PRESCRIBING PATTERNS OF LONG ACTING INJECTABLE ANTIPSYCHOTICS AT COMMUNITY PSYCHIATRIC CLINICS IN JOHANNESBURG

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Declaration

I, Nabila Veyej, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine (Psych) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University

(Signature of candidate)

On this 18th day of March 2021 at Johannesburg

Dedication

To my parents;

My father Muhammed, for your unwavering support through everything,

My mother Shamima, for being my role model and my strength,

Words are not enough to express my gratitude; I would be nothing without you both.

To my brother;

Suhayl, you inspire me every day with your tenacity and kindness.

To my husband;

Ya'eesh, thank you for your encouragement and unconditional love, always.

And lastly, to my son;

Israar, you've spent your first weeks of life dozing peacefully by my side, patiently waiting as I pored through textbooks and typed away feverishly at my laptop

You are my greatest accomplishment

Abstract

Although long-acting injectable antipsychotics (LAI - APs) improve adherence and reduce the risk of relapse in schizophrenia, they are prescribed late, after functional deterioration has occurred. There is a paucity of information regarding prescribing practices for LAI - APs in South Africa. A retrospective review of the charts of 206 patients on LAI - APs attending three psychiatric clinics in Johannesburg was conducted. Significantly more patients were male (74.8%), single (94.2%) and, unemployed or in receipt of a social grant (96.1%) ($p<0.001$). A comorbid substance use disorder was diagnosed in 47.6%, and the indication for the prescription of a LAI - AP was non-adherence in 66.0 %. In 90.3 % of the patients, some other psychotropic medication was prescribed in combination with the LAI – AP. This study confirms a missed opportunity in that LAI - APs were prescribed after patients were non–compliant with oral antipsychotics. We highlight the high prevalence and problem of LAI - AP polypharmacy.

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List of Acronyms

FGA	First-generation antipsychotics
DSM	Diagnostic and Statistical Manual of Mental Disorders 5th edition
LAI - AP	Long-acting injectable antipsychotic
RCT	Randomized control trial
SA	South Africa
SD	Standard deviation
SMI	Severe mental illness
USA	United States of America

Prescribing patterns of long acting injectable antipsychotics within a community setting

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Short title: Prescribing long acting injectable antipsychotics

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ABSTRACT

Background: Long-acting injectable antipsychotics (LAI - APs) improve adherence to antipsychotic medication and decrease functional decline in schizophrenia. Yet, they are prescribed late, in patients with established functional decline. Although LAI - APs are widely prescribed in South Africa, there is a paucity of research regarding the prescription profile for LAI - APs.

Aim: To describe prescribing practices for LAI - APs in patients attending three psychiatric clinics in Johannesburg.

Setting: Chiawelo, Westbury and, Lenasia South community psychiatric clinics in Johannesburg, South Africa.

Methods: A retrospective review of the medical files of all patients on LAI - APs attending the clinics over the study period was conducted. Socio-demographic, clinical and, information regarding the LAI – AP prescribed was extracted from the files.

Results: A total of 206 charts were examined. The mean age of the study population was 46 (SD±12) years. Significantly more patients were male (74.8%), single (94.2%) and, unemployed or in receipt of a social grant (96.1%) ($p<0.001$). Approximately half had a comorbid substance use disorder (47.6%). The most common indication for the prescription of a LAI - AP was non-adherence (66.0%). Only 9.7 % of the patients were prescribed a LAI - AP alone. There were no significant socio–demographic and clinical characteristics associated with this prescribing habit. A LAI - AP was prescribed in combination with an oral antipsychotic, mood stabiliser or, antidepressant in 53.9 %, 44.7% and, 7.8% of patients respectively.

Conclusion: LAI - APs were prescribed mainly for patients after they were non-compliant with oral antipsychotics. This may represent a missed opportunity to initiate LAP – APs earlier in the course of illness, as a means to prevent future relapses and functional decline. We highlight the high prevalence of LAI - AP polypharmacy.

Keywords
Long acting injectable antipsychotics, polypharmacy, community, Africa

INTRODUCTION

The introduction of oral antipsychotic medication in the early 1950s transformed the treatment of schizophrenia globally (1). However, the problem of non- or partial adherence to oral antipsychotic medications is common. Up to 50% of patients with schizophrenia do not take their medication as prescribed, resulting in a four–fold higher risk of relapse (2,3). The goal of treatment is to avoid relapses because relapses are associated with serious psychosocial, biological and, economic consequences (4). Several patient, provider, and medication-related factors are associated with non or partial adherence to antipsychotic medication (3). One such medication-related factor, the prescribing of long acting injectable formulations of antipsychotic medication has been shown to improve adherence to antipsychotic medication (3,5). Long-acting injectable antipsychotics (LAI - APs) decrease the potential for missed doses because they are administered either once or twice per month compared to the daily ingestion of an oral antipsychotic. LAI - APs also provide continuous drug delivery with a more favourable pharmacokinetic profile, higher bioavailability and, stable receptor occupancy (6).

Several studies have shown a definite advantage of LAI - APs in reducing relapses (7–9). However, some of the early studies in favour of LAI - APs over oral medications were called into question by Schooler et al. (10) because they were retrospective, did not control for changes in service delivery patterns over time, and treatment was not randomised. Even some subsequently conducted randomised control trials (RCTs) failed to confirm a clear advantage of LAI - APs over oral antipsychotics (11,12). A possible explanation for these inconsistent findings is the methodological differences and bias associated with observational studies compared to RCTs. RCTs do not investigate real-world patients under real-world conditions and therefore, may produce spurious results (8,13). Compared to oral antipsychotics, the improved adherence associated with the prescription of LAI - APs has been shown to decrease the relapse rate (9,14), as well as the number and duration of hospitalisations (15) with a consequent decrease in the cost of care (16). Despite the improved adherence and the subsequent benefits conferred by LAI - APs, they are on average only prescribed in 20 – 37% of patients with schizophrenia (5,17,18).

Various socio-demographic and clinical factors have been associated with the prescribing of LAI - APs. These factors include the duration of illness (19), gender (19–22), ethnicity (23,24), education (24), socioeconomic status (22,24–26), comorbid substance use disorders (24), inpatient versus out-patient care (21), acceptability to patients (27), adherence to antipsychotic medication (3,5), and attitude of psychiatrists towards LAI - APs (28).

A key advantage of LAI - APs over oral antipsychotics is that they improve adherence to antipsychotic medication because they do not have to be taken daily. Yet, it is reported internationally that concurrent prescriptions of oral psychotropic medication are frequent, with 46 -75% of patients on LAI - APs also receiving concurrent prescriptions of an oral psychotropic (24,27,29–32). It is possible that combining LAI – APs with oral psychotropic medication is an augmentation strategy in patients who show a partial response to the LAI – AP (31). It has been reported anecdotally that the co-prescribing of LAI -APs with oral psychotropic medication is a common practice in South Africa (SA).

