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A COMPARISON OF ANTICHOLINERGIC USE BY SCHIZOPHRENIC PATIENTS ON POLYPHARMACY AND THOSE RECEIVING MONOTHERAPY

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of requirements for the degree of Master of Medicine in the branch of psychiatry.

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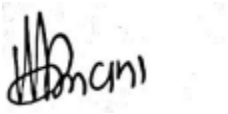
University of the Witwatersrand Department of Psychiatry

Johannesburg 2022

DECLARATION

I, Dr Marcia Tsakani Ntimani, declare this thesis as my own unaided work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Medicine in Psychiatry at the University of the Witwatersrand, Johannesburg. It has never been submitted before for any degree or examination at any other University.



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August 14, 2023 at Johannesburg

PLAGIARISM DECLARATION FOR WRITTEN WORK

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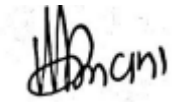
Signature: 

Date: August 14, 2023

DEDICATION

This work is dedicated to my partner, Jabu Ngobeni, for all his endless support. To my boys, Nkateko, Ndzalama, and Sagwati, for all the family times I spent staring at the laptop. To my mother, Christina, and my siblings, Matimu and Nkhensani, thank you for being there throughout this journey.

To Dr. Wisani Makhomisane, the academic journey would have been a nightmare if I did not have you by my side. And lastly, to my friend, Dr Tsakani Nkuna, who made sure I started this journey; your daily calls to ask when I am applying for a registrar post kick-started this process.

I thank each of you from the bottom of my heart and everyone who has helped to make this dream a success.

To God be the glory, with him, nothing is impossible.

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PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT

The work was presented at the Wits Department of Psychiatry Research Day on 22nd June 2022.

PUBLICATIONS ARISING FROM THIS STUDY

None

ABSTRACT

Introduction

Schizophrenia is one of the most debilitating mental disorders globally and one of the most challenging illnesses to treat. Although guidelines consistently caution against antipsychotic polypharmacy (APP) in clinical practice, their prescription rate is still significant and leads to a greater side-effect burden in patients. Therefore, this study aimed to document the prevalence of APP-related anticholinergic use compared to monotherapy in patients with schizophrenia in the community psychiatric clinics in Soweto, Johannesburg.

Methods

A retrospective record review was conducted. Data from clinical files of patients (18 years and above) diagnosed with schizophrenia attending four clinics in Soweto in September was analysed. Information such as age, gender, presence of extrapyramidal side-effects (EPSEs), comorbid conditions, and current treatment records was collected. Logistic regression assessed the association between APP, anticholinergic use, and sociodemographic and clinical characteristics.

Results

One hundred files that met the inclusion criteria were reviewed. The study population consisted mainly of males (n=73, 73%), with an average age of 47.6 years and an average illness duration of 18.5 years. Of the 100 selected patients with schizophrenia, 35% were on APP, and 57.7% of those were prescribed an anticholinergic agent. Of the patients on anticholinergic agents, 92% had a prescription for a single first-generation antipsychotic (FGA) or an FGA in combination with a second-generation antipsychotic (SGA). The most prescribed antipsychotics were risperidone and flupenthixol decanoate, either as monotherapy or combined.

Conclusion

The findings in this study correlated with the existing literature. Anticholinergic prescription rates are still high and associated with APP, male gender, and the use of FGAs.

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LIST OF ABBREVIATIONS

APP - Antipsychotic polypharmacy

CATIE - Clinical antipsychotic trials of intervention effectiveness

ELAN -The effects of long-term atypical neuroleptic agents

EPSEs - Extrapyramidal side-effects

FDA - The Food and Drug Administration

FGA - First-generation antipsychotic

GBDS - Global burden of disease study

ID - Intellectual disability

LAI - Long-acting injectable

MDD - Major depressive disorder

MNCD - Major neurocognitive disorder

NICE - National Institute for Health and Care Excellence

SGA - Second-generation antipsychotic

USA - United States of America

WHO - World Health Organisation

Chapter 1 INTRODUCTION

Schizophrenia is a complex, severe, and chronic mental illness that negatively impacts the person's ability to think, feel, and behave. It is one of the leading causes of disability worldwide; the World Health Organisation (WHO) estimates it to be one of the top 25 causes of disability worldwide, and it is a catastrophic economic disease (Chong, 2016). Symptoms include delusions, hallucinations, disorganised speech, and behaviour (Stahl, 2018).

