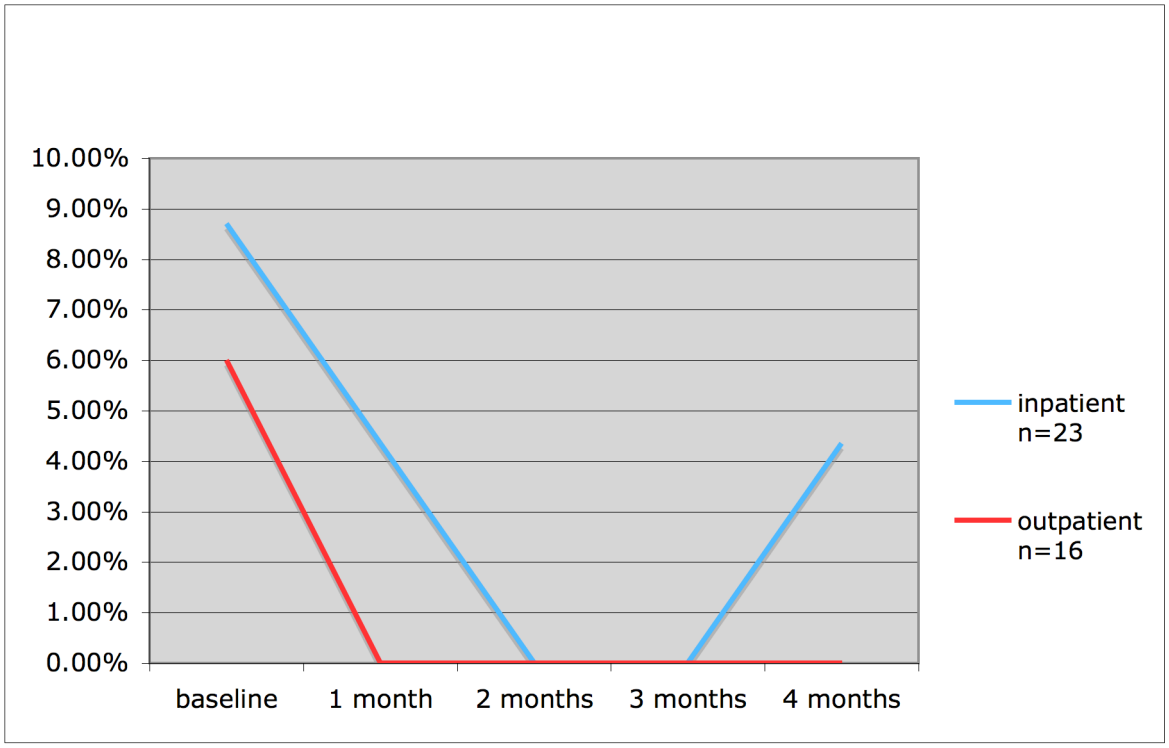
Figure 5: Comparing inpatient versus outpatient initiated treatment screening of glucose



(iv) Cholesterol

In Figure 6 at baseline more patients initiated on treatment as inpatients were screened for cholesterol than patients initiated on treatment as outpatients (8.7% vs 6%). Screening then dropped to zero for both groups until the 4th month were inpatient initiated screening increased to 4.35%.