Despite over two decades of research on prescribing practices for LAI - APs globally (25), there remains a gap in the literature with regard to the prescription patterns for LAI – APs in SA. Only a few local studies have included information on the prescription of LAI - APs, and these were either limited to patients of only one ethnic group (33), patients recently

discharged from a psychiatric hospital (34), or out-patients attending tertiary psychiatric hospital clinics (27)

Hence, this study aimed to examine the prescribing practices for LAI - APs in patients attending community psychiatric clinics in Johannesburg, SA. The objectives were to describe the socio–demographic characteristics, the clinical characteristics, the types, dosages and, frequency of the LAI - APs that were prescribed. Specific objectives were to determine the prevalence of the concurrent prescriptions of LAI - APs and oral psychotropic medication and to examine if any significant socio-demographic and clinical characteristics were associated with this prescribing habit.

METHOD

The study was a retrospective chart review that was conducted at three community psychiatric clinics in Chiawelo, Westbury and, Lenasia South, Johannesburg, SA. These clinics were randomly selected from the 23 clinics in the Johannesburg Health District. Each clinic in the district was assigned a number, and three numbers were randomly drawn. The numbers drawn corresponded to the clinics included in this study. The psychiatric clinics are staffed by psychiatric nurses and medical officers or registrars in training for psychiatry. The psychiatric clinics' patient records are filed separately from the community health center's clinical records.

All adult patients (aged 18 and older) attending Chiawelo, Westbury and, Lenasia South clinics who had received a LAI - AP during August 2018 were included in the study. There were no exclusion criteria.

Each clinic's nursing staff maintains a monthly register of all patients for whom a LAI - AP is administered. The principal investigator accessed the clinical files of the patients who met the inclusion criteria and used a data collection form to manually record the following socio-demographic, clinical and, treatment variables from the clinical notes: age; gender; population group; relationship status; the highest level of education achieved; employment status; primary psychiatric diagnosis; duration of illness; family history of mental illness; comorbid illnesses (psychiatric, medical and substance use); prescription of oral medication and details of the LAI - AP prescribed (the main indication for the initiation, date of initiation, LAI - AP prescribed, frequency of administration and dose).

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (M181062). Permission to conduct the study was obtained from the research committee of Johannesburg Health District. As this was a retrospective study, we were not required to obtain written informed consent from each patient (or family member) for the use of his/her medical information. All records made on the data collection sheet were kept confidential. The name and patient numbers were anonymised on the populated databases bases in Microsoft Excel and raw data was only viewed by the principal investigator.

DATA ANALYSIS

A descriptive analysis of the socio-demographic and clinical variables was performed. All statistical analyses were conducted using R software (version 3.50, http://www.R-project.org). All tests were two-tailed probability values, and statistical significance was accepted when $\alpha \leq 0.05$. The data set for this study was generated from assessments of

categorical scores, which are usually non-normal, so appropriate non-parametric analyses were used.

For meaningful statistical analysis, the patients were subsequently divided into two other groups namely: those on LAI - AP alone, and those on LAI - APs combined with oral antipsychotic medication, and the categories of some of the variables were collapsed. The chi-square test or Fisher's exact test was applied to determine if there was a significant relationship between the socio-demographic and clinical variables in patients receiving LAI - APs only versus those receiving concurrent prescriptions of LAI - APs and oral psychotropic medication. Multivariate logistic regression analysis was performed with 95% confidence intervals to adjust for relevant covariates

RESULTS

This study comprised of 206 patients who received a LAI - AP when attending one of three community psychiatric clinics. The mean age of the study population was 46 (SD±12) years. Approximately half (n=100; 48.5%) were in the 40 – 59 year age group. The majority were males (n=154; 74.8%), black (n=155; 75.2%), single (n=194, 94.2%) and unemployed or in receipt of a social grant (n=198; 96.1%) ($p< 0.001$) (Table1).

The majority of the study patients had a primary psychiatric diagnosis of a schizophrenia spectrum or a related disorder (n=144; 69.9%), no comorbid psychiatric diagnosis (n=164; 79.6%), no comorbid substance abuse (n=108; 52.4 %) and no comorbid medical illness (n=138; 66.9%). The most commonly abused substance was cannabis (n=42; 20.4), followed by alcohol(n=32; 15.5 %).The mean duration of the primary psychiatric illness was 19 years (SD±11.5), and the majority (n=153; 74.3%) had a duration of illness of 0 – 19 years (Table 1).

The LAI – APs prescribed were either flupenthixol decanoate (n=132; 64.1 %) or zuclopenthixol decanoate (n=74; 35.9 %). The frequency of either form of injection was monthly (n=197; 95.6%) or two-weekly (n=9; 4.4%). The mean duration of prescription was 11.58 (SD ± 10.3) years, with the majority (n=119; 57.8%) being on it for less than19 years The indications for prescribing an LAI - AP was non-adherence to oral medication (n=136; 66%), followed by low level of functioning (n=17; 8.3%), comorbid substance use (n=16; 7.8%), non-response to orals (n=12; 5.8%) and patient preference (n=14; 6.8%).The dose of flupenthixol decanoate ranged from 10mg to 80mg ,with a mean of 29.0 mg (SD±12.4) .The most frequently prescribed monthly dose was 20mg (n=57; 43.2%). The dose of zuclopenthixol decanoate ranged from 80mg to 800mg with a mean of 271 mg (SD±107). The most frequently prescribed monthly dose was 200mg (n=32; 43.2%)(Table 2).

Of the 206 patients in the study population, only 9.7 % (n=20) were prescribed a LAI - AP alone. The other 90.3 % (n=186) was prescribed some oral psychotropic medication in addition to the LAI - AP. In more than half of these patients, it was an oral antipsychotic (n=111, 53.9%). A mood stabiliser (n=92; 44.7%) or antidepressant (n=16; 7.8%) was prescribed less frequently (Table 3). Anticholinergic medication was prescribed for approximately one in three patients (n=75; 36.4%).

The majority of the patients in the group that were prescribed a LAI - AP combined with another oral antipsychotic were males (n=81; 72.9%), black (n=79; 71.2%), single (n=101;

90.9%), had achieved a secondary/tertiary level of education (n=58; 52.3%) and were unemployed (n=105; 94.6%). Close to half (n=48; 43.2%) of the patients were in the 40–59 year age group. Also, the majority (n=75; 67.6%) had a primary diagnosis of schizophrenia spectrum disorder, no comorbid psychiatric diagnosis (n=57; 51.4%), no comorbid substance use disorder (n=58; 52.3%) and no comorbid medical illness (n=72; 64.9%). The majority (n=87; 78.3%) had a duration of illness of less than 19 years (Table1).

The LAI - APs prescribed in this group was either flupenthixol decanoate (n=70; 63.1 %) or zuclopenthixol decanoate (n=41; 36.9 %). The frequency of either injection was monthly (n=106; 95.5%) and two-weekly (n=5; 4.5%), with the majority being on it for less than19 years (n=87; 78.4%) The indications for prescribing an LAI - AP was non-adherence to oral medication (n=69; 62.2%), followed by comorbid substance use (n=10; 9%), low level of functioning (n=9; 8.1%), non-response to oral medications (n=8; 7.2%), and patient preference (n=7; 6.3%). The indication was not recorded in three (2.7%) patients. The indications for prescribing LAI -APs were extracted from the files as recorded by the treating doctor. Non-response to oral medications includes patients with an inadequate response to oral medication, where treatment was augmented with the addition of a LAI – AP. The investigator's interpretation is that prescribers used "low level of functioning" to describe patients with varying degrees of intellectual disability; and that prescribers used a "comorbid substance abuse" diagnosis in patients who abused substances concurrently with a primary psychiatric diagnosis (Table 2).

There were no statistically significant differences between the group that was on LAI -AP alone compared to the group that was on LAI - AP combined with an oral antipsychotic with respect to gender (x^2=0.435; p=0.5), age (x^2 =3.845; p=0.1), race (x^2=1.665; p=0.2), marital status (p=0.359), level of education achieved (x^2=1.526; p=0.5), employment status (p=0.59), primary psychiatric diagnosis (p=0.363), duration of illness (p=0.346), and the presence of comorbid psychiatric illness (x^2=1.813; p=0.2) or comorbid substance use (x^2=1.018; p=0.3) (Table 1). There was a statistically significant difference with regards to comorbid medical illness (x^2= 4.979, p=0.03); however, on multivariate analysis, the p-value was 0.6.

There was also no statistically significant difference between the two groups with regards to the specific LAI – AP prescribed (x^2=0.027; p=0.87), the duration of LAI – AP prescribed (p=0.346), the injection interval (p=1.000), and the indications for LAI- AP prescription (p=0.912) (Table 2).

Table 1. Frequency distribution of the characteristics of the study population, the group of patients on LAI - APs only, and the group on LAI - AP combined with oral antipsychotics

VARIABLES	Study population (N=206) n (%)	LAI-AP only (N=20) n (%)	LAI-AP and oral antipsychotic (N=111) n (%)	Statistics
GENDER				
Male	154 (74.8%)	16 (80.0%)	81 (72.9.%)	X^2=0.435
Female	52 (25.2%)	4 (20.0%)	30 (27.1%)	p=0.5
AGE (YEARS)				
Mean age 46 (SD±12) years.				
18-39	74 (35.9%)	9 (45.0%)	45 (40.5%)	X^2=3.845
40-59	100 (48.5%)	11 (55.0%)	48 (43.2%)	p=0.1
>60	32 (15.5%)	0 (0.0%)	18 (16.2%)	
RACE				
Black	155 (75.2%)	17 (85.0%)	79 (71.2%)	X^2=1.655
Non black	51 (24.8%)	3 (15.0%)	32 (28.8%)	p=0.2
MARITAL STATUS				
Married	12 (5.8%)	0 (0.0%)	10 (9.0%)	0.359*
Single	194 (94.2%)	20 (100%)	101 (90.9%)	
HIGHEST LEVEL OF EDUCATION				
None/primary	65 (31.6%)	4 (20.0%)	35 (31.5%)	X^2=1.526
Secondary/tertiary	109 (52.9%)	11(55.0%)	58 (52.3%)	p=0.5
Unknown	32 (15.5%)	5(25.0%)	18 (16.2%)	
EMPLOYMENT STATUS				
Employed	8 (3.9%)	0 (0.0%)	6 (5.4%)	p=0.590*
Unemployed/on a grant	198 (96.1%)	20 (100%)	105 (94.6%)	
PRIMARY PSYCH DISORDER				
Schizophrenia spectrum	144 (69.9%)	18 (90.0%)	75 (67.6%)	p=0.363*
*Mood disorder***	29 (14.1%)	1 (5.0%)	12 (10.8%)	
Intellectual disability/neurocognitive	21 (10.2%)	1 (5.0%)	16 (14.4%)	
Substance use disorder	12 (5.8%)	0 (0.0%)	8 (7.2%)	
DURATION OF ILLNESS (YEARS)				
*Mean duration of illness*19 *(SD±11.5)*				
0-19	153 (74.3%)	13 (65.0%)	87 (78.4%)	p=0.346*
20-29	37 (18.0%)	5 (25.0%)	15 (13.5%)	
>30	13 (6.3%)	1 (5.0%)	8 (7.2%)	
Unknown	3 (1.4 %)	1 (5.0%)	1 (0.9%)	
COMORBID PSYCH ILLNESS				
Yes	42 (20.4%)	13 (65.0%)	54 (48.6%)	X^2=1.813
No	164 (79.6 %)	7 (35.0%)	57 (51.4%)	p=0.2
COMORBID SUBSTANCE USE				
Yes	98 (47.6%)	12 (60.0%)	53 (47.7%)	X^2=1.018
No	108 (52.4%)	8 (40.0%)	58 (52.3%)	p=0.3
COMORBID MEDICAL ILLNESS				
Yes	68 (33.0%)	2 (10.0 %)	39 (35.1%)	X^2=4.979
No	138 (66.9%)	18 (90.0%)	72 (64.9%)	p=0.03

**Fisher's exact test*

***2% of patients had a mood disorder other than bipolar disorder*

**Fisher's exact test*

Table 2. Frequency distribution of the characteristics of the LAI - AP prescribed in the study population, the group of patients on LAI -APs only, and the group on LAI - APs combined with oral antipsychotics

VARIABLES	Study population (N=206) n (%)	LAI-AP only (N=20) n (%)	LAI-AP and oral antipsychotic (N=111) n (%)	Statistics
TYPE PRESCRIBED				
Flupenthixol	132 (64.1%)	13 (65%)	70 (63.1%)	X^2=0.027
Zuclopenthixol	74 (35.9%)	7 (35.0%)	41 (36.9%)	p=0.87
DURATION OF PRESCRIPTION				
Mean 11.58 years (SD±10.3)				
0-19 years	119 (57.8%)	13 (65.0%)	87 (78.4%)	p=0.346*
20-29 years	50 (24.3%)	5 (25.0%)	15 (13.5%)	
>30 years	37 (17.9%)	2 (10.0%)	9 (8.1%)	
FREQUENCY OF DOSE				
Monthly	197 (95.6%)	20 (100%)	106 (95.5%)	p=1.000*
Two-weekly	9 (4.4%)	0 (0%)	5 (4.5%)	
MEAN DOSE (mg)				
Flupenthixol 29.0 mg (SD±12.4)				
Zuclopenthixol 271 mg (SD±107)				
INDICATION FOR PRESCRIPTION				
Non adherence	136 (66.0%)	15 (75%)	69 (62.2%)	p=0.912*
Low level of functioning	17 (8.3%)	1 (5.0%)	9 (8.1%)	
Treatment resistance	4 (1.9%)	0 (0.0%)	4 (3.6%)	
Intolerable side effects	1 (0.5%)	0 (0.0%)	1 (0.9%)	
Comorbid substance use	16 (7.8%)	2 (10.0%)	10 (9.0%)	
Long untreated psychosis	1 (0.5%)	0 (0.0%)	0 (0.0%)	
Non-response to orals	12 (5.8%)	0 (0.0%)	8 (7.2%)	
Patient preference	14 (6.8%)	1 (5.0%)	7 (6.3%)	
Not recorded	5 (2.4%)	1 (5.0%)	3 (2.7%)	
**Fisher's exact test*				

Table 3. Concurrent prescription of LAI – APs and psychotropic medication

Variables	N (N=206)
LAI – AP only	20 (9.7%)
LAI – AP combined with an oral antipsychotic	111 (53.9%)
LAI –AP combined with a mood stabiliser	92 (44.7%)
LAI – AP combined with an antidepressant	16 (7.8%)
LAI – AP combined with any psychotropic medication	186 (90.3%)

DISCUSSION

Approximately 70% of the study patients who were prescribed a LAI - AP had a primary diagnosis of schizophrenia or related disorder. This is consistent with several studies that have reported that LAI - APs are most frequently prescribed for patients with a diagnosis of schizophrenia (9,11,18,27,35,36). Schizophrenia is a chronic mental illness that is associated with poor adherence to oral medication resulting in a high risk for relapse and admission to hospital (3,37). Adherence to antipsychotic medication is critical for the recovery and restoration of occupational and social dysfunction in schizophrenia (3). Compared to oral antipsychotics, LAI - APs dispense with the need for daily antipsychotic administration, provide more stable blood levels and, can be prescribed at lower therapeutic doses, resulting in a reduced potential for adverse events (38). Several studies have confirmed that prescribing LAI - APs is an effective strategy to improve treatment adherence in schizophrenia (8,25). Consequently, several international schizophrenia management guidelines (8,18,39) and the Standard Treatment Guidelines and Essential Medicines List for SA (40) recommends the prescription of LAI-APs in schizophrenia. Hence, the prescribing of LAI -APs was therefore in accordance with these guideline recommendations and the manufacturer's labelled indication for LAI - APs (41).

Doctors in this study prescribed LAI - APs more frequently for older, male, unemployed patients who were in the more advanced stages of their illness. Similar prescription patterns for LAI - APs have been reported internationally (19,20,26,35,36). The prescribing practice in this study was therefore in keeping with the traditional profile of patients for whom LAI - APs are prescribed globally. LAI - APs have long been prescribed for patients who are not compliant with oral medication, relapse frequently and, who pose a danger to others (18). In this study, doctors' prescribing practices may also have been influenced by their attitudes towards LAI – APs. A study from the United Kingdom found that individual psychiatrists were reluctant to prescribe LAI – APs because they viewed LAI - APs as coercive, stigmatising and, less acceptable to patients (28). Even in Africa, where medical paternalism is common, some psychiatrists still viewed LAI - APs as coercive (42).

Furthermore, there is evidence that the prescription of LAI - APs in younger patients after a first episode of schizophrenia is beneficial because LAI - APs have also been shown to improve adherence, prevent relapses and reduce hospitalisations in patients with a first episode of schizophrenia (14,43). Doctors should be encouraged to consider the prescription of LAI - APs as a viable treatment strategy in younger patients after a first-episode of schizophrenia, because effective management of the early critical stages of the illness may result in better overall long- term outcomes (5,8,18,44).

Flupenthixol decanoate was prescribed more frequently than zuclopenthixol decanoate in this study (64% vs. 36%). This preference of flupenthixol over zuclopenthixol was also reported in New Zealand (45), Australia (46) and, Nigeria (32). Although earlier studies reported that zuclopenthixol decanoate had greater anti-aggressive efficacy and flupenthixol decanoate had greater antidepressant properties (25), subsequent systematic reviews found no real differences in global outcome measures or adverse events between them (47,48). The choice of prescription between the two LAI – APs in this study was therefore, most probably due to a local prescribing habit, general availability and, familiarity with the drug (49). In the public sector of SA, only first-generation LAI - APs are available on the national formulary (40). Second generation LAI – APs are obtainable, but on a named patient basis, and by prior motivation through a buy–out process at tertiary and specialised hospitals (and at clinics supplied by those hospital pharmacies). However, a recent systematic review and meta-

analysis found no difference in efficacy and discontinuation rates between first- compared to second-generation LAI - APs in the management of schizophrenia (50).

Approximately 10% of the patients who were prescribed LAI - APs in this study had a primary diagnosis of bipolar disorder. This figure is similar to the range of 4.8–8.0% reported in other studies (23,31,36) but lower than the 18% reported by Ostuzzi et al. (35). Bipolar disorder is a potentially lifelong chronic mental illness, and adherence to medication is also critical for effective control of symptoms, prevention of relapse and, rehospitalisation (51,52). Recently, the indications for LAI - APs have been expanded beyond schizophrenia to include approval for use in the maintenance phase of bipolar disorder. It has been shown that LAI -APs are also effective for reducing relapse rates in patients with bipolar disorder who are poorly adherent to medication (52). Consequently, the prescription of LAI - APs as both monotherapy and adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar disorder has been approved in some guidelines including that of the Canadian Network for Mood and Anxiety Treatments (53), the United States Food and Drug Administration and the European Medical Agency (52)

However, it is only the second-generation LAI-APs, and not the first-generation LAI - APs, that are approved for use in bipolar disorder (51). Yet, in this study, first-generation LAI - APs were prescribed for bipolar disorder. As previously discussed, due to the lack of availability of second-generation LAI - APs on The South African National Department of Health. Standard Treatment Guidelines and Essential Medicines List, it is likely that first-generation LAI - APs became the only available pharmacological option for patients with bipolar disorder who were not adherent to oral medication.

The main indication for using LAI - APs was non-adherence to oral psychotropic medication. Yet, this study found that only 9.7 % of the patients were prescribed a LAI - AP alone. The remaining 90.3 % were prescribed an oral psychotropic medication (another antipsychotic and/or a mood stabiliser and/or an antidepressant) in combination with the LA - AP.
In approximately half of the patients, the other oral psychotropic medication co-prescribed was an antipsychotic. Similar high prescription rates have been reported in clinical practice globally, including several studies from the United States (24,29–31,54), Nigeria (32), SA (27) and, Korea (55). The authors explain that some of the patients in these studies had recently been discharged from psychiatric institutions, and that either the oral antipsychotic supplementation was used to augment the LAI - AP during the period of stabilisation, or that they were being 'weaned off' oral antipsychotics that had been initiated during hospitalization (24,31,54). However, our finding is significant because ours was a community-based sample of patients, many of who had been prescribed this combination for prolonged periods. Combining LAI - APs with oral antipsychotic medication is a questionable prescribing habit because, it argues against the main indication of non-adherence, increases the potential for drug-drug interactions, a range of side effects, cost of care, medico-legal liability and results in higher mortality rates (17,56). However, because the practice is so widespread in real-world settings, it is possible that the response to LAI - APs monotherapy in published clinical trials is overestimated. It may also be a reflection of the illness severity and complexity in patients for whom LAI - APs are prescribed (29). Our study did not find any significant socio-demographic and clinical characteristics associated with this prescribing habit.

Our finding of a high prevalence of comorbid substance abuse (47.6 %) was not unexpected, given that almost 50% of patients with schizophrenia have a history of comorbid substance

abuse globally (57). There is little doubt that individuals with comorbid substance use have a consistently higher prevalence of non–adherence to antipsychotic medication than those without (3, 37). Although the evidence is not robust, there is evidence of improved adherence and symptom control in patients with dual diagnoses on LAI – APs; with better outcomes for patients on second-generation LAI – APs compared to first -generation LAI – APs (58). Considering the magnitude of the problem, future research investigating the utility of LAI - APs in patients with comorbid substance use is warranted (57).

Similar to the high rate of concurrent oral antipsychotic prescriptions, approximately half of the patients in this study (44.7 %) were prescribed a mood stabiliser in addition to the LAI-AP. Our figure is in keeping with those in previous reports of concurrent mood stabiliser co-prescriptions ranging from 19% (29) to 47% (54). It is possible that in our study the mood stabiliser was used to augment the LAI - AP in patients with treatment resistance who had a poor response to antipsychotic medication (56), or that LAI - APs were used in non-adherent patients with bipolar disorder because an injectable mood stabiliser is not yet available, or that the mood stabiliser was combined with a LAI – AP for the treatment of a schizoaffective disorder.

About eight percent of the study population was prescribed an antidepressant in addition to the LAI - AP. Joo et al. (55) and Olfson et al. (54) also reported similar prescribing patterns, but their findings cannot be directly compared to our study, because concurrent antidepressant use in their studies was in the first few months after initiation of a LAI - AP only. Although the reasons for the co-prescribing of antidepressants were not investigated in our study, it was most likely to treat a depressed mood.

This study was unable to establish any significant socio-demographic and clinical characteristics that were associated with the prescribing of LAI - AP combined with oral psychotropic medication. There is a paucity of published research regarding this comparison. Doshi et al. (30) reported no association, whilst Aggarwal et al. (29) reported an association with the abuse of alcohol. However, the authors could not account for this finding, except to note that prescribers may have thought that patients with alcohol abuse may have warranted both forms of medication as they were more likely to be unreliable and have cognitive impairment.

LIMITATIONS

Limitations of our study include the lack of generalisability to other clinics in SA, information on symptom severity and, the cross-sectional study design. To the best of our knowledge, this is the first report of prescription patterns for LAI - APs in a community health setting in SA. Globally, there is minimal information regarding prescription patterns of LAI-APs in community-based health systems (49). Therefore, the strengths of the study are the community-based setting and the information on real-world patients in usual care, given the general lack of data on antipsychotic utilisation in clinical practice from Africa (59). Furthermore, this study provides some information on the prevalence of combining LAI – APs and oral psychotropic treatment, which is not well established in low- and middle-income countries with restricted formularies.

CONCLUSIONS

The results of this study confirm that, despite calls for the increased utilisation of LAI-APs in the earlier phases of schizophrenia (5,8,18,43), LAI - APs in SA were prescribed mainly for

older, male patients who were not gainfully employed, with dual diagnoses and who were not adherent to oral medication. We highlight the high prevalence of polypharmacy in patients receiving LAI - APs and the lack of second-generation LAI - APs in community psychiatric clinics in Johannesburg. Further research is needed to establish the prescribing habits for LAI -APs in other provinces in SA, and to investigate the adherence and quality of life of patients on LAI - APs compared to oral antipsychotics.

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COMPETING INTERESTS

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

AUTHOR CONTRIBUTIONS

NV was the principal investigator and was responsible for the study concept, design, data collection and, the preparation of the manuscript.
MYHM was the primary supervisor and contributed substantially to the study proposal, critical revision and, approval of the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, NV. The data are not publicly available due to restrictions (e.g. they contain information that could compromise the privacy of research participants).

DISCLAIMER

The content is solely the responsibility of the authors and does not represent the official view of any organisation or institution.

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APPENDIX A: Protocol

Prescribing patterns of long acting injectable antipsychotics at community psychiatric clinics in Johannesburg

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1. BACKGROUND

The introduction of oral antipsychotic medication in the 1950's revolutionized the treatment of schizophrenia and other severe mental illness (SMI) globally (58). However, up to 50% of patients do not take their medication as prescribed and the risk of relapse in schizophrenia is up to six times higher without antipsychotic medication than with antipsychotic medication (3). There are serious psychosocial, biological and economic consequences associated with a relapse of the illness (4) Therefore, strategies to improve medication adherence in the treatment of schizophrenia are important.

Long acting injectable (LAI) or depot antipsychotic formulations have been shown to improve adherence to antipsychotic medication (9) and to lower mortality (59). Yet, LAI antipsychotics remain underutilized (60). The rates of LAI antipsychotics prescription vary by country (17),ethnicity (23), gender (26) and socioeconomic status (24) .
Although LAI antipsychotics have been available in South Africa (SA) for over 50 years, there is limited information regarding prescribing patterns for LAI antipsychotics among inpatients (33,34) and no published studies among outpatients from SA. The aim of this study is to examine prescribing patterns for LAI antipsychotics among out patients with SMI from SA, and to describe the profile of patients for whom they are prescribed. This information will assist managers and clinicians to identify disparities in prescribing practices for LAI antipsychotics in a community setting and to promote the prescribing of LAI antipsychotics earlier in the course of illness before the deleterious effects of multiple relapses occur.

2. LITERATURE REVIEW

2.1. Pharmacology of LAI antipsychotics

Of the eleven LAI antipsychotics available worldwide (8), only two first generation antipsychotics (FGA), zuclopenthixol decanoate and flupenthixol decanoate are available as LAI antipsychotics on the Essential Medicines List of SA (61).

2.2 Benefits of using long acting injectable antipsychotics

2.2.1 Improved adherence

Two large meta – analyses found improved adherence and reduced relapse rates in patients taking LAI antipsychotics compared to oral antipsychotics (9,62). In spite of the evidence supporting the use of LAI antipsychotics (59), LAI antipsychotics are generally underutilized with a wide variation in prescribing rates between and within countries (60,63). Rates vary from 6.2 % in Japan (19) , 29 % in the United Kingdom (UK) (64), 36.7% in Hong Kong (65), 25.3% in one study from Australia (66) and 66 % in another study from the same country (45). Literature regarding the utilization of LAI in Africa is sparse. Hospital based studies from Nigeria (32), Uganda (67) and the Western Cape of South Africa (33) (34) reported that 58.4 % ,40.9 % , 49.4 % and 31.4 % respectively of the participants in their studies received a first generation LAI antipsychotic .

2.2.2 Decreased cost of care

A systematic review that included 28 studies showed that LAI antipsychotics were associated with a decrease in the number and duration of hospitalizations with a consequent decrease in the cost of care (16)

2.2.3 Improved outcomes for first-episode schizophrenia

LAI antipsychotics have been shown to be safe and effective in the early critical phase of schizophrenia (5)

2.3. Socio –demographic factors associated with the prescription of LAI

(i) **Age**

The age of onset of schizophrenia is in the early twenties, but the calculated mean weighted age at treatment with LAI is from 38.5 years to 39.5 years (26).

(ii) **Gender**

Previous research has found that more males received LAI to females (26) (63)

(iii) **Race**

There are reports from the United States (US) that African American patients with schizophrenia had significantly higher rates of LAI antipsychotic prescriptions compared to white Americans (23,24)

(iv) Level of education

A United States (US) study found that patients with lower levels of education were significantly more likely to be prescribed LAI antipsychotic than oral antipsychotic medication ($p< 0.001$) (24).

2.4. Clinical Factors associated with the prescription of LAI

(i) **Treatment setting**

Remington et al (21) found that outpatients at a provincial hospital in Canada received depot antipsychotics more frequently than patients treated at a community health centre and university- affiliated hospital.

(ii) **Primary psychiatric diagnosis**

Although earlier research on LAI antipsychotics included only patients with psychotic disorders, there is good evidence for the utility of LAI antipsychotics in non – adherent patients with Bipolar disorder (68).

(iii) **Duration of illness**

Compared to oral antipsychotics, older patients with a longer duration of illness were more likely to receive LAI antipsychotics (8).

(iv) **Comorbid substance abuse**

Patients with comorbid substance use disorders are likely to be more non - adherent, and there is evidence for the more frequent use of LAI antipsychotics in patients with schizophrenia and comorbid substance use disorders(69).

2.5. Concurrent Prescription of LAI antipsychotics with other psychotropics

A key advantage of LAI antipsychotics over oral antipsychotics is that LAI antipsychotics do not have to be taken daily. However, three US studies and a study from SA found that 68%, 47 % 75.9 % and, 84.6% respectively of the patients treated with a LAI antipsychotic also received oral antipsychotics (24,29,34,70)

Despite over two decades of research regarding prescribing practices for LAI antipsychotics globally (25), there is no information on prescribing patterns for LAI antipsychotics among patients attending community clinics in SA, how they are used in practice and the socio-demographic and clinical characteristics of patients for who LAI antipsychotics are prescribed. Hence the need for this study

3. HYPOTHESIS/ RESEARCH QUESTION

1. The prescription of LAI antipsychotics is associated with advancing age, male gender, a longer duration of illness and, multiple episodes of illnesses.
2. The prevalence of concurrent prescription of LAI antipsychotics and oral antipsychotics is high (> 50 %)

4. AIM

The aim of this study is to describe the prescribing practices of doctors for LAI antipsychotics in patients attending community psychiatric clinics in Johannesburg.

5. OBJECTIVES

In a group of patients with severe mental illness receiving LAI antipsychotics and attending community clinics in Johannesburg, the main objectives are:

i) To describe the socio-demographic characteristics of the study population.
ii) To describe the clinical characteristics of the study population.
iii) To describe the types, dosages and, frequency of the LAI antipsychotic prescribed.
iv) To determine the prevalence of patients receiving concurrent prescriptions of LAI antipsychotics and oral psychotropic agents
v) To determine, if any, significant socio- demographic and clinical characteristics that are associated with concurrent prescriptions of LAI and oral psychotropic agents.

6. METHODS

6.1. Study Design

This is a retrospective chart review.

6.2. Study site

Data collection will be conducted at five randomly selected community clinics of the 23 clinics in Johannesburg Health District, namely Chiawelo, Orlando, Lenasia South, Westbury and, East Bank community clinics.

6.3. Study Population

It will comprise adult patients (18 years and older) with SMI attending the Chiawelo, Lenasia South, Westbury, East Bank and Orlando community clinics and who have received a LAI in the past month . There will be no exclusion criteria.

6.4. Sample Size

Approximately 20 patients are prescribed LAI antipsychotics at each clinic per week. Based on this it is estimated that the sample size over one month will be approximately 200 patients. From an assessment of Z scores of expected frequencies, a sample size of 200 patients will detect statistical significance for factors tested at the 5% level. Realistically, statistical significance can be expected with a minimum sample of 150 patients (the lowest number recommended).

6.5 Method

The investigator will inform the operations managers and registry clerks of the clinics about the purpose of the study. As part of the standard operating procedure, the clinic nursing staff maintains a register of all patients to whom LAI antipsychotics are administered. The investigator will compile a master list of patients for whom LAI antipsychotics were prescribed during the study period from 1 August 2018 to 31 August 2018. This master list will be used to retrieve the files of these patients from the registry. The investigator will then

review the patients' charts and extract the necessary information. The information will be manually recorded on the specifically designed data collection form (Annexure A). The following variables will be recorded

6.5.1 Demographic variables:

Age (years), Gender (male/female/unknown), Population group (African/ White/ Indian/Coloured/other/unknown), Relationship status (single/married/widowed/other Highest level of education (none/primary/secondary/tertiary /unknown), Employment status (employed/ unemployed/ disability grant/ student /unknown)

6.5.2. Clinical variables

Primary psychiatric diagnosis, Duration of illness (years), Family history of mental illness (yes/no/unknown),Comorbid psychiatric diagnosis (yes/no/unknown) Comorbid medical illness (yes/no/unknown), Comorbid substance abuse (yes - substance specified /no/unknown)

6.5.3. Treatment variables

LAI prescribed (Flupenthixol Decanoate , Zuclopenthixol Decanoate ,Risperidone LAI),Date of initiation of LAI, Main indication for initiation (non-adherence / patient preference/ non – response to oral antipsychotics/ treatment resistance / other /unknown) ,Current dose, Prescription of concurrent medication (mood stabilizer /oral antipsychotic/ anticholinergic medication / other)

6.6. Data Analysis

A statistician will be assisting with the statistical analysis. The questionnaire data will be captured in Microsoft Excel spreadsheets. A descriptive analysis of the socio-demographic and clinical variables will be performed. Variables will be illustrated by frequency (continuous variables) or proportion (categorical variables) in bar charts. All statistical analyses will be conducted using R software (version 3.50, http://www.R-project.org). All tests will be two-tailed probability values, and statistical significance accepted when $\alpha \leq 0.05$. The data set for this study will be generated from assessments of categorical scores, which are usually non-normal, so appropriate non-parametric analyses will be used. The prevalence of patients receiving LAI antipsychotics only versus those receiving concurrent prescriptions of LAI antipsychotics and oral psychotropic agents will be compared using a frequency distribution graph. Moreover, prevalence will be compared between groups using a Chi-squared test, together with their 95% confidence intervals. Univariate analyses of relationships between variables (socio-demographic and clinical) and patients receiving LAI only versus those receiving concurrent prescriptions of LAI and oral psychotropic agents will be analysed using a logistic regression with a binomial error structure and logit link function. In these analyses, χ^2 statistics will be used for overall model significance. Z statistics, including estimate, SE values and confidence intervals (CI), will be generated for specific components of fixed factors. Here, reference categories will be selected using sequential entry and/or were based on logically meaningful categories to obtain Z statistics for each component. Socio-demographic and clinical variables which are significant in the univariate analyses (above) will be included in a multiple binomial regression model. The selected variables will first be screened for autocorrelations (strongly positive or negative associations using χ^2 tests) and some will be selectively removed in the final models.

7. LIMITATIONS

The accuracy and completeness of the clinical records is a challenge and a limitation of the study. The study is conducted in one community in Gauteng and may not be generalizable to other communities in the country

8. ETHICAL CONSIDERATIONS

Permission to conduct the research will be obtained from the University Bioethics Research Committee, Gauteng Department of Health (health and research ethics committee), Johannesburg Health District Research Committee and the clinic managers. Requests for patients' charts will be made on the basis of psychiatric file numbers and a study code will be assigned consecutively to each one. The code will be used on the study data collection form instead of names or psychiatric file numbers to ensure confidentiality. There is no immediate benefit or risk to the individuals involved in this study. This study is scientifically valid and in informed by current literature. Observational studies regarding utilization of LAI antipsychotics are valid and reflect real – life prescribing practices (71).

9. TIME – FRAMES

	July – Sept 2018	Oct. – Dec 2018	Jan – March 2019	April – July 2019
Study Approval				
Data Collection				
Data analysis				
Write up				

10. COSTS

The cost of printing the data collection sheets will be approximately R 2 000.00 and will be borne by the investigator.

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Data Collection Form

STUDY NUMBER

DEMOGRAPHIC INFORMATION

AGE (years) _____

GENDER

- ☐ MALE
- ☐ FEMALE
- ☐ UNKNOWN

POPULATION GROUP

- ☐ BLACK AFRICAN
- ☐ WHITE
- ☐ INDIAN
- ☐ COLOURED
- ☐ OTHER
- ☐ UNKNOWN

RELATIONSHIP STATUS

- ☐ SINGLE
- ☐ MARRIED
- ☐ DIVORCED
- ☐ WIDOWED
- ☐ UNKNOWN

HIGHEST LEVEL OF EDUCATION

- ☐ NONE
- ☐ PRIMARY
- ☐ SECONDARY
- ☐ TERTIARY
- ☐ UNKNOWN

EMPLOYMENT STATUS

- ☐ EMPLOYED

- ☐ UNEMPLOYED
- ☐ STUDENT
- ☐ DISABILITY GRANT
- ☐ PENSIONER
- ☐ OTHER_____
- ☐ UNKNOWN

CLINICAL INFORMATION

PRIMARY PSYCHIATRIC DIAGNOSIS

- ☐ DEPRESSIVE DISORDER
- ☐ BIPOLAR DISORDER
- ☐ SCHIZOPHRENIA SPECTRUM DISORDER
- ☐ NEUROCOGNITIVE DISORDER
- ☐ SUBSTANCE USE DISORDER, _____
- ☐ INTELLECTUAL DISABILITY
- ☐ PERSONALITY DISORDER
- ☐ OTHER, _____
- ☐ UNKNOWN

COMORBID PSYCHIATRIC DIAGNOSIS

- ☐ DEPRESSIVE DISORDER
- ☐ BIPOLAR DISORDER
- ☐ SCHIZOPHRENIA SPECTRUM DISORDER
- ☐ NEUROCOGNITIVE DISORDER
- ☐ SUBSTANCE USE DISORDER, _____
- ☐ INTELLECTUAL DISABILITY
- ☐ PERSONALITY DISORDER
- ☐ OTHER, _____
- ☐ UNKNOWN

DURATION OF ILLNESS (years)_____

COMORBID MEDICAL DIAGNOSIS

- ☐ HYPERTENSION
- ☐ DIABETES MELLITUS
- ☐ EPILEPSY
- ☐ RETROVIRAL DISEASE
- ☐ HYPOTHYROIDISM
- ☐ OTHER,_____
- ☐ UNKNOWN

COMORBID SUBSTANCE USE

- ☐ ALCOHOL
- ☐ CANNABIS
- ☐ STIMULANTS
- ☐ NICOTINE
- ☐ OTHER,_____
- ☐ UNKNOWN

FAMILY HISTORY OF MENTAL ILLNESS

- ☐ DEPRESSIVE DISORDER
- ☐ BIPOLAR DISORDER
- ☐ SCHIZOPHRENIA SPECTRUM DISORDER
- ☐ SUBSTANCE USE DISORDER, _____
- ☐ OTHER,_____
- ☐ UNKNOWN

<u>TREATMENT VARIABLES</u>

LAI TYPE PRESCRIBED

- ☐ FLUPENTHIXOL DECANOATE
- ☐ ZUCLOPENTHIXOL DECANOATE
- ☐ FLUPHENAZINE DECANOATE
- ☐ RISPERIDONE MICROSPHERES

DATE OF LAI INITIATION _____

CURRENT LAI DOSAGE: _____

FREQUENCY OF LAI DOSAGE:

- ☐ MONTHLY
- ☐ TWO WEEKLY
- ☐ WEEKLY
- ☐ OTHER_____

REASON FOR LAI INITIATION:

- ☐ NON-ADHERENCE
- ☐ PATIENT PREFERENCE
- ☐ NON RESPONSE TO ORAL TREATMENT

- ☐ TREATMENT RESISTANCE
- ☐ OTHER,_____
- ☐ UNKNOWN

CONCURRENT ORAL MEDICATION PRESCRIPTION

ANTIPSYCHOTIC

- ☐ RISPERIDONE
- ☐ HALOPERIDOL
- ☐ OLANZAPINE
- ☐ QUETIAPINE
- ☐ AMISULPIRIDE
- ☐ CLOZAPINE
- ☐ CHLORPROMAZINE
- ☐ OTHER_____

MOOD STABILIZER

- ☐ LITHIUM
- ☐ SODIUM VALPROATE
- ☐ LAMOTRIGINE
- ☐ CARBAMAZEPINE
- ☐ OTHER _____

ANTIDEPRESSANT

- ☐ SSRI
- ☐ SNRI
- ☐ TRICYCLIC

OTHER

- ☐ ANTICHOLINERGIC_____
- ☐ BENZODIAZEPINE_____
- ☐ OTHER HYPNOTIC_____
- ☐ OTHER_____

APPENDIX B: Assessor Group Approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PROTOCOL ASSESSORS MEETING

Candidate Full Name: **DR NABILA VEYEJ**

Student Number: **361441** Date: **12 SEPTEMBER 2018**

School / Department / Division: **DEPARTMENT OF PSYCHIATRY**

1. **Type of study** *(tick all that apply)*:

- o Quantitative
- X Qualitative
- o Mixed Methods
- o Laboratory
- o Clinical
- o Other, please specify.....

2. **Is title of the study appropriate** (*preferably fewer than 20 words*)? Yes / No

Comments: Yes.

3. **Are the study objectives clear and linked to the research aim and title?** Yes / No

Comments:

4. **Is the design of the study appropriate to meet the study objectives?** Yes / No

Comments:

12/09/2018

APPENDIX C: Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr N Veyej

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M181062

NAME: (Principal Investigator)	Dr N Veyej
DEPARTMENT:	School of Clinical Medicine Department of Psychiatry Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Prescribing patterns of long acting injectable antipsychotics at community psychiatric clinics in Johannesburg
DATE CONSIDERED:	26/10/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor MYH Moosa
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/02/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore reports and re-certification will be due early in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D: Ethics Clearance Johannesburg District

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Joburg
a world class African city

JOHANNESBURG HEALTH DISTRICT

Wits - Human Research Ethics Committee(Medical)
University of The Witwatersrand,
Johannesburg, South Africa
nvayej@gmail.com

Enquiries: Dr EM Ohaju
Tel: 011 694 3888 Cell: 076 8831659
Email: Elizabeth.Ohaju@gauteng.gov.za
Hillbrow CHC: Administration Building
Cr Smith Str. & Klein Street
Private Bag X21, Johannesburg
South Africa, 2017

DRC Ref: 2018-11-002

NHRD Ref no: GP_201811_011

Dear: DR Nabila Veyej

TITLE: Prescribing patterns of long acting injectable antipsychotics at community psychiatric clinics in Johannesburg

Your application for research approval refers.

The District Research Committee has reviewed your application. This letter serves as an in-principle approval to access the Districts Health facilities (mentioned below) for the above project subject to following conditions:

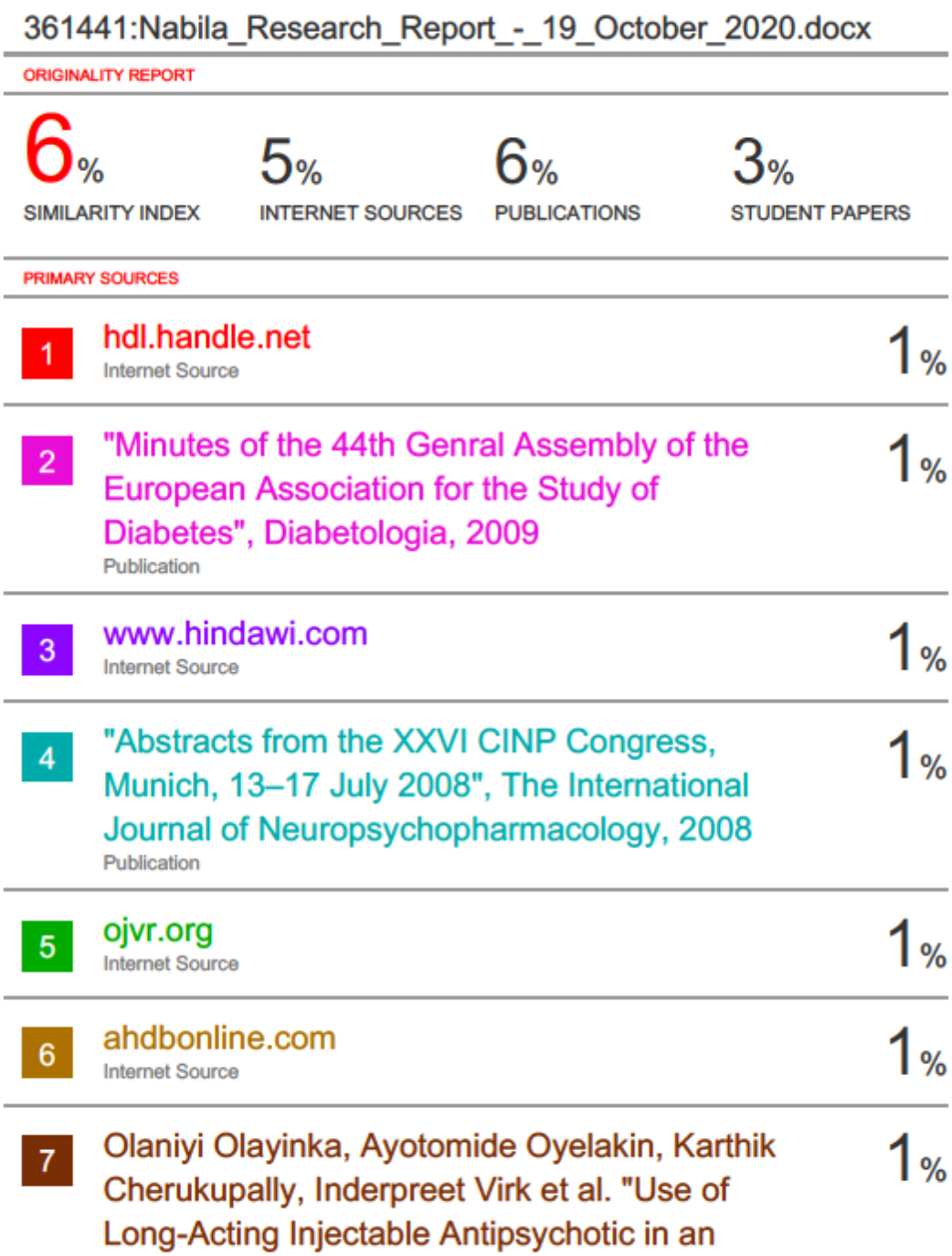
- The facility to be visited: **ALEXANDRA EAST BANK CLINIC, CHIAWELO CHC, LENASIA SOUTH CHC, ORLANDO PROV CLINIC, WESTBURY CLINIC**
- This facility will be visited from **03/01/2019 to 03/01/2020**
- The research can only commence after you submit an ethics clearance certificate from a recognized institution.
- You will report to the Facility Manager before initiating the study.

Region	Regional Health Manager	Contact No.	Cell phone
ABCEF	Ms L Matlala	011 440 1259	082 307 0267
D	Ms. Maria Mazibuko	011 674 1200	082 781 9919
G	Ms. T Cebekhulu	011 213 9708	071 678 7561
D (LA)	Busi Phiri	011 986 - 0164	082 467 9386

The following conditions must be observed:

- Participants' rights and confidentiality will be maintained all the time.

APPENDIX E: Turnitin Report



361441:Nabila_Research_Report_-_19_October_2020.docx

ORIGINALITY REPORT

6%	5%	6%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	hdl.handle.net Internet Source	1%
2	"Minutes of the 44th Genral Assembly of the European Association for the Study of Diabetes", Diabetologia, 2009 Publication	1%
3	www.hindawi.com Internet Source	1%
4	"Abstracts from the XXVI CINP Congress, Munich, 13–17 July 2008", The International Journal of Neuropsychopharmacology, 2008 Publication	1%
5	ojvr.org Internet Source	1%
6	ahdbonline.com Internet Source	1%
7	Olaniyi Olayinka, Ayotomide Oyelakin, Karthik Cherukupally, Inderpreet Virk et al. "Use of Long-Acting Injectable Antipsychotic in an	1%

APPENDIX F: South African Journal of Psychiatry –Cover Letter

MANUSCRIPT COVER LETTER

DOCUMENT VERSION 14 MAY 2019

This scholarly journal MANUSCRIPT COVER LETTER (title page) must be completed and submitted to AOSIS by the corresponding author as a supplementary document, at the manuscript submission point on to the journal website.

MY MANUSCRIPT			
Manuscript title: Prescribing patterns of long acting injectable antipsychotics within a community setting			
No of words (cross-check your word count with author guidelines): 3768	No of tables: 2	No of figures: 0	No of pages: 18

MY CHECKLIST
By completing this form I/we agree to the following: 1. I/we certify that the manuscript is within the scope of the journal. 2. I/we acknowledge that the research is novel and describes research that advances the field and adds to an active research field. 3. I/we have carefully prepared and formatted the manuscript with all the required sections present. 4. I/we certify that the language is clear and concise and relays a scientific message that clearly explains the importance of the study. 5. (if applicable) I/we certify that the study has been approved by the relevant bodies, research ethics committee(s) or institutional review board(s), e.g. institutional review board, research ethics committee, data and safety monitoring board, and regulatory authorities including those overseeing animal experiments.

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