The mainstay of treatment Is antipsychotic drugs which come with unwanted cardiovascular, metabolic, and extrapyramidal side-effects (EPSEs), also known as neuroleptic-induced movement disorders (Stahl, 2018). The National Institute for Health and Care Excellence (NICE) guidelines recommend antipsychotic monotherapy and discourage using more than one agent (Taylor, 2018). The EPSEs result from dopamine blockade in the nigrostriatal pathway, especially by first-generation antipsychotics (FGAs) (Stahl, 2018). The stigma related to schizophrenia is exacerbated by EPSEs, which significantly affect employment opportunities and usually lead to non-adherence to medication (Novak, 2009).

The EPSEs can either be hypokinetic or hyperkinetic and are common, stigmatising, and potentially disabling, leading to reduced quality of life. EPSEs may occur shortly after the introduction of antipsychotics (acute dystonia and akathisia, and parkinsonism) or as delayed manifestations (tardive dyskinesia, dystonia, and akathisia) (Martino, 2018). Anticholinergic agents in patients with schizophrenia are used for the treatment and prophylaxis of EPSEs caused by antipsychotics but can cause unwanted side effects (Ogino, 2013). The NICE guidelines for treating schizophrenia do not recommend the prophylactic use of anticholinergic agents, but some literature reports evidence of their long-term use (Ogino, 2013).

Most studies have reported that SGAs have minimal risk for developing EPSEs and might have some efficacy in negative mood and cognitive symptoms (Swingler, 2013). SGAs, however, come with an increased risk of metabolic and cardiovascular risk factors, which have been implicated in reducing the life expectancy of patients with schizophrenia leading to premature deaths (Ventriligo, 2015). Except for clozapine, all SGAs have the potential for producing EPSEs as they also block the dopamine receptors (Abouzaid, 2012)

The literature is consistent regarding antipsychotic combinations and the need for anticholinergic agents to treat EPSEs (Corell, 2013). Anticholinergic agent use is higher in patients on antipsychotic combinations than in patients on single agents due to the high total antipsychotic dose (Correll, 2013). An investigation of the association between APP and anticholinergic use was undertaken in this study because of the highlighted disadvantage of APP due to related side-effects, including EPSEs, (Fleischhacker, 2014), hoping that it may inform future clinical practice.

The study was conducted in community outpatient psychiatry services at Johannesburg Metro District clinics. The district has 26 adult specialist psychiatric clinics, eight of which are in Soweto. A simple random sampling was done in four clinics: Zola, Chiawelo, Orlando and Lillian Ngoyi. Patients in these clinics are usually referred from primary health care services, the private sector, or down referred from surrounding psychiatric hospitals. They are attended at the clinics by professional psychiatric nurses and psychiatry trainees under the supervision of a specialist psychiatrist. In this study, an anticholinergic drug in the patient's medication list was used to indicate the presence of neuroleptic-induced movement disorders (EPSEs)

Chapter 2 : LITERATURE REVIEW

2.1 Epidemiology of Schizophrenia

2.1.1 Prevalence

Schizophrenia is among the top ten illnesses contributing to the global disease burden. Although its prevalence is generally low (1.7% worldwide), estimates from the 2017 Global Burden of Disease Study (GBDS) suggest there has been about a 62% increase in global incident cases of schizophrenia since the first GBDS in 1990 (He, 2020). As it stands, there are 21 million cases of schizophrenia in the world; 1.13 million (5.4%) of these cases were diagnosed in 2017 alone (Charlson, 2018; He, 2020; Black, 2014). The incidence and prevalence of schizophrenia are expected to increase as low- and middle-income countries' populations integrate into urban life. Colodro-Conde (2018) suggested that urban life is an environmental risk factor for a higher prevalence of schizophrenia.

Apart from the GBDS regional estimates, no comprehensive South African statistics on schizophrenia exist. For example, the 2016 GBDS reported at least 500 000 people with schizophrenia in the Southern sub-Saharan Africa region (Charlson, 2018). Purgato et al (2012) reported that over four million people had schizophrenia in Africa. However, these estimates may be underrepresenting the regional burden of schizophrenia due to a lack of epidemiological data. The South African Human Rights Commission's report on the state of mental health conceded to the lack of epidemiological data on mental health, especially severe mental illnesses such as schizophrenia. The commission also noted that severe mental illness may be more common than estimated in South Africa when factors such as HIV/AIDS, high levels of substance abuse, and violence are considered (SAHRC, 2017). Due to underestimating the burden of schizophrenia and other severe mental illnesses, health expenditure is under-allocated to addressing mental health, leading to treatment gaps. Purgato et al (2012) observed that most African countries allocate less than 1% of their health budget to mental health, leading

to a lack of policies and research infrastructure resulting in shortfalls in research about mental health. With these estimates and data deficiencies in mind, it is clear that the region, and South Africa as a country, might carry a more significant burden of disease attributable to schizophrenia than recorded.

The GBDS illustrates that the load from schizophrenia is primarily due to disability rather than mortality. As South Africa is undergoing an epidemiological transition (Bradshaw, 2019), it is essential to reflect on and monitor the risk factors for morbidity and mortality observed in countries such as the USA that have closely documented their epidemiological transitions and their effects on population mental health and those living with schizophrenia.

2.2 Role of the Treatment for Schizophrenia

The first-line treatment for schizophrenia is antipsychotic medication. The NICE guidelines always recommend monotherapy and discourage the use of combined antipsychotics. However, the biopsychosocial management model is still recommended in patients with schizophrenia (Taylor, 2018). Antipsychotics in patients with schizophrenia are indicated for managing acute symptoms and preventing relapse. Patients with untreated psychotic symptoms have high mortality, increased suicide rates, more hospitalisation, and a poor prognosis (Vertriligo, 2015).

FGAs were the first antipsychotics to be discovered in the 1950s. Their side-effect profile, especially EPSEs, led to the discovery and use of SGAs. SGAs have less propensity for EPSEs; however, except for clozapine, they start behaving like FGAs at very high doses, which can lead to EPSEs (John, 2015). Though they have a much lower risk of EPSEs, SGAs have significant cardiovascular side effects that have been shown to reduce the overall life expectancy in patients with schizophrenia. There is a two to three-fold increased risk of death from these metabolic adverse events (Vertriligo, 2015).

Despite most clinicians preferring SGAs over FGAs due to their reduced side effect profile, prescription remains low as they are ten times more expensive than FGAs,

making their cost problematic in some countries (Park, 2014). Although prescriptions of SGAs have remained low, the literature showed a marked increase in 2009-2010 when compared to 1997 (Park, 2014).

2.3. Polypharmacy in Schizophrenia

APP or combination antipsychotic treatment uses two or more antipsychotic agents for a single patient (John, 2015). They can be in the same or different classes and are used in many settings, although no clear clinical indication has been documented (John, 2015). The prevalence of APP use was 27.5% in the USA, 28.6% in South Africa, 28.2% in Ethiopia, and the highest in East Asian countries, with a prevalence of 45.7% (Tesfaye, 2016). International surveys have identified regular use of polypharmacy, with some clinical settings having a prevalence rate of up to 50% (Barnes, 2011).

Of all antipsychotics, clozapine has the strongest evidence of efficacy in treatment-resistant schizophrenia. In cases where treatment-resistant schizophrenia has been established, initiation of clozapine must not be delayed (Taylor, 2021). Furthermore, of all antipsychotics, clozapine is the only drug approved by the FDA for treatment-resistant schizophrenia. John (2015) reported that 50-60% of patients with treatment-resistant schizophrenia would respond to clozapine monotherapy.

Although most prescribing guidelines discourage the use of APP, there are instances in practice where it is accepted, for example, to augment clozapine in treatment-resistant schizophrenia, the addition of aripiprazole to help reverse metabolic side effects, and during cross-titration (Taylor, 2018). One common reason for polypharmacy is to gain greater efficacy than that achieved by one antipsychotic agent. Some clinical indications for polypharmacy include targeting difficult symptoms such as refractory aggression, anxiety, unstable mood, and insomnia (Barnes, 2011). Corell (2011) found that 10% of prescribers reported using a combination of antipsychotic agents, and 27% did not attempt to switch to clozapine monotherapy.

Many clinicians choose APP rather than starting patients on clozapine; commonly, patients with schizophrenia are prescribed a combination of the depot and oral

preparations (Taylor, 2018). Risk factors associated with increased APP prescription include male gender, long hospital admission, use of anticholinergic agents, and poor symptom control. These factors have been found to indicate illness severity (Barnes, 2011). It was reported that busy doctors were most likely to prescribe APP due to the unavailability of time to discuss non-pharmacological interventions (Pristed, 2017).

There is delay and underuse of clozapine in most clinical settings. It involves multiple factors which are either patient or clinician related. The most common reasons are concern regarding compliance with medical treatment, overestimation of life-threatening side effects and patients refusing due to repeated blood sampling (John, 2018).

The disadvantages of APP include complicated regimens leading to non-adherence, cumulative drug toxicity, increased risk of side effects, and high costs (Masand, 2008). Also, there is an absence of guidelines for using polypharmacy (Masand, 2008). Regarding some of the findings in the literature on APP, using a single antipsychotic agent was cheaper and had better outcomes when compared to APP (Killan, 2018). It has additionally been found that patients on FGA/SGA combinations were prescribed anticholinergics as commonly as patients on FGA alone (Paton, 2011).

A longitudinal chart review in Japan found that APP was prescribed within two months of non-response to monotherapy without first optimising treatment (Tsutsumi, 2010). The review's results indicated that APP was efficacious in difficult-to-treat patients. It was recommended that polypharmacy be given cautiously due to the increased risk of QT prolongation caused by antipsychotic agents (Tsutsumi, 2010). A large national cohort trial in Finland concluded that APP was more prevalent in an outpatient setting and more common in patients with a longer duration of schizophrenia (Suokas, 2013). Patients on APP are more likely to receive high doses and experience a more significant side-effects burden when compared to patients on monotherapy; however, efficacy has been reported to be the same in both groups (Langle, 2012).

Schizophrenic patients are not only on combination antipsychotic regimens but also combinations of antipsychotics with other psychiatric drugs. The results from the ELAN (the effects of long-term atypical neuroleptic treatment) study found that 50% of patients

on a single antipsychotic agent were also prescribed other agents; 50% of these were antidepressants, 35% mood stabilisers, and 38% benzodiazepines (Langle, 2012). In addition, mood stabilisers were prescribed for aggressive behaviour, violence, and unstable mood, with sodium valproate being the most prescribed mood stabiliser (Choi, 2011).

In severe cases of schizophrenia and poor symptom response, APP is recommended as a last resort in treatment-resistant schizophrenia (Barnes 2011). Other recommendations include giving several monotherapy trials with different agents, optimising doses for an adequate duration, and only prescribing polypharmacy when there is a clear benefit (Langle 2012). Stahl (2013) reported that patients on APP usually have impulsivity, violence, aggression, and substance use and noted that a third of patients on polypharmacy relapse when switched to monotherapy. All studies have been consistent with the recommendation of starting a trial of clozapine before starting polypharmacy and confirming the diagnosis of schizophrenia. The antipsychotic prescribing guideline by Stahl is not against prescribing APP but recommends that it be used when there is practice-based evidence (Stahl, 2013).

2.4. Extrapyramidal Side Effects Associated with Antipsychotic Use and the Neurochemistry Associated with Developing EPSEs

2.4.1 Extrapyramidal side-effects associated with antipsychotic use

EPSEs, also known as neuroleptic-induced movement disorders, have been recognised as common side effects since the development of antipsychotic drugs in the 1950s (Desmarais, 2014). They occur because of dopamine (D_2) blockage in the nigrostriatal pathway (Desmarais, 2014). Most studies have reported a decline in the prevalence of EPSEs since the introduction and increased use of SGAs (Park, 2014). Some studies have highlighted that EPSEs are more prevalent when using high-potency antipsychotic agents such as haloperidol (Rybakowski, 2014). The CATIE study (clinical antipsychotic trial of intervention effectiveness) reported no differences in EPSEs measured by rating scales when comparing SGAs (olanzapine, quetiapine, risperidone, and ziprasidone) with the FGA perphenazine (Rybakowski, 2014).

EPSEs (acute dystonia, akathisia, parkinsonism, and neuroleptic malignant syndrome) can be acute and can occur hours to weeks after initiation or up-titrating medication. (Rybakowski, 2014). They can also have delayed onset, usually occurring after six months of treatment, i.e., tardive dyskinesia and dystonia (Desmarais, 2014). With the introduction of SGAs, clinicians believed there would be a lower prevalence of EPSEs; however, except for clozapine, at high doses and when compared to placebo, SGAs also have the propensity of producing EPSEs (Sadock, 2014).

Neuroleptic induced movement disorders: parkinsonism, dystonia, akathisia, and tardive dyskinesia are the most common side effects of patients prescribed FGAs with high potency (Widschwendter, 2014). Below are some of the EPSEs seen in patients treated with antipsychotic agents.

1. Neuroleptic-induced parkinsonism may occur within 5 - 90 days of drug initiation or dose increases (Sadock, 2014). It has prevalence rates of 30 - 60% in patients on FGA compared to 5 - 20% on SGA (Widschwendter, 2014). It consists of a triad of tremors (postural tremor being more common than resting), muscle rigidity, and bradykinesia (Sadock, 2014). It may also include slowed cognition, shuffling gait, and excessive salivation (Sadock, 2014). Parkinsonism symptoms may continue for up to three months after stopping the offending drug (Sadock, 2014). Therefore, these patients will need anticholinergic agents to be continued for longer until symptoms resolve (Sadock, 2014).

2. Neuroleptic-induced dystonia also known as acute dystonia can occur at any time during treatment with antipsychotic drugs, but usually, onset can be noticed within 3 - 9 days of treatment initiation (Widschwendter, 2014). It is more common in young males who are antipsychotic naïve, and 25 - 40% of patients on FGAs have a dystonic reaction (Kirgarval, 2017). It is uncomfortable and the most unfortunate side effect as it can be painful (Sadock, 2014). It is defined as brief or prolonged contractions of different muscle groups, resulting in abnormal or unintentional movement and postures, for example, oculogyric crises, torticollis, tongue protrusion, trismus, opisthotonos postures, and at times life-

threatening laryngeal spasm (Kirgarval, 2017). Dystonic symptoms are usually treated with intramuscular or intravenous biperiden (Sadock, 2014; Kirgarval, 2017).

3. Neuroleptic-induced akathisia occurs weeks to three months after initiation and increasing treatment doses with antipsychotic agents (Sadock, 2014). However, it can also be seen in patients on antidepressants, antiemetics, or cocaine (Kirgarval, 2017). It occurs in about 20 - 52% of patients treated with FGAs and 10 - 20% of patients treated with SGAs, and it remains unknown how it happens (Sadock, 2014). It is common in female patients and usually occurs during the up-titration of antipsychotic agents (Sadock, 2014). It is defined as a subjective feeling of restlessness, objective signs of restlessness, and an irresistible urge to move, which can sometimes come across as anxiety (Sadock, 2014). These patients describe discomfort, dysphoria, and agitation. The discomfort often causes patients to pace up and down, alternate between sitting and standing or rocking back and forth in a chair (Kirgarval, 2017). Management includes reducing the dose of the offending agent, changing drugs, and using beta-adrenergic receptor antagonists (e.g., propranolol), benzodiazepines, and cyproheptadine (Sadock, 2014; Kirgarval, 2017).

4. Tardive dyskinesia (TD) is one of the most delayed side effects of antipsychotic agents and may be irreversible even upon discontinuing the offending agent (Kirgarval, 2017). It rarely occurs in under six months of antipsychotic treatment. The risk factors include older age, females, brain injury, dementia, use of anticholinergics, long duration of treatment with antipsychotics, and previous history of EPSEs (Trosch, 2004). TD is set apart from other movement disorders by its persistence with uncommon remissions; however, it has not been reported with clozapine (Kirgarval, 2017). Thus, management includes stopping the offending agent and changing to clozapine (Trosch, 2004) (Kirgarval, 2017). Tardive dyskinesia is irreversible and worsened by anticholinergic agents.

Therefore, these agents are not recommended for patients with tardive syndromes (Desmarais, 2014).

EPSEs have played a significant role in non-adherence to medication, eventually leading to a relapse of psychotic symptoms. Early identification and management of EPSEs will improve adherence, reducing relapse and associated costs (Abouzaid, 2014)). Kirgarval (2017) found a 34.28% prevalence rate of EPSEs in patients aged 30 - 39 years.

Recommendations for the management of EPSEs include stopping or reducing the dose of the offending agent, but this comes with a risk of giving sub-therapeutic doses and relapse (Abouzaid, 2014). Switching to another drug with a low potential for causing EPSEs is recommended over starting pharmacological treatment with anticholinergic agents, beta-adrenergic agonists, benzodiazepines, or dopamine agonists (Kamin, 2000).

At times EPSEs can be mistaken for psychotic symptoms (Caroff, 2011). Additionally, some can be irreversible, disfiguring, and fatal, affecting adherence and leading to high relapse rates (Caroff, 2011). EPSEs also present some of the problems that increase stigma towards patients with schizophrenia, which include incoordination, gait issues and rigidity (Novak, 2009). Some patients reported being called drug addicts due to tremors and therefore having to disclose their illness at work against their will (Novak, 2009)

In addition to being difficult to treat, EPSEs are costly to the state and patients, mainly because of the drugs used to treat them, relapse of psychotic symptoms, and hospitalisation (Abouzaid, 2012). Patients with EPSEs have worse illness outcomes than those without. Suffering from EPSEs is associated with poor quality of life and significantly impacts the patient's physical health, and they can be lethal, e.g., laryngeal dystonia (Widschewendter, 2014).

2.4.2. Neurochemistry associated with the development of EPSEs

There are four key dopamine pathways in the brain. They involve the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular dopamine pathways. The mesolimbic pathway is responsible for the positive symptoms of schizophrenia due to excessive dopamine activity. The mesocortical pathway plays a role in cognitive, negative, and affective symptoms of schizophrenia and is hypothesised to result from dopamine hypoactivity (Stahl, 2018).

The dopamine pathway postulated to be responsible for the development of extrapyramidal side effects is the nigrostriatal pathway. It is part of the extrapyramidal nervous system. When the number of D_2 receptors that are blocked in the nigrostriatal pathway is excessive (more than 80%), EPSEs occur, leading to tardive dyskinesia with chronic blockage. Though said to be irreversible, early blockage removal may lead to a reversal of tardive dyskinesia. Furthermore, the D_2 blockages lead to dopamine deficiency in the basal ganglia, leading to dystonia and akathisia (Stahl, 2018).

2.5. Anticholinergic agents used in the treatment of EPSEs

2.5.1. Mechanism of action of anticholinergic agents

Five subtypes of muscarinic receptors have been identified: M1, M2, M3, M4, and M5. M1 is the most common muscarinic receptor in the brain (Sadock,2014). It is said to play a significant role in executive functioning in the prefrontal cortex and episodic memory in the hippocampus (Stahl, 2018). M2 receptors regulate memory processing, with acetylcholine levels regulated by M4 receptors (Alvarez, 2019). The anticholinergic side effects in the brain are postulated to be linked to the M1, M2, and M4 receptors.

There is a reciprocal relationship between dopamine and acetylcholine in the nigrostriatal pathway. Acetylcholine release is usually inhibited by dopamine in the nigrostriatal pathway. Muscarinic cholinergic receptor blockage reduces EPSEs caused by dopamine (D2) receptor-blocking agents, i.e., FGAs. Blockage of dopamine receptors leads to overactivity of acetylcholine, which can cause excessive drooling often observed in patients with parkinsonism taking FGAs (Stahl, 2018).

Anticholinergic agents compensate for acetylcholine hyperactivity, which would otherwise be managed by dopamine. Consequently, D_2 blocking and anticholinergic properties are less likely to cause EPSEs. As noted, antipsychotic agents such as clozapine, with high anticholinergic potency, are less likely to cause EPSEs and haloperidol, which has weak anticholinergic potency, will have a high propensity of causing EPSEs (Stahl, 2018).

Absorption of all anticholinergic agents occurs in the gastrointestinal tract. They are lipophilic, enabling them to enter the central nervous system. Anticholinergic agents are available in oral, intramuscular, and intravenous preparations. However, due to common side effects, the intramuscular route is preferred over intravenous use. After oral administration, anticholinergic activity reaches a peak in under 2 hours, and their action lasts 1-12 hours (Sadock, 2014). The most commonly available anticholinergics in the community psychiatric clinics of Soweto are orphenadrine and biperiden. Sadock (2014) lists four other anticholinergic agents that can be used for EPSEs: benztropine, ethopropazine, procyclidine, and trihexyphenidyl.

2.5.2. Types and side effects profile of anticholinergic agents

Sadock (2014) listed six types of anticholinergic agents: benztropine, biperiden, ethopropazine, orphenadrine, procyclidine, and trihexyphenidyl as the commonly used agents for managing EPSEs. The standard treatment guidelines and essential medicine list for South Africa only have orphenadrine and biperiden as available anticholinergic agents for managing EPSEs, at the primary health and hospital level (The national department of health, 2020)

Anticholinergic agents come with their own side-effect burden, which emanates from the blockage of their muscarinic acetylcholine receptors. Muscarinic receptors are found in the heart, gastrointestinal and urogenital tracts, and salivary glands. Their location in these areas explains their side-effect profile: constipation, dry mouth, urinary retention, and blurred vision (Stahl, 2018). Patients with dry mouth caused by anticholinergic agents present to dentists with chewing and swallowing problems, speaking difficulties, oral lesions, dental caries, and tooth loss due to reduced saliva (Arany, 2021).

Additionally, the muscarinic receptors are located in the cortical area in the central nervous system, which also explains the central adverse effects such as cognitive blunting (Sadock, 2014). The cognitive deficits due to anticholinergic agents are independent of the severity of the symptoms of schizophrenia or the dose of antipsychotic the patient is on (Joshi, 2020). Blockage of the M1, M2, and M3 receptors in the brain is responsible for cognitive deficits and related cell death in the brain. As a result, patients on anticholinergic agents have an increased risk of dementia (Alvarez, 2019). The cognitive deficits caused by anticholinergic agents are associated with reduced quality of life and rising death rates in the elderly with dementia living in nursing homes (Kim, 2019).

Some anticholinergic effects, such as those occurring with biperiden, are said to work on many systems, including the dopaminergic system. Their mechanism of action on the dopamine system may increase positive and reduce negative symptoms of schizophrenia (Stroup, 2018). Fifty per cent of patients with schizophrenia are said to be abusing substances. Some studies hypothesised that, since anticholinergic agents induce euphoria, they might be associated with abuse potential. However, Gjerden (2009) found that the abuse of anticholinergic agents was rare.

Concurrent prescription of anticholinergic drugs with drugs that have high anticholinergic activity can lead to a rare but life-threatening condition called anticholinergic intoxication syndrome (Sadock, 2014). This can present with peripheral and central manifestations, such as hallucinations, delirium, seizures, and urinary retention due to inhibition of the peripheral and central muscarinic receptors (Broderick, 2022). The syndrome is primarily and initially treated by discontinuing all anticholinergic drugs (Sadock, 2014).

2.5.3. Indications for the use and discontinuation of anticholinergic agents in schizophrenia

Anticholinergic drugs are used for the treatment and prophylaxis of antipsychotic-induced movement disorders (Ogino, 2013). Although guidelines do not recommend chronic and prophylactic use of these agents, they are still commonly used in clinical

practice (Ogino, 2013). There is good evidence of the efficacy of anticholinergic agents in treating acute dystonia and parkinsonism; however, their use in akathisia is still limited. Anticholinergic agents are also not recommended in patients with tardive dyskinesia as they have been found to worsen it (Desmarais, 2018). The use of anticholinergic agents in the treatment of akathisia is not as effective as beta-adrenergic antagonists, clonidine, and benzodiazepines (Sadock, 2014).

It is recommended to stop anticholinergic agents once EPSEs are stable for three months (Desmarais, 2014). However, patients still on FGA have a relapse rate of 10 - 77% (of EPSEs) when anticholinergic agents are stopped, while the relapse rate on SGA is 33%. Most studies report improved cognition after weaning off anticholinergic drugs (Desmarais, 2014). Due to cognitive effects, prophylactic and long-term use of anticholinergic agents is not recommended in clinical practice (Ogino, 2013). Gjerden (2009) showed that 28.4% of patients prescribed orphenadrine were successfully weaned off without needing another anticholinergic agent or antipsychotic dose reduction.

2.5.4. Prevalence of anticholinergic use in schizophrenia

A study by Su (2017) proposed an increased prevalence of anticholinergic use in outpatients with schizophrenia mainly because they are prescribed prophylactically due to a lack of close monitoring of EPSEs. A study in Singapore reported an anticholinergic prescription rate of 64% (Chong, 2000). The anticholinergics in the Singapore study were mainly prescribed prophylactically, and even patients who were not on anticholinergics during the study had been on one in the past.

An Asian study done in 2009 found that more than 50% of patients with schizophrenia were prescribed an anticholinergic agent (Xiang, 2013). The Asian study was compared to the Japanese and European literature, which found prevalence rates of 56 - 75% and 33%, respectively, even though the patients were on SGAs. A REAP study (research on Asian psychotropic prescription patterns) conducted between 2001 and 2009 showed that anticholinergic prescription patterns have decreased from 72.4%, 61.9%, and

59.5% in 2001, 2004, and 2009 respectively (Xiang, 2013). Although the REAP study reported a reduction in anticholinergic prescription, rates of almost 60% are still relatively high. The hypothesis made from the REAP study was that that the numbers remain high because patients might be reluctant to stop anticholinergic use related to fear of relapse in their EPSEs or because some are still experiencing EPSEs (Xiang, 2013).

2.5.5. Prevalence of anticholinergic use in monotherapy and APP

Hori (2022) found that patients on APP are more likely to be prescribed an anticholinergic agent than patients on antipsychotic monotherapy. The study reported prevalence rates of 7 - 36% in the monotherapy group and 20-65% in patients on APP. Hori also found that patients on FGA monotherapy have a high anticholinergic rate when compared with patients on SGA monotherapy, mainly due to the pharmacological properties of FGAs (Hori, 2022). About 77.1% of patients on FGA monotherapy receive an anticholinergic agent compared to 58.5% of patients on SGA monotherapy. The literature consistently links the use of anticholinergic agents with FGAs.

FGA-FGA combinations are most likely to be prescribed an anticholinergic agent, followed by SGA polypharmacy, FGA monotherapy, and SGA polypharmacy (Hori, 2022). The high prescription rate in SGA polypharmacy might be related to increased total antipsychotic dose. The most common APP combination in clinical settings is FGA-SGA (Broekema, 2004). A study by Paton (2003) found that FGA-FGA combinations had an anticholinergic prescription rate of 40.2% compared to 22.7% in patients with SGA-SGA combinations. However, this study found no differences in FGA-FGA and FGA-SGA combinations with anticholinergic use rates of 40.2% and 40.9%, respectively (Paton, 2003). With the increased prescription of FGA-SGA, it could still be hypothesised that anticholinergic use is related to the use of FGA and increased antipsychotic dose in APP.

2.5.6. Factors associated with the use of anticholinergic agents in patients with schizophrenia

Patient risk factors associated with using anticholinergic agents include older age, early-onset schizophrenia, use of FGAs, APP, and high-dose antipsychotic prescriptions (Pristed, 2017). Su (2017) found that women and outpatients were most likely to be prescribed anticholinergic agents. Women were prescribed anticholinergic agents because they are more susceptible to akathisia and parkinsonism, but it was unclear why outpatients were. It could be hypothesised that outpatients are prescribed anticholinergic agents more due to a lack of monitoring of side effects in this setting.

Other factors that could be associated with anticholinergic prescription patterns, though not noted in the literature, could be treatment duration and prescribing attitudes of treating doctors. Hori (2022) found that anticholinergic prescription patterns also differ from hospital to hospital.

2.6 Other Interventions Used for the Management of EPSEs

The general approach for the management of EPSEs includes discontinuing those antipsychotic agents that are not essential or beneficial (Stroup, 2018). Other management strategies are lowering the antipsychotic dose (because most EPSEs are dose-dependent) to a low effective dose, switching to an antipsychotic with a different side-effect profile if dose adjustment is impossible, or treating side effects with medication, such as anticholinergic agents (Stroup, 2018). Unfortunately, there is an absence of non-pharmacological approaches to managing EPSEs (Stroup, 2018).

Besides anticholinergics, other agents that can be used to manage neuroleptic-induced acute dystonia include antihistaminic agents and benzodiazepines (Stroup, 2018). In addition to these strategies, the NICE guidelines report the effectiveness of electroconvulsive therapy and botulinum toxin (Taylor, 2018).

Anticholinergic agents have been used as third-line treatment/therapy in managing akathisia, as their effectiveness has not been proven (Stroup, 2018). The first-line management of akathisia is a beta-adrenergic antagonist, with propranolol being the most used, and benzodiazepines are second-line agents (Stroup, 2018).

Withdrawal of anticholinergic agents has been recommended with early signs of tardive dyskinesia. (Stroup,2018). The use of clozapine and quetiapine have been recommended as agents to be used in patients who develop tardive dyskinesia (Stroup, 2018)

2.7 Research Question

Does the use of APP increase the prescription of anticholinergic agents?

2.8 Study Aim

The study aimed to determine the prevalence of anticholinergic use and the association, if any, with the use of APP compared to monotherapy in patients with schizophrenia at the community psychiatric clinics in Soweto.

2.9 Objectives

The objectives of this study were:

1. To determine the prevalence of anticholinergic use amongst patients with schizophrenia in psychiatric community clinics in the Soweto area.

2. To compare the prevalence of anticholinergic use between those patients on antipsychotic monotherapy and those on polypharmacy.

3. To describe the patients' clinical and demographic variables of patients on anticholinergic agents.

4. To assess whether clinical and socio-demographic factors have any influence on anticholinergic use.

2.10 Hypothesis

We hypothesised that patients with schizophrenia on APP are more likely to be prescribed anticholinergic agents than patients on monotherapy.

Chapter 3 : METHODOLOGY

3.1 Study Design

The study design was a cross-sectional retrospective clinical record review of patients with schizophrenia seen at some Johannesburg Metro Health District clinics.

3.2 Study Population

The Johannesