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A clinical audit of antipsychotic prescriptions and associated clinical profile at Helen Joseph Hospital, Johannesburg, South Africa

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A clinical audit of antipsychotic prescriptions and associated clinical profile at Helen Joseph Hospital, Johannesburg, South Africa

Dr. Jones Mwenda

Supervisors: Dr. Sapinoso and Prof. Subramaney

A research report submitted in a submissible format to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Psychiatry in May 2022

Declaration

I, Dr. Jones Mwenda, declare that this research report is my own work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Medicine in Psychiatry. It has not been submitted before for any degree or examination at this or any other university.



_____

7th day of September 2022

Authors' Contributions

Dr. Jones Mwenda:

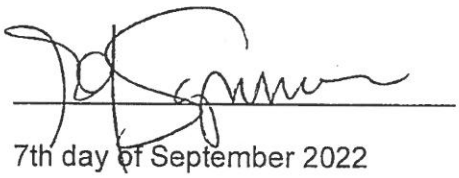
Developed research question, collaboratively wrote the protocol and methods, coauthored the final article.



7th day of September 2022

Dr. Sapinoso:

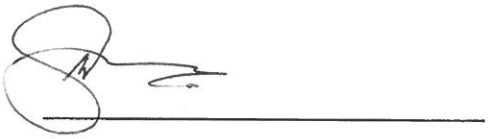
Supervisor who co-developed the study design and co-authored the article.



7th day of September 2022

Prof. Subramaney:

Supervisor who assisted with editing and co-authored the article.



7th day of September 2022 .

Dedication

To my Amys, Amanda and Amora.

Presentations

This work has never been presented at a congress or any academic programme.

Prizes and Awards

None.

Author Guidelines for the South African Journal of Psychiatry

Original Research Article

The guidelines for submission of original research articles to the South African Journal of Psychiatry are the following:

Word limit	3000-4000 words (excluding the structured abstract and references)	3900 words
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion	248 words
References	60 or less	25 references
Tables/Figures	No more than 7 Tables/Figures	3 Tables 2 Figures
Ethical statement	Should be included in the manuscript	Page 4
Compulsory supplementary file	Ethical clearance letter/certificate	Appendix B

Abstract

Background

Antipsychotics are a group of agents used to treat symptoms of several psychiatric disorders. Multiple global guidelines recommend treatment with second-generation antipsychotic (SGA) agents as a first line of treatment for psychotic disorders.

Aim

The aim was to examine the pattern of antipsychotic prescription and associated factors at Helen Joseph Hospital over a six-month period.

Methods

The researcher conducted a retrospective record review of 104 patients who were treated at various times over six months from 1 July to 31 December 2018. The data on demographic information, psychiatric diagnoses, medication, side effects were extracted from available clinical records.

Results

The mean age of patients in this study was 35.4 years with more being male (n=65, 62.5%) than female (n=39, 37.5%). Antipsychotics were used mostly for treating psychotic disorders (n=39; 37.5%) followed by mood disorders (n=31; 29.8%), substance-induced disorders (n=26; 25%), and psychiatric disorders due to another medical condition (n=8; 7.7%).

Majority of patients were on oral SGAs (n=86), mostly risperidone (n=59) followed by olanzapine (n=24). LAIs were used in 27 cases with flupenthixol (n=17) being the main one. Oral FGAs were used in 13 patients and clozapine was used in four.

Three-quarters of the patients (76.2%) were on monotherapy, the only statistically

significant finding. Risperidone was implicated in most side effects reported (n=8) with EPSEs (n=6) occurring most commonly in the study population.

Conclusion

The use of antipsychotics at Helen Joseph Hospital was found to be in line with the local Essential Medicines List and global trends.

Acknowledgements

I would wholeheartedly like to acknowledge my supervisors, Prof. Subramaney and Dr. Sapinoso, for their guidance and patience throughout this journey.

Thanks to the late Prof. B J van Rensburg, a great teacher and a pillar for the discipline of psychiatry.

I am grateful to Dr. Brummerhoff at Helen Joseph Hospital who fought invisible battles for us to be able to provide a great service to our patients while being students of the amazing world of psychiatry.

Lastly, to the unsung heroes and heroines of my daily life, the patients that day in day out live with mental illnesses who allow us to be part of their journey of healing.

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List of Abbreviations

EML	Essential Medicines List
EPSE	extrapyramidal side effects
FGA	first generation antipsychotic
LAI	long acting injectable
SGA	second generation antipsychotic
STG	Standard Treatment Guidelines

Submissible Paper

A clinical audit of antipsychotic prescriptions and associated clinical profile at Helen Joseph hospital, Johannesburg, South Africa.

Introduction

Antipsychotics are a group of agents used to manage symptoms of several psychiatric disorders. They possess various properties, including antipsychotic, anti-manic, and mood-stabilising properties.[1,2] There are two categories of antipsychotics, first-generation antipsychotics (FGAs), the dopamine receptor antagonists, also known as typical antipsychotics, and second-generation antipsychotics (SGAs), the serotonin-dopamine receptor antagonists, also known as atypical antipsychotics. Antipsychotics are the first-line pharmacological intervention for severe mental illnesses , such as schizophrenia and a variety of other psychiatric diseases.[3]

Globally, the American Psychiatric Association recommends use of either FGA or SGA depending on clinical factors and patient preference.[4] The National Institute for Health and Care Excellence clinical guidelines recommend treatment with SGAs as a first-line of treatment for psychotic disorders.[5] FGAs are still often prescribed, frequently for historical reasons in the instance of a specific individual.

In South Africa, the Standard Treatment Guidelines (STG) and Essential Medicines List (EML) for tertiary hospitals recommends haloperidol, an oral FGA, or risperidone, an oral SGA, as the first-line of treatment. In the event of poor adherence to treatment, long-acting injectables (LAI) such as flupenthixol decanoate, or zuclopenthixol decanoate are recommended.[6] For extrapyramidal side effects (EPSE), the STG

recommend using the lowest effective dose or switching from haloperidol or chlorpromazine to risperidone. Clozapine is reserved for treatment-resistant cases.[7]

A study conducted in the Eastern Cape in South Africa observed the rate of use to be at 48.5% (n=82) for FGAs and 51.5% (n=87) for SGAs on inpatients. However, the use of FGA was higher on admission at 74% with haloperidol as the drug of choice[1]. This was thought to be largely influenced by cost, in line with a study published in the Bulletin of the World Health Organisation in 2008, that looked at the treatment of schizophrenia in the developing world and found that treatment with a FGA was the most cost-effective.[8]

An Australian study reported a 77.3% use of atypical antipsychotics as the first-line treatment for schizophrenia, with the main drug of choice being olanzapine[9]. Conversely, in East Asia, more patients (55%) on single antipsychotics were on a typical antipsychotic.[10]

Cost, demographics, and medical comorbidities have emerged as the drivers when choosing an antipsychotic. Cost specifically remains the most influential factor in the choice of antipsychotics in both developed and developing countries, even in cases where standard treatment guidelines advocate otherwise.[1,6]

There is a need for local data as there have been disparities across countries and regions in the prescription patterns of antipsychotics and it is not clear which of these trends are transferable to South Africa[11]. Hence, it was useful to study local prescription patterns to compare with global trends and local standard treatment guidelines.

This study aimed to investigate the choice of antipsychotics (oral FGAs, oral SGAs, LAIs and clozapine) and determine whether these were associated with demographic variables, psychiatric diagnoses, and side effects of antipsychotics in patients treated at Helen Joseph Hospital. In line with the STG, it was hypothesised that the most frequently used oral FGA would be haloperidol and the most frequently used oral SGA would be risperidone, while LAIs would be used in cases of non-adherence.

The objectives of the study were outlined as follows:

1) To describe the demographic and clinical profile of patients discharged or transferred from HJH on antipsychotic medication.

2) To describe the choice of antipsychotic; class of antipsychotic, potency, oral vs. LAI, and ascertain prescribing as monotherapy or antipsychotic polypharmacy.

3) To determine the association, if any, between antipsychotic choice and demographic and clinical profile.

Method

Study design and setting

This study was a descriptive retrospective record review. Data collection was conducted at Helen Joseph Hospital in Johannesburg, South Africa. Helen Joseph Hospital is a government public hospital with a psychiatric unit providing emergency, outpatient, and inpatient care.

Study population and sample

The clinical records of all patients over 18 years admitted to the psychiatry ward at Helen Joseph Hospital between 01 July 2018 and 31 December 2018 were eligible for inclusion. This included the records of patients who had been discharged or transferred. All patients were on antipsychotic medication, either FGAs, SGAs, or LAIs. Records of patients below 18 years of age were excluded from this study. In total, clinical records from 104 patients were reviewed.

Data collection and analysis

The relevant information was extracted from the available clinical records, the psychiatry department database, discharge summaries, and patient files over the six-month period. It was entered on a Microsoft Excel spreadsheet and analysed using R software (R version 3.4.2). Demographic data included gender, age, and employment status or source of income. The clinical information included the primary psychiatric diagnosis, any comorbid psychiatric diagnosis, psychiatric history, any substance use, and medical comorbidities. The pharmacological information included the antipsychotic prescribed, other psychiatric medication, other chronic medication prescribed, (EPSEs, metabolic side effects, and others).

For the descriptive analyses, categorical data were analysed as frequencies and percentages and presented in tables and graphs. Continuous variables were reported as means and standard deviations. When further analysis was appropriate, categorical data were analysed using a chi-squared test, while the Kruskal-Wallis test was used for continuous data.

Ethical considerations

Ethical clearance was obtained from the University of the Witwatersrand's Human Research Ethics Committee (Medical), protocol number M200402, and approval to conduct the study and access clinical records was obtained from the chief executive officer at Helen Joseph Hospital and the Helen Joseph Hospital Research Committee.

As a retrospective clinical record review, this study did not involve any therapeutic intervention, and no risk to participants was involved. No identifying information was captured, and each record was given a unique study number known only to the researcher.

Results

Demographic variables

The mean age of patients in this study was 35.4 (±14.2) years old, ranging from 18 to 68 years old. More patients were male (n=65, 62.5%) than female (n=39, 37.5%). Most patients were unemployed (n=54, 51.9%), followed by employed (n=15, 14.4%), on a pension or a disability grant (n=17, 16.3%). There were 18 patients (17.3%) with unknown employment status.

Diagnoses

The number of patients with various psychiatric diagnoses is shown in Table 1. The percentages represent the proportions within each group of disorders. The most frequently treated disorders were schizophrenia (n=27), bipolar I disorder (n=27), and substance-induced psychotic disorder (n=22) (Table 1).

Table 1: Patients with various primary psychiatric diagnoses receiving antipsychotic medication

Psychotic disorders (n=39)	**n**	**%**
Schizoaffective disorder	7	17.9
Schizophrenia	27	69.2
Schizophreniform disorder	4	10.3
Brief psychotic episode	1	2.6
Mood disorders (n=31)	**n**	**%**
Bipolar I disorder	27	87.1
Bipolar II disorder	1	3.2
Major depressive disorder with psychotic features	2	6.5
Persistent depressive disorder	1	3.2
Substance/medication induced and related psychiatric disorders (n=26)	**n**	**%**
Substance-induced bipolar and related disorder	2	7.7
Substance-induced psychotic disorder	22	84.6
Efavirenz-induced psychotic disorder	2	7.7
Psychiatric disorders due to another medical condition (AMC) (n=8)	**n**	**%**
Psychotic disorder due to AMC – human immunodeficiency virus (HIV)	5	62.5
Psychotic disorder due to AMC – traumatic brain injury (TBI)	1	12.5
Psychotic disorder due to AMC – neurosyphilis	1	12.5
Psychotic disorder due to AMC – HIV and temporal lobe epilepsy	1	12.5

As expected, antipsychotics were used mostly for treating psychotic disorders (n=39; 37.5%), followed by mood disorders (n=31; 29.8%), substance-induced disorders (n=26; 25%), and psychiatric disorders due to another medical condition (n=8; 7.7%) (Figure 1).

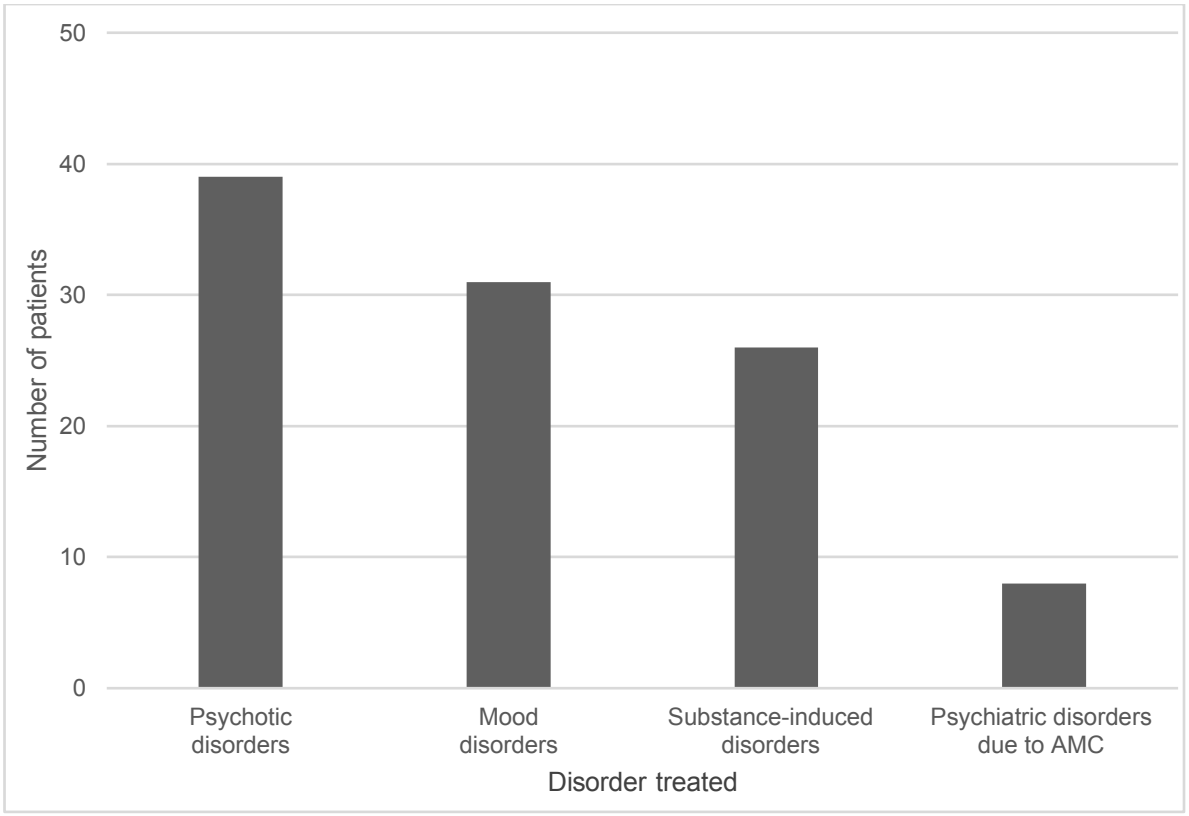


Figure 1: Number of primary psychiatric disorders treated with antipsychotics

Class of antipsychotic medication

The number of patients on various medications is shown in Figure 2. The only oral FGA used was haloperidol, which was used in 13 cases. The most frequently used antipsychotics were oral SGAs (n=86) including risperidone (n=59) and olanzapine (n=24). LAIs were used in 29 cases with flupenthixol (n=17) being the main one. Clozapine was used for four patients. There were 77 patients on monotherapy while those on polypharmacy had a LAI most commonly co-prescribed (n=29).

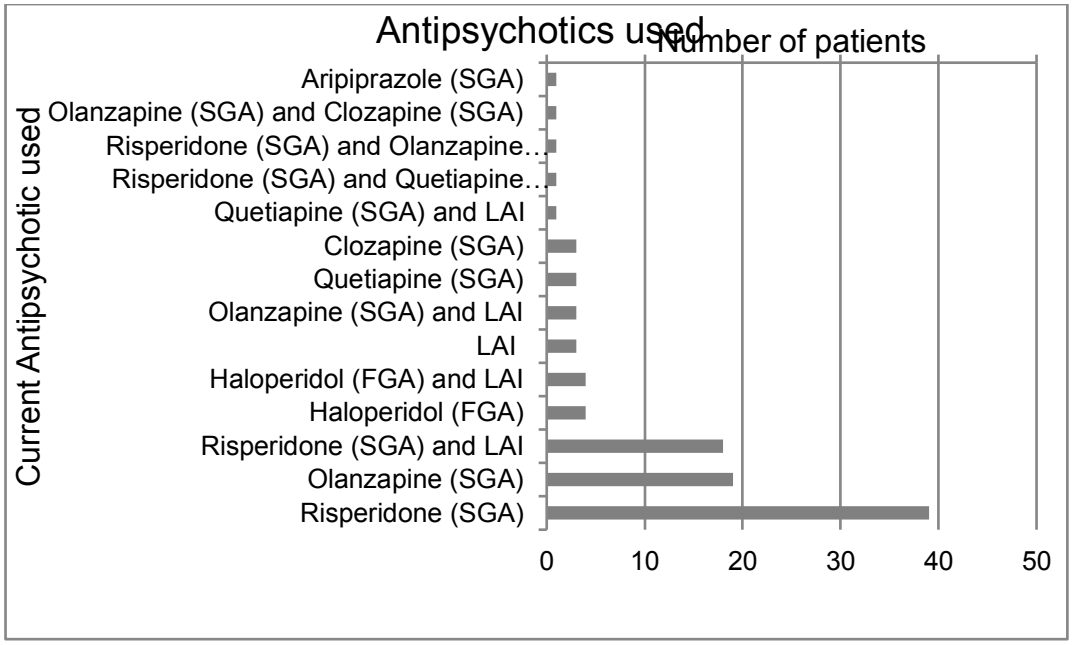


Figure 2: Current antipsychotics used

Side effects

Side effects were noted due to both previous trials of medication and current medications as shown in Table 2. Nine types of side effects were recorded from 21 occurrences in total. Fifteen occurrences of side effects were due to previous trials and six due to current medication. Risperidone was implicated in most side effects (n=8) followed by olanzapine (n=5) and haloperidol (n=4). Chlorpromazine, quetiapine, and clozapine were implicated in one side effect each.

In total, EPSEs occurred in six cases; five cases reported weight gain, three reported hypertension, and two reported galactorrhoea. Only one case each of dyslipidemia, neutropaenia, hyper-salivation, diabetes, and breast enlargement was reported.

Table 2: Side effects

	Current medication						
Side effects (n=6)	**Haloperidol**	**Chlorpromazine**	**Risperidone**	**Olanzapine**	**Quetiapine**	**Clozapine**	**Total**
EPSE	1		1				2
Weight gain				2			2
Dyslipidemia				1			1
Neutropaenia						1	1
Sub total	**1**	**0**	**1**	**3**	**0**	**1**	**6**
	Previous medication trials						
Side effects (n=15)	**Haloperidol**	**Chlorpromazine**	**Risperidone**	**Olanzapine**	**Quetiapine**	**Clozapine**	
EPSE	2	1	1				4
Hypersalivation	1						1
Diabetes			1				1
Galactorrhoea			2				2
Hypertension			1	1		1	3
Weight gain			1	1	1		3
Breast enlargement/gynaecomastia			1				1
Sub total	**3**	**1**	**7**	**2**	**1**	**1**	**15**
Total	**4**	**1**	**8**	**5**	**1**	**1**	**21**

Factors associated with antipsychotic prescription

Patients were grouped into four antipsychotic classes (oral FGAs, oral SGAs, LAIs, and clozapine) by several socio-demographic and clinical variables (Table 3).

Table 3: Sociodemographic and clinical details of patients on antipsychotic medications

Variables	Oral FGA (n=13)	Oral SGA (n=86)	LAI (n=27)	Clozapine (n=4)	Statistics
Demographic variables					
Age	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Mean (SD)	35 (13.6)	35.8 (14.1)	37.5 (13.3)	34.5 (14.4)	H(3;129)=1.61; p=0.655
Gender	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Female	2 (15.4)	37 (42.5)	6 (22.2)	0 (0)	$x^2(3)=5.877$; p=0.118
Male	11 (84.6)	49 (57.4)	21 (77.8)	4 (100)	
Employment status or income	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Employed	2 (15.4)	13 (15.1)	3 (11.1)	0 (0)	$x^2(9)=6.980$; p=0.639
Unemployed	3 (23.1)	47 (54.7)	19 (70.4)	3 (75)	
Disability grant or pension	3 (23.1)	14 (16.3)	3 (11.1)	0 (0)	
Unknown	5 (38.5)	12 (14.0)	2 (7.4)	1 (25)	
Diagnoses					
Primary psychiatric diagnosis	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Primary psychotic disorder	6 (46.2)	28 (32.6)	14 (51.9)	4 (100)	$x^2(15)=10.038$; p=0.347
Primary mood disorder	2 (15.4)	30 (34.9)	4 (14.8)	0 (0)	
Substance or medication-induced psychiatric disorders	5 (38.5)	20 (23.3)	9 (33.3)	0 (0)	
Psychiatric disorder due to another medical condition	0 (0)	8 (9.3)	0 (0)	0 (0)	
****Co-morbid psychiatric diagnoses**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
None	11 (84.6)	63 (73.3)	21 (77.8)	4 (100)	$x^2(6)=10.087$; p=0.343
Neurocognitive and neurodevelopmental disorder	1 (7.7)	7 (8.0)	1 (3.7)	0 (0)	
Personality disorders and traits	1 (7.7)	15 (17.4)	5 (18.5)	0 (0)	
Post traumatic stress disorder	0 (0)	1 (1.2)	0 (0)	0 (0)	
Antipsychotic medication					
Monotherapy vs polypharmacy	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Monotherapy	9(69.2)	62(75.6)	3 (11.1)	3 (75)	$x^2(3)=36.805$; p<0.001*
Polypharmacy	4 (30.8)	24(24.4)	24 (88.9)	1 (25)	
Other psychiatric medication	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
None	10 (76.9)	48 (55.8)	20 (74.1)	2 (50)	$x^2(12)=8.029$; p=0.531
Antidepressant	0 (0)	5 (5.8)	0 (0)	0 (0)	
Antidepressant and mood stabiliser	0 (0)	1 (1.2)	0 (0)	0 (0)	

Variables	Oral FGA (n=13)	Oral SGA (n=86)	LAI (n=27)	Clozapine (n=4)	Statistics
Mood stabiliser	2 (15.4)	29 (33.7)	7 (25.9)	2 (50)	
Two mood stabilisers	1 (7.7)	3 (3.5)	0 (0)	0 (0)	
Side effects on current medication	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
EPSE	1 (7.7)	1 (1.2)	0 (0.0)	0 (0)	
Metabolic (weight gain and dyslipidemia)	0 (0.0)	3 (3.5)	0 (0.0)	0	$x^2(6)=0.430$; p=0.999
Neutropaenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	
None documented	12 (92.3)	82 (95.3)	27 (100.0)	3 (75.0)	
Non-adherence	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Yes	5 (38.5)	38 (44.2)	18 (66.7)	4 (100)	
No	4 (30.8)	34 (39.5)	4 (14.8)	0 (0)	$x^2(6)=7.399$; p=0.286
Unknown	4 (30.8)	14 (16.3)	5 (18.5)	0 (0)	

**Significant*

***Substance use disorders were studied but were not included in this table as they in themselves were not an indication for antipsychotics. They do however represent an important psychiatric comorbidity.*

Demographic variables

None of the demographic variables of the patients differed significantly. Patients in the four antipsychotic groups did not differ significantly (p=0.655) with respect to age (oral FGA 35±13.6 years, oral SGA 35.8±14.1 years, LAI 37.5±13.3 years, clozapine 34.5±14.4 years).

The other variables were analysed using chi-squared analyses, and the Yates correction was applied in cases where cell frequencies were equal to zero. With respect to gender, there were more males than females. Both genders were mainly on oral SGAs, and there were more males than females on LAIs. However, this difference was not significant (p=0.118).

While it seemed that there were proportionally more unemployed patients on LAIs (n= 19, 70.4%), no differences with respect to employment status or income reached statistical significance (p=0.639).

Diagnosis

There was no statistically significant association between the primary psychiatric diagnosis and the class of antipsychotic medication used (p=0.347). Psychiatric co-morbidities present were not significantly associated with the class of antipsychotic medication prescribed (p=0.343).

Antipsychotic medication

The only variable to reach statistical significance was monotherapy versus polypharmacy ($x^2(3)=36.805$; $p<0.001$), indicating that significantly more patients, a majority of just over three-quarters, were on monotherapy (n=80, 76.9%) compared to polypharmacy.

Most of patients (n=80, 76.9%) did not receive other psychiatric medication. When other psychiatric medication was administered it was a mood stabiliser, used mainly in conjunction with an oral SGA (n=29, 33.7%). This result, however, was not statistically significant (p=0.531).

Side effects were noted more in oral SGAs than other class of antipsychotics, however there were no statistically significant associations (p=0.999).

Non-adherence was a problem (n=65, 62.5%), but its association with any particular class of antipsychotic was not statistically significant (p=0.286).

Summary

Taken together, these results have shown that oral SGAs were the most frequently used antipsychotics, with risperidone prescribed in most cases. The only oral FGA used was haloperidol, and chlorpromazine was only noted in previous trials. Side effects reported were mainly attributed to risperidone. LAIs were used mostly in cases where adherence was a problem. In most cases monotherapy was used.

Discussion

This study focused on assessing the factors associated with the choice of antipsychotics by doctors in the psychiatry department at a tertiary hospital. It identified four classes of disorders that were associated with the choice of antipsychotics, including psychotic disorders, substance or medication-induced psychiatric disorders, mood disorders, and psychiatric disorders due to another medical condition. As it was not clear that comorbid disorders influenced type of antipsychotics used, personality disorders were not included in this study, which focused on primary psychiatric diagnoses only.

Antipsychotics and psychotic disorders

The study results revealed that psychotic disorders were the main diagnoses associated with the use of antipsychotics. These results are consistent with Berrouiguet et al.,[12] who noted that the presence of psychotic symptoms was the most common reason for clinicians to prescribe antipsychotics.

Out of the 39 patients that were reviewed in this category, 27 (69.2%) were suffering from schizophrenia, and seven (17.9%) from schizoaffective disorder. This is in

keeping with another study that showed antipsychotics to be the primary medication effective in treating psychotic illnesses such as schizophrenia.[13]

Antipsychotics and mood disorders

The study showed that a mood disorder was also a diagnosis associated with prescribing antipsychotics. The prescription of antipsychotics was common among bipolar I disorder patients who made up 87.1% (n=27) and bipolar II disorder accounting for only one patient 3.2% of patients with mood disorders. This trend has been evident in other studies that have established that antipsychotic medication has been effective in treating the signs and symptoms in mood-induced illnesses such as bipolar I disorder.[14,15]

Antipsychotics and substance-induced or medication-induced psychiatric disorders

This study established that both substance or medication-induced psychiatric disorders were associated with the prescribing of antipsychotics as 26 of the study sample had substance-induced or medication-induced disorders (substance-induced bipolar and induced disorder, substance-induced psychotic disorder, or efavirenz-induced psychotic disorder).

Nine of the 34 patients with substance or medication-induced disorders were on LAIs, likely due to their history of non-adherence. This is in line with a meta-analysis by Semahegn et al.,[16] that showed an increased rate of non-adherence in both substance induced psychotic disorders and primary psychotic disorders with comorbid substance use disorder

Choice of antipsychotic

The present study proved the hypotheses that risperidone would be the most common oral SGA drug prescribed, with haloperidol being the most common oral FGA type, and that depot injectables would be used in cases of non-adherence in line with South African treatment guidelines.[6]

The study results showed that most patients were on SGAs (n=86). Out of the 86 patients, 59 were on risperidone only, and another 20 were on risperidone in combination with another drug. Thus, risperidone was the most common atypical antipsychotic drug prescribed for patients with psychiatric disorders.

Of the LAIs, the most common choice was flupenthixol which was used in 17 cases. Most of the patients on LAIs were noted to have non-adherence as hypothesised. Use in those without non-adherence is in line with data showing safety, efficacy and even better outcomes in patients on LAIs.[17]

The findings also showed that the oral FGA of choice was haloperidol, used in thirteen cases. Further, all clozapine users had been on at least two other antipsychotics previously (including olanzapine) as recommended by the Maudsley prescribing guidelines[18]. It was interesting to note that all patients on clozapine were non-adherent. This finding raises the question whether previous trials had been adequate, which per definition requires adherence.[19] Schizophrenia on the other hand itself raises a challenge in adherence due to declining cognition, social isolation, stigma, and comorbid substance use, all of which affect adherence. Up to a third of patients with schizophrenia are non-adherent.[19]

The study originally hypothesised that the choice of antipsychotic would be determined by cost and availability. It was not possible to test this hypothesis fully due to choice of antipsychotic at public sector facilities being largely influenced by the EML.

The hypothesis of availability was not tested for various reasons. Availability was originally conceptualised from the medication options provided by the hospital at the time of a patient's admission. Such information was however not found in the clinical records. In hindsight, availability could have also referred to any out-of-stock occurrences noted in the clinical records as a reason for changing antipsychotics. Further studies could incorporate this and highlight systemic causes rather than only clinical factors in antipsychotic prescription.

Due to the above reasons, the use of antipsychotics was largely based on the clinical indication.

Side effects

There were 21 occurrences of side effects reported as a result of antipsychotics. The types of side effects reported included EPSEs, diabetes, dyslipidemia, hypertension, weight gain, gynaecomastia, hypersalivation, and neutropaenia.

According to Atik et al.,[16] and Sørup, Brunak, and Eriksson,[21] side effects are an important factor to consider when choosing an antipsychotic.

Side effects are time-dependent and can occur in the short, medium, or long term. Helen Joseph Hospital is a general hospital with an average length of stay of about 15.4 days.[22] This could explain the few (n=6) side effects reported on current medication as in comparison to side effects on previous trials of medication (n=15).

Duration of stay as a factor was not studied but could be included in future studies to better describe this association.

It is worth noting that the nine types of side effects were recorded from 21 occurrences. Hypersalivation and neutropaenia, both well-known side effects of clozapine, were noted in only one patient each. It could be postulated that patients might not have volunteered information about side effects, did not have side effects to report or possibly that doctors did not ask about side effects According to a study by Read and Williams[23] involving 832 participants, 72 of the participants could not recall experiencing any side effects after using antipsychotics. Further, it could be a clinician issue, where doctors may not have documented them.

Monotherapy and polypharmacy

A significant majority of patients (n=80, 76.9%) were on monotherapy compared to polypharmacy. This is standard practice as antipsychotic monotherapy has been the recommended principle of treatment. Polypharmacy has been associated with higher medication costs, more side effects, and no clearly documented improvement in efficacy and, in fact, worse outcomes.[24] Antipsychotic polypharmacy has been justified in some cases in clinical practice in antipsychotic augmentation, treatment of residual symptoms, and in cross-titrating between antipsychotics. In general, however, polypharmacy practice lacks robust evidence.[25]

Study Limitations

As this was a retrospective study and the results were dependent on clinical records, incomplete, unavailable, and vague information was an obstacle.

There was a limitation due to the lack of uniformity of nomenclature such as “cluster B traits”. Although clinically useful in acute stages as a reminder to explore symptoms once a patient has recovered, it presents a challenge in research. Also, recording “EPSEs” remains vague. Parkinsonism, the most frequently occurring EPSE was not recorded individually and were most likely included under EPSEs.

This study assessed inpatients that were admitted from 01 July 2018 to 31 December 2018. The results therefore concern this specific time period and do not cover a long-term period.

Another limitation was that clinicians in the public setting are limited in the choice of antipsychotics by the available medication as per the EML. The choice of medication and rationale might be different if a wider variety of antipsychotics was available.

Finally, it was not within the scope of this study to explore the reasoning behind prescribing decisions such as patient load, forensic risk, high rate of non-compliance, and so on, which could have highlighted the nuances of clinical practice.

Conclusion and Recommendations

This study found that the most frequent conditions requiring antipsychotic medication were psychotic disorders, mood disorders and substance-induced or medication-induced disorders. The most frequent class of medication prescribed was SGAs, the main SGA being risperidone. LAIs were used largely in cases of non-adherence. Most common side effects were EPSEs with risperidone overall implicated in most side effects. Monotherapy was used significantly more often than polypharmacy.

The choice of antipsychotics at Helen Joseph Hospital was found to be associated with the diagnoses and history of non-adherence, in line with local guidelines.

A recommendation to deal with inconsistent recording of clinical information could be the use of a standardised clerking sheet with important clinical important information explicitly requested for clarity and uniformity.

Further studies could look at the same variables investigated in this study over a longer time period and in another setting out of hospital (e.g., clinics) to public setting . The scope could be extended to include the reasoning behind prescription decisions to treat psychiatric patients in the best way possible.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Author contributions

The first author undertook this study for his MMed degree. The second and third authors supervised this study. All authors contributed to the design and implementation of the research, the analysis of the results, and the manuscript's writing.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclaimer

The views expressed in the submitted article are the author's views and not an official position of the institution.

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Appendix A: Approved Research Protocol

University of the Witwatersrand

Faculty of Health Sciences

Division of Postgraduate Academic Management

M.Med (Psychiatry) Protocol

A Clinical Audit of Antipsychotic Prescriptions and Associated Clinical Profile at Helen Joseph Hospital, Johannesburg, South Africa

Protocol submitted to the Faculty of Health Sciences, University of the Witwatersrand, for a research report to be conducted in partial fulfilment for the degree of Masters in Medicine (Psychiatry)

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List of Abbreviations

EDL	Essential Drug List
EML	Essential Medicines List
EPSE	Extrapyramidal Side Effects
FGA	First Generation Antipsychotic
GCP	Good Clinical Practice
HJH	Helen Joseph Hospital
LAIs	Long-acting Injectables
SA	South Africa
SGA	Second Generation Antipsychotic
SPSS	Statistical Package for Social Sciences
STG	Standard Treatment Guidelines

1. Introduction

Drug utilisation research examines the factors that influence antipsychotic drug selection and prescribing patterns, which is defined by the World Health Organisation as "the marketing, distribution, prescription, and use of drugs in a society, with a special emphasis on the medical, social, and economic consequences." Over time, this definition has included other definitions, such as the pattern of use, which describes the extent and profiles of drug use and the trends in use and costs over time. For the purposes of this study, we will focus on the factors influencing the choice of antipsychotics by doctors in the Psychiatry department at a tertiary hospital. Such studies in themselves do not necessarily provide answers, but they contribute to rational drug use[1].Factors that affect antipsychotic choice will be further explored in the literature review.

2. Literature Review

A review of the literature points to possible factors influencing the choice of antipsychotics, and discussions of these factors below will yield variant scientific gaps to be addressed within the present study. The study thus proposes the evaluation of such factors by means of a retrospective clinical records review of patients admitted for six months at Helen Joseph Hospital.

2.1 The Indications of Antipsychotic Medication

The term antipsychotic refers to a group of agents used to manage symptoms of several psychiatric disorders as they possess various properties, including antipsychotic, anti-manic, and mood-stabilising properties (Eloff et al.[9]; Emsley[11]). Antipsychotic medication indications include a wide spectrum of disease, ranging from

schizophrenia, schizoaffective disorders, acute mania, and major depressive disorder with psychotic features. They may also be used in conditions such as delusional disorder, Tourette disorder, borderline personality disorder, dementia, and delirium. This spectrum of mental disease poses a burden, both globally and in the South African context, often remaining undiagnosed and untreated. Those treated often face unwanted side effects.

A meta-analysis conducted by Steel et al., (2014) found that 17.6 of people surveyed across 63 countries experienced a common mental disorder in 12 months, and 29.2 (about 1 in 3) did so in the course of their lifetime. Similar numbers were reported in a South African study conducted in the Western Cape that showed the incidence of common mental disorders among SA adults of 16.5, while lifetime prevalence for any psychiatric disorder was 30.3 (Jacobs et al., 2018).

2.2 Prevalence of Antipsychotics Use

Antipsychotics are commonly prescribed drugs for various psychiatric disorders and are broadly categorised into First- and Second-Generation Antipsychotics, FGA and SGA, respectively. Studies have shown that there are variations in prescribing choice globally (Shaifali et al., 2018). These variations are due to factors such as:

- Standard treatment guidelines
- Side effect
- Adherence
- Medical comorbidities
- Drug availability and Cost (Khan et al., 2018).

An illustration of such variations can be seen when comparing certain scenarios. For example, a study in Australia reported 77.3 use of atypical antipsychotics as the first-line treatment for Schizophrenia, with the main drug of choice being Olanzapine. Conversely, more patients (55) were on typical antipsychotics (of patients on single antipsychotics) in East Asia[1]. Through such studies, it has emerged that cost remains the most influential factor in the choice of antipsychotics in both developed and developing countries, even in cases where standard treatment guidelines advocate otherwise.

2.3 The Commonly Seen Considerations in the Choice of Antipsychotics

2.3.1 Standard Treatment Guidelines

The National Department of Health includes or removes a drug from the Essential Medicines List (EML) using an evidence-based review of safety and effectiveness, followed by considerations of cost. It also anticipates that each province will review the EML and prevailing tenders to compile a formulary which selects the preferred member of the therapeutic class based on cost (Bera et al.[4]).

The South African Standard Treatment Guidelines EML for tertiary hospitals lists the use of antipsychotics for psychotic disorders as well as other psychiatric conditions such as bipolar mania and major depression. The guidelines recommend haloperidol or risperidone as first-line treatment with a switch to chlorpromazine for consideration if optimal doses of first-line treatment show a partial response. In the event of problems with adherence, depot antipsychotics such as flupenthixol decanoate, fluphenazine decanoate, or zuclopenthixol decanoate are recommended. In the event of EPSEs,

the STG recommend using the lowest effective dose or switching from haloperidol or chlorpromazine to risperidone. Clozapine is reserved for treatment-resistant cases (Bera et al.[4])

2.3.2 Side-Effect Profile and Effectiveness Against Symptoms

First-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) are commonly referred to as “typical” and “atypical” antipsychotics, respectively (Eloff et al.[1]). The difference between them arises from the mechanism of action whereby FGA show a high affinity for dopamine 2 (D2) receptors, while the SGAs are dopamine-serotonin antagonists with a high affinity for serotonin 2A (5HT-2A) receptors (Eloff et al. [1]).

FGAs are older drugs that are effective in treating positive psychotic symptoms and are relatively inexpensive. The greatest disadvantage, however, remains the side effects of extrapyramidal side effects (EPSE) and tardive dyskinesia, which often impede adherence and, at times, lead to irreversible damage (Kendall, 2011; Siever et al., 2004). Adverse effect burden, including EPSE’s, central nervous system effects (sedation, cognitive slowing), cardiovascular abnormalities, and anticholinergic side effects, are linked to a higher dose of antipsychotics. A reduction in antipsychotic dose may improve negative and cognitive symptoms (Taylor et al., 2018).

Due to the side effects associated with FGAS, the search for antipsychotics that were effective against symptoms without the risk of EPSEs began, leading to the advent of SGAs (Eloff et al.[1]). SGAs are also known to alleviate negative symptoms and are better tolerated than FGAs (Weinbrenner et al., 2009). They are, however, costlier (Krakowski Czobor et al., 2009). The verdict on whether SGAs are superior to FGAs is unclear. Although SGAs lower the risk of drug-induced movement disorders, as well

as the apparent superior efficacy, doubt has been expressed over their safety advantages due to the metabolic side effects of weight gain and alteration of glucose and lipid metabolism (Eloff et al.[1]; Taylor et al., 2018).

2.3.3 Adherence

The likelihood of adherence is another consideration in the choice of an antipsychotic. Partial and non-adherence are common in patients receiving oral antipsychotics. Various factors attributed to this are side effects, ongoing substance abuse, cognitive deficits, and poor insight into illness (Kane et al., 2009; Law, 2008; Tandon et al., 2009). Studies have shown a 40 or higher rate of non-adherence in patients with first-episode psychosis (FEP) (Kreyenbuhl et al., 2011; Miller et al., 2011). Accordingly, long-acting injectables (LAIs) were developed in 1966 to address this issue, the first of which was fluphenazine enanthate. Brissos and colleagues (2014) found that good adherence results in better outcomes seen as improvement in clinical symptoms, social and occupational functioning, a reduction in polypharmacy, and a decline in the rate of hospitalisation and duration of hospital stay.

2.3.4 Medical Comorbidities

Medical comorbidities such as diabetes and cardiovascular disease are common in patients with severe mental disorders such as schizophrenia and bipolar disorder. Patients with serious mental disorders, according to studies in the United States, have a greater chance of premature mortality than the general population. Untimely cerebrovascular and coronary heart diseases are the major causes of shortened life expectancy among service users, with up to 60 of this mortality owing to avoidable and curable medical conditions. Furthermore, people with mental illnesses have a difficult time accessing and receiving adequate care from public health facilities

(Cranwell et al., 2016). Antipsychotic medicines, in particular, are linked to greater metabolic adverse effects, which might exacerbate pre-existing medical problems. As a result, medical comorbidities should be addressed before selecting an antipsychotic (Newcomer, 2009).

2.3.5 Cost

Cost remains an important factor in the choice of antipsychotics and has an economic bearing on budgets for health services, particularly in low-resourced settings like South Africa. Factors such as polypharmacy for severely ill patients results in higher health services costs and higher utilisation rates of services (Razzouk et al., 2015). Schizophrenia, for example, is seen to be the costliest psychiatric illness. In the USA, schizophrenia and other psychotic disorders account for 2.5 of the annual total health budget (Emsley[9]. In South Africa, an Eastern Cape study found that haloperidol was the most prescribed antipsychotic due to its low cost and availability. Overall, 66 of patients were on FGAs, while 34 were on SGAs (Eloff et al.1).

There is a paucity of research regarding antipsychotic use exploring the incidence of antipsychotic use in the South African context, with the only available study limited by sample size and research site (Purcell et al., 2019). Nonetheless, the World Health Organisation estimates that almost 50 of medication prescribed is not necessary, and this is a major concern in the global health system (Shaifali et al., 2018). Due to high variation globally, there is a need for local data as it is evident from the literature that there are disparities across countries and regions in the prescription patterns of antipsychotics. It is not clear which of these trends are transferable to South Africa (Emsley et al.[11]) Hence, it would be a valuable exercise to study local prescription patterns to compare to global trends and also to local standard treatment guidelines.

The findings of this study can then inform robust rational and cost-effective use of antipsychotics and reinforce the need to prevent the misuse of antipsychotics (Shaifali et al., 2018).

So, it is with this background that the intent of this study is to answer the following questions:

- What are the most commonly used antipsychotics in the patient population at a tertiary academic hospital?
- What are the reasons behind our choice of antipsychotics?

3. Hypothesis

We hypothesise that:

- ❖ The choice of antipsychotics, regardless of psychiatric diagnosis, will be determined mainly by availability, followed by side effects.
- ❖ Risperidone will be the most common atypical drug prescribed, with haloperidol being the most common typical, and depot injectables will be used in cases of non-adherence, all in line with South African Treatment Guidelines.

4. Study Aim

The aim of the study is to describe the choice of antipsychotics at discharge (typical vs. atypical, low vs. high potency, oral vs. LAI) and any associations with clinical factors (demographics, psychiatric diagnoses, and medical comorbidities) in patients admitted to Helen Joseph over a 6-month period.

5. Specific Objectives

4) To describe the demographic and clinical profile of patients discharged or transferred from HJH on antipsychotic medication.

5) To describe the choice of antipsychotic; class of antipsychotic, potency, oral vs. LAI, and ascertain prescribing as monotherapy or antipsychotic polypharmacy.

6) To determine the association, if any, between antipsychotic choice and demographic and clinical profile.

6. Methods

The study will be a quantitative retrospective analysis with a cross-sectional chart review. It will be conducted at Helen Joseph Hospital in, South Africa. Helen Joseph Hospital is a government public hospital with a psychiatric unit providing emergency, outpatient, and inpatient care. Data will be extracted from the available clinical records (psychiatry department database, discharge summaries, and patient files) of patients who were admitted to the hospital from 01 July 2018 to 31 December 2018 and will be statistically analysed. For clinical data where indicated, information on obesity will be obtained and any changes in weight are noted on admission and at discharge. In the assessment of side effects patients with pre-existing comorbities e.g., Diabetes, Hypertension, Parkinson's will be excluded from analysis relating to side effects secondary to antipsychotic medication.

Helen Joseph admits about 30-40 patients per month, which averages at 210 patients per six-month period. Most admitted patients are severely ill, requiring an antipsychotic. Assuming about 80 are discharged on antipsychotics, this yields about

168 patients per six-month period. From an assessment of Z scores of expected frequencies, a sample size of 144 patients will detect statistical significance between the choice of antipsychotics at the 5 level. Realistically, statistical significance can be expected with a minimum sample of 84 patients (the lowest number recommended) based on the number of sub-categories of the clinical profiles. This target will, therefore, be reached by including patients admitted in the period 01 July 2018 to 31 December 2018**.** Cases will be selected in a retrograde manner, working backward from December 2018 until the sample size of 144 is attained.

6.1 Patient Selection

i) Inclusion criteria:

iv. All subjects must have had admission to the Psychiatry ward at Helen Joseph Hospital between 01 July 2018 to 31 December 2018.

v. Subjects must have been discharged (including transferred patients) on antipsychotic medication, either FGA, SGA, or LAI.

vi. All subjects must be over 18 years old.

ii) Exclusion criteria:

i. The subjects must be below 18 years old.

6.2 Study Overview

Several steps will be followed to complete this study. Specifically, a list of all the names of patients admitted to Helen Joseph Hospital between 01 July and 31 December 2018 will be obtained from the hospital clinical records. Information will be collated from

discharge summaries patient files and if available the Helen Joseph Hospital electronic database. The names of patients treated and discharged from the psychiatric department at Helen Joseph Hospital between 01 July and 31 December 2018 will be obtained.

i) All patients discharged on any antipsychotic agent during the study period (1 July to 31 December 2018) will be included in the study.

ii) The demographic information, psychiatric diagnoses, medical comorbidities, and medication data will be extracted from available clinical records.

6.2.1 Data Collection

Data will be obtained from the clinical records (discharge summaries, patient files, and the departmental electronic database), and will include both demographic and clinical variables.

6.2.2 Data Variables

Variables such as age, source of income, gender, marital status, and source of income for individuals discharged on antipsychotic agents will be gathered.

6.3 Data Cleaning

A chart review will be conducted, and the data will be captured on a data capture sheet (Appendix 1), which is given a case number, and the patients' personal information will be anonymised. Subsequently, the data will be populated into an Excel database and assessed for any omitted or missing information, as well as for possible erroneous

entries. The variables will be coded appropriately, and the now relevant dataset will be used for further statistical analysis.

6.4 Data Analysis

The software used for statistical analysis is Stata, and a statistician will be consulted when analysing the data. A confidence interval of 95 with a p-value of 0.05 shall be chosen. Descriptive statistical tests to measure central tendency (mean, median, mode) and measures of data spread (standard deviation, variance, quartiles, and interquartile range) will be conducted. Data will be tested for parametric distribution. Inferential statistics will then be conducted and reported on as conclusive findings in this cohort. Data will be analysed using comparative statistics using paired t-test/chi squared tests/analysis of variance (ANOVA) for parametric data. The Mann-Whitney test will be used for non-parametric data, unless otherwise advised by the statistician.

7. Study Limitations

As this is a retrospective study, and the results are dependent on clinical records, incomplete or unavailable data will be an obstacle. The study assesses inpatient subjects that were admitted from 01 July 2018 to 31 December 2018. There will be no long-term follow up for patients.

8. Ethical Considerations

Ethics clearance will be sought from the University of the Witwatersrand's Human Research Ethics Committee (Medical), and approval to conduct the study and access patients' clinical records will be obtained from the Chief Executive Officer of Helen Joseph Hospital and the Helen Joseph Hospital Research Committee. As a

retrospective clinical record review, this study does not involve any therapeutic intervention, and no risk to participants is involved. A study number will be assigned to each record. The investigator will conduct the study at the site as a clinical audit. All the data will only be accessed by the primary researcher. Data protection will be ensured, and all records collected will be stored safely for a minimum of 5 years in accordance with Good Clinical Practice (GCP) Guidelines. There are no noted conflicts of interest.

9. Feasibility

9.1 Timing

Data collection will commence as soon as the protocol is approved by the Postgraduate Committee and the Ethics Committee.

	2019			2020								
	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Oct
Literature Review												
Preparing Protocol												
Protocol Assessment												
Ethics Application												
Data Collection												
Data Capturing and Analysis												
Thesis write up and supervisor review												

9.2 Budget

Due to the low-cost nature of the study, all costs will be borne by the researcher.

Item	Estimated cost (R)	Funder
Travel	R1000.00	Dr Jones Mwenda
Photocopies and printing	R1000.00	Dr Jones Mwenda
Stationary	R500.00	Dr Jones Mwenda
Total cost	R2,500.00	

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Data Capture Sheet

Patient information			
Study case number			

Demographic data				
Age				
Gender	Male		Female	
Income	Employed	Grant	Pension	None

Psychiatric variables			
Diagnosis (DSM-5)			
Psychoactive substance	Yes	No	Unknown
Delusional disorder	Yes	No	Unknown
Schizophrenia	Yes	No	Unknown
Schizophreniform	Yes	No	Unknown
Schizoaffective	Yes	No	Unknown
Brief psychotic episode	Yes	No	Unknown
Bipolar I disorder	Yes	No	Unknown
Bipolar II disorder	Yes	No	Unknown
Depressive disorder with psychotic disorder	Yes	No	Unknown
Intellectual disability	Yes	No	Unknown
Neurocognitive disorder	Yes	No	Unknown
Personality disorder	Yes	No	Unknown
Other psychiatric disorder	Yes	No	Unknown
Index admission (year)			
Number of previous admissions			Unknown

Medication			
Oral first generation antipsychotic	Haloperidol	Yes	No
	Chlorpromazine	Yes	No
Oral second generation antipsychotic	Risperidone	Yes	No
	Olanzapine	Yes	No
	Aripiprazole	Yes	No
	Amisulpiride	Yes	No
	Quetiapine	Yes	No
	Clozapine	Yes	No
Long acting injectable	Flupenthixol LAI	Yes	No
	Zuclopenthixol LAI	Yes	No
	Paliperidone LAI	Yes	No
	Risperidone LAI	Yes	No
Anticholinergics	Yes	No	
Other medication	Yes	No	
Previous trials	Yes	No	Unknown
Treatment non-adherence	Yes	No	Unknown
Pharmacy	Monotherapy	Polypharmacy	

Side effects				
Extrapyramidal side effects	Acute dystonia	Yes	No	Unknown
	Akathisia	Yes	No	Unknown
	Parkinsonism	Yes	No	Unknown
	Tardive dyskinesia	Yes	No	Unknown
Metabolic side effects	Diabetes	Yes	No	Unknown

	Dyslipidemia	Yes	No	Unknown
	Hypertension	Yes	No	Unknown
	Renal dysfunction	Yes	No	Unknown
	Obesity (BMI > 30 kg/m^2)	Yes	No	Unknown
Galactorrhoea		Yes	No	Unknown
Erectile dysfunction / decreased libido		Yes	No	Unknown
Other side effects		Yes	No	Unknown

Pre-existing medical comorbidities			
HIV	Yes	No	Unknown
Diabetes	Yes	No	Unknown
Hypertension	Yes	No	Unknown
Renal dysfunction	Yes	No	Unknown
Other medical comorbidities	Yes	No	Unknown

Appendix B: Ethical Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr J Mwenda
School of Clinical Medicine
Department of Psychiatry
Medical School
University

E-mail: drjonesmwenda@gmail.com

CC: Supervisor: Dr R Sapinoso and Professor U Subramaney
<rhodiesapinoso@gmail.com>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/09/14

REF: *R14/49*

PROTOCOL NO: **M200402** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *A clinical audit of antipsychotic prescriptions and associated clinical profile at Helen Joseph Hospital, Johannesburg, South Africa*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain2007/Clearscan.wps

Appendix C: Permission to Carry Out Research

HREC 2019

Signatures:

I understand that no data may be collected until I have received the full ethics clearance certificate.

Title of the Research Project:

A Clinical Audit of Antipsychotic Prescriptions and Associated Clinical Profile at Helen Joseph Hospital, Johannesburg, South Africa

Applicant's Signature: **Date:** 01 Feb 2020

WHO WILL SUPERVISE THE PROJECT? (Where applicable)

Name: Dr Sapinoso **Department:** Psychiatry

Telephone No: **Email:** [illegible]

Signature: **Date:** 10 February 2020

HEAD / RESEARCH COORDINATOR OF DEPARTMENT / ENTITY IN WHICH STUDY WILL BE CONDUCTED (Where applicable) (Wits Students Academic HOD must sign)

Name: [illegible] **Department / Entity**

Tel No: 011 489 0620 **Email:** albert.jansevanrensburg@wits.ac.za

Signature: **Date:** 3/2/20

Acting Head HOD, SOZM.

SECTION 9