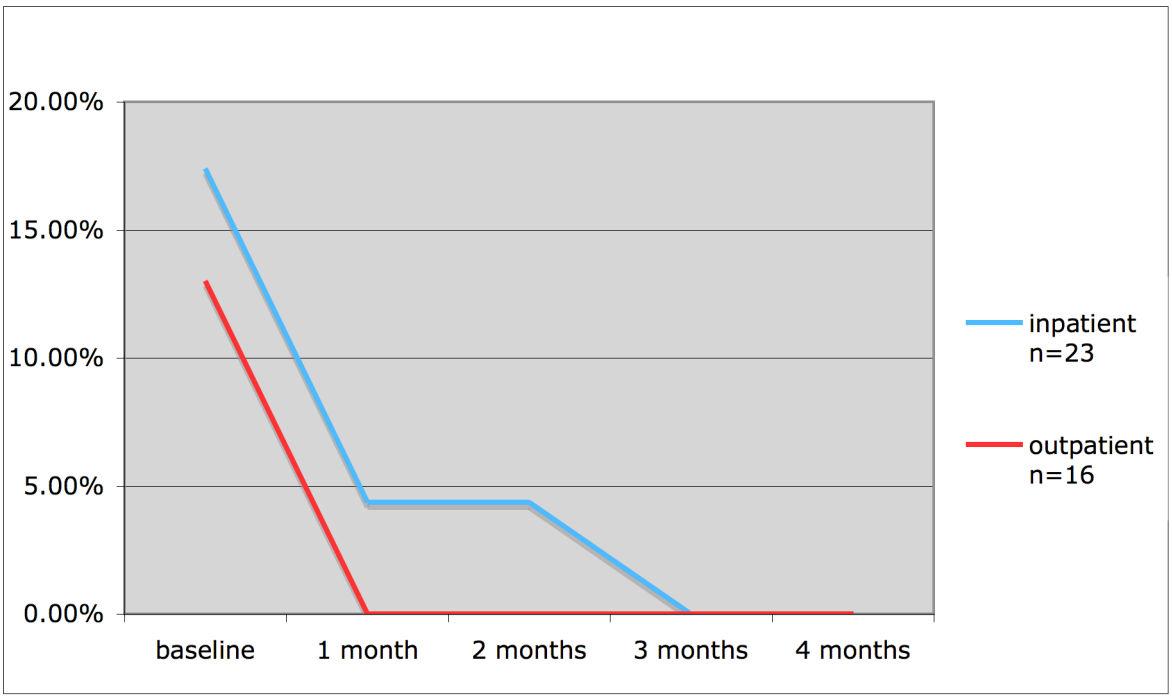
Figure 6: Comparing inpatient versus outpatient initiated treatment screening of cholesterol



(v) Lipid studies

Screening of lipid studies (Figure 7) was greater for inpatient initiated treamtment than outpatient initiated treatment (17.39% vs 13%). The frequency showed a downward trend to 4 months where it was zero for both groups.

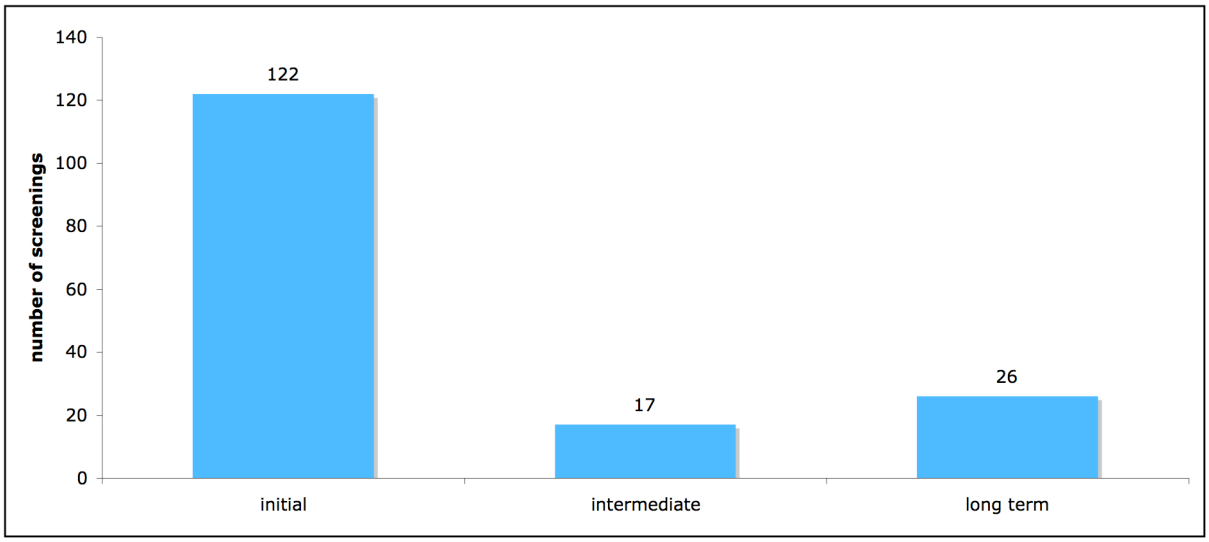
Figure 7: Comparing inpatient versus outpatient initiated treatment screening of lipid studies



Number of screenings in each time period

Data as percentages was not reported for the intermediate and long term time periods due to very little screening being done. The total number of screenings in each time period (initial, intermediate, long term) were as follows: during the initial time period a total of 122 screening tests was done; in the intermediate and long term time periods 17 and 26 screening tests were done respectively. (Figure 8)

Figure 8 : Number of screenings in each time period



Variables associated with screening

The variables of diagnosis, gender and patient group were normally distributed, and their association with screening in each time period (initial, intermediate, long term) was studied using the Fisher extact test. The Fisher exact test was used as a test for association because the variables were independent and categorical (Table 5)

Table 5: Variables associated with screening – p values

	Initial time period	***Intermediate time period***	***Long term time period***
Diagnosis	*p=0,68*	*p=0,13*	*p=0,13*
Gender	*p=1,0*	*p=0,13*	*p=0,48*
Patient group	$p=1,69x10^{5}$	*p=0,29*	*p=0,72*

No statistical significance (p-values > 0.05) was established. This confirms that there is no significant association between these variables and screening. This was most likely due to very little screening being undertaken or recorded.

Discussion

The majority of patients in this sample were middle aged, white, single and diagnosed with schizophrenia. Most patients had completed secondary or tertiary education, but were in the lowest income group.

Demographic profile

Age and Gender

The mean age of the sample was 46 years, which indicates that this sample comprises mostly middle aged patients who have possibly had a psychotic illness since their 20's. This suggests that they are not a neuroleptic naive group, and have most likely been on other antipsychotic treatment before they were changed to olanzapine. The mean age of males was about 10 years younger than the mean age of females. Males usually have an earlier onset of psychotic illness than females[25], however this does not necessarily account for the gender difference in age noted in this study.

Race

White patients comprised the majority of the sample. This demographic profile was not reflective of the South African population

Marital status

Premorbid personality of patients with schizophrenia is characterised by shy, schizoid behaviour.[26] These traits as well as communication and interpersonal deficits may account for the high proportion of unmarried patients with severe mental illness.[27] Demographic data of patients with severe mental illness shows that a high percentage of these patients are unmarried.[28,29]

Educational level

The finding of a generally higher level of education within the context of olanzapine prescribing is in keeping with a study by Wang et al, where it was found that factors associated with being prescribed one of the second generation antipsychotics like olanzapine include being elderly, having more education and being white.[24] One could speculate that better educated patients may report more side effects, than less educated patients. This is potentially why they have been prescribed olanzapine, which does have an improved extra pyramidal side effect profile. It is necessary for further studies to clarify the reason for this discrepancy in educational level in patients prescribed olanzapine.

Socio economic status

Most patients in this sample were classified as falling into a lower socioeconomic group. H1 is the code used by the National Department of Health to describe the lowest level of income in patients registering for medical services. Patients are charged according to their income, therefore if they are registered as H1 patients they pay only a small nominal fee for services. This is not unexpected, as patients with severe psychotic illness display a phenomenon called 'downward drift'.[25] After multiple relapses and time spent unemployed, a patient's financial position deteriorates, moreover Tara is a state hospital. Patients who can afford private care would perhaps be seeing private psychiatrists. Of interest is that it appears that educational level does not predict socioeconomic status, in the sample studied, and that educational level in this setting is a better predictor of prescribing.

Risk factors

In 35.9%; (n=14) of the sample, no risk factors were documented with 15.38% (n=6) documented as having no risk factors. Specific risk factors were as follows; 10,26% (n=4) with hypertension, 5,13% (n=2) with diabetes, 2,56% (n=1) with hyperlipidaemia, 5,13% (n=2) with obesity, 20,51% (n=8) were smokers. 5.13% (n=2) had more than one or more risk factors documented. None of the sample had cardiovascular disease as a risk factor. Of concern, with regard to risk factors for metabolic syndrome, is that in more than a third of the sample the risk factors were not documented. It is not clear whether this was on the basis of there being no risk factors or simply that they were not elicited for whatever reason. 80% of schizophrenic patients have significant co-morbid medical problems, and in 50% of patients the problem may not have been diagnosed.[25] This highlights the need for adequate history taking and accurate record keeping in relation to medical aspects of psychiatric patient care. The potential association between extent of risk factors documented and screening was not subject to formal statisical analysis. However, based on the documented existence of risk factors and the extent of screening, it does not appear that the former influenced the latter.

Patient group

More patients were initiated on olanzapine as inpatients (n=23) as opposed to as outpatients. This is because inpatients are likely to be more severely ill than outpatients. During an admission it is more likely that medication will be reviewed and changed especially when treatment failure or adverse side effects negatively impact on recovery and remission of mental illness.

Screening

The percentage of screening for each of variables for outpatient initiated treatment was less than 20% and it continued to decline to less than 20% until 4 months. Beyond this there was so little screening as to render data interpretation of no value. The exception was weight, where frequency increased slightly

over time. The extent of screening for inpatient initiated treatment, for the relevant screening variables, differed to those for outpatient initiated treatment. In general there was a higher level of screening, although it declined over time. Weight and blood pressure were most frequently assessed at baseline followed by lipogram, glucose and cholestrol levels. For all variables measured, the trend was for screening to decline over time. Comparing inpatient versus outpatient initiated treatment there were apparent differences in the extent of screening i.e. greater for inpatient initiated treatment, specifically with respect to weight and blood pressure. It was clearly noted that inpatient screening is superior to screening undertaken as an outpatient. However weight and BP monitoring are a part of standard nursing procedure in the wards at Tara: The H. Moross Centre and is therefore undertaken on all patients and is not specific to patients on olanzapine. Hence one should be cautious in over interpreting the apparent screening. In summary, screening for metabolic syndrome in patients on olanzapine is not being undertaken according to recommened clinical guidelines.

Number of screenings in each time period

Screening was most frequently undertaken during the initial period, with a marked reduction during the subsequent periods. The study did not allow for exploration of the basis, nonetheless the finding is noteworthy and requires elucidation.

Factors associated with screening

No significant relationship was established regarding the extent to which the patient gender, diagnosis or patient group influenced the treating doctor's adherence to screening guidelines. The limited sample size and paucity of data, suggests that this finding should be cautiously interpreted.

Adherence to guidelines

The findings of this study revealed that screening for metabolic syndrome in patients on a second generation antipsychotic is not being conducted according to recommended clinical practice, in the site studied. In essence, guidelines are being overlooked or ignored for whatever reason. Perhaps one of the main limitations of any guideline is its implementation. It is therefore worth exploring some of the pitfalls in implementation. Firstly, it may be that treatment options are not available.[22] It may be that we lack some of the basic tools needed to follow the guidelines accurately. For example, in order to measure waist circumference one needs a tape measure, which is not a piece of equipment commonly found in a psychiatric outpatient department. The guidelines may be too extensive, and not user friendly.[22] The guideline that was analysed in this study required 8 measurements to be taken at numerous time periods.[16] This is time consuming for both the patient and the doctor, and one may question whether these measurements are indeed necessary. In the pathogenesis of metabolic syndrome, one of the first steps is weight gain, which results in the subsequent insulin resistance and

dyslipideamia. One could argue that monitoring weight is an adequate screening tool for metabolic syndrome and once weight gain is noted then all the other tests/measurements can be performed. Hence it may be that local circumstances prompt reappraisal and modifcation of guidelines rendering them user friendly without compromising outcomes. Another limitation to guidelines is the credibility of the authors.[30] The authors of the guidelines appear reputable and the guidelines were formulated at an international consensus conference. Possibly the most likely causes of non compliance to guidelines are a lack of awareness of the guideline and/or a resistance to change. These guidelines were published in 2004, but only in recent years has more attention been drawn to them. Perhaps one of the factors in our setting was the lack of familiarity with the guidelines, hence the non-adherence.

As mentioned previously; a study to evaluate the implementation of the guidelines was undertaken.[23] Before the guidelines were released 7.8% of patients had their lipids tested at baseline. After the guidelines were released only 8.5% had lipids tested at baseline.[23] This is comparable to the current study where at baseline 6-8.7% of patients had their lipids tested.

Hence one sees that baseline rates of testing locally are comparable to international data. However, one sees that in the international setting, guideline publication appears not to have influenced clinical practice. Guidelines do have many benefits. They inform doctors of evidence based practices thereby striving to minimise inadequate practices as well as standardise practices. They can be useful in enabling the professional to evaluate what they are doing.[23] Clearly they do not always succeed.

Based on the findings of the current study it appears there is a need to actively encourage the benefits of guidelines locally.

Limitations

This study consisted of a cohort of 39 patients from Tara: The H. Moross Centre. Not only is this a small sample size, but the data cannot be generalized beyond this setting i.e. a tertiary, specialised hospital. As in all retrospective studies poor record keeping is a limitation. In the current study this appears to have been an issue. Again this highlights the importance of good record keeping by medical professionals. This study is also a cross sectional anaylsis and refers to information gathered at a particular point in time only i.e. patients who were prescribed olanzapine in 2008.

Conclusion

There is strong evidence that people with mental illness have less access to primary health care. They also receive poorer care for conditions such as diabetes and heart disease.[19] The rates of physical illness are high in mentally ill patients, especially the rates of cardio-vascular disease, obesity, diabetes and Human immuno-deficiency virus (HIV). The combination of high rates of physical illness and poorer quality of treatment exacerbates both discrimination and neglect. Thus patients with mental illness have an increased risk of premature death.[19] The suggestion is that psychiatric patient's physical health is being overlooked. Thus, the issue of physical health in persons with severe mental illness has assumed both public health and ethical relevance on a global scale.[20] This key issue needs to be made a priority in order to protect the civil rights of our patients.[20]

The hypothesis of the study has been confirmed i.e. screening was suboptimal. Refining clinical practice will hopefully contribute to a greater awareness, both specifically and generally of the physical needs of psychiatric patients and ultimately their care. The current study has in a very specific setting, demonstrated an area requiring attention i.e. adherence to acceptable clinical practice. Whilst one can only speculate on the basis for non-adherence, having established the status quo, there is a requirement for an appropriate strategy to address this apparent deficit in patient care. Awareness of clinical guidelines addressing the physical needs of patients needs to be highlighted to doctors and patients. In addition healthly lifestyle should not be overlooked as an effective intervention. Perhaps further studies should aim to collect similar data in other settings, in order to establish the extent of the problem on a regional or even national scale. It may also by useful to research and identify the key reasons for non-adherence to guidelines. This may ultimately result in an adapted protocol being designed, specifically for the South African setting.

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Appendix A

Data collection sheet :

Number:

Demographics

Age:

Gender: male ☐ female ☐

Race: White ☐ Black ☐ Coloured ☐ Indian ☐

Marital status: single ☐ married ☐ divorced ☐ widowed ☐

Highest level of education: actual level: primary ☐ secondary ☐ tertiary ☐

Hospital classification : H1 ☐ H2☐ H3☐ P☐

Diagnosis

1.Schizophrenia 2. Bipolar Mood Disorder 3. Other (specify)

Date of starting Olanzapine: dd/mm/yy

Patient group

initiated as inpatient ☐

initiated as outpatient ☐

Risk factors

1. Hypertension 2. Diabetes 3. Hyperlipideamia 4.Cardiovascular disease

5.Obesity 6. Smoking 7. Not documented 8. Nil

Monitoring

	BP	HGT	formal glucose	weight	BMI	waist circumference	cholesterol	fasting lipogram
Baseline								
1 month								
2 months								
3 months								
4 months								
> 4 months								

1 year
yearly
every 5 years

Diagnosis of any non-psychiatric illness by any medical professional post intervention with second generation antipsychotics.

1. Hypertension 2. Diabetes 3. Hyperlipidaemia 4. Cardiovascular disease

Date of diagnosis of non-psychiatric illness: dd/mm/yy

Appendix B

Name of Patient _____ Age _____

METABOLIC AND CARDIOVASCULAR SCREENING CARD

MONITORING FOR PATIENTS ON SECOND GENERATION ANTIPSYCHOTICS*

	Baseline	1 month	2 months	3 months	Every 4 months	Every year	Every 5 years
DATE:							
Personal/Family history of obesity, diabetes, dyslipidaemia, cardiovascular disease							
Weight (kg)	_____ (kg)	_____ (kg)	_____ (kg)	_____ (kg)	_____ (kg)		
Height (cm)	_____ (cm)	_____ (cm)	_____ (cm)	_____ (cm)	_____ (cm)		
(BMI)*							
Waist circumference (cm)	_____ (cm)					_____ (cm)	
Blood Pressure (mmHg)	____/____ SBP/DBP			____/____ SBP/DBP		____/____ SBP/DBP	
Fasting plasma glucose (mmol/ℓ)	_____			_____		_____	
Fasting lipogram (mmol/ℓ)	Total cholesterol _____ LDL _____ HDL _____ Triglycerides _____			Total cholesterol _____ LDL _____ HDL _____ Triglycerides _____			Total cholesterol _____ LDL _____ HDL _____ Triglycerides _____
ECG if history indicates							

*** MORE FREQUENT ASSESSMENTS MAY BE WARRANTED BASED ON CLINICAL STATUS**

Adapted from ADA Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes[2]

Clinical identification of the metabolic syndrome

Risk factor	Defining level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥1.7 mmol/ℓ
HDL-cholesterol	
Men	<1.0 mmol/ℓ
Women	<1.3 mmol/ℓ
Blood pressure	≥135/85 mmHg
Fasting glucose	>6 mmol/ℓ

*BMI calculation:[3]
Weight (kg)/Height^2 (cm)
Overweight: 25-30
Obese: ≥30

Adapted from Newcomer JW[4]

GEODON
Oral Capsules
and Injection
Power to restore potential

References: 1. Meltzer HY, Davidson M, Glassman AH, Viewig WVR.Assessing Cardiovascular Risks Versus Clinical Benefits of Atypical Antipsychotic Drug Treatment. *J Clin Psych* 2002; **63** (Suppl. 9):25-29. **2.** American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *J Clin Psych* 2004; **65**(2): 267-272. **3.** Flier JS. Obesity. In: Harrison's Principles of Internal Medicine. Braunwald E, Fauci AS eds. 15th Edition.McGraw Hill, New York.2001; 479-481. **4.** Newcomer JW. Second Generation (Atypical) Antipsychotics and Metabolic Effects. A Comprehensive Literature Review. *CNS Drugs* 2005; **19**(Suppl.1): 1-93.

24/GEO/11/2005/LB

blue parrot 7272

Appendix C

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Marsay

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070446**
PROJECT	Second Generation Antypsychoctic Treatment and an Assessment of Metabolic and Cardiovascular Status: A Retrospective Review
INVESTIGATORS	Dr C Marsay
DEPARTMENT	Psychiatry/Neurosciences
DATE CONSIDERED	07.05.04
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.06.26 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Szabo C Prof

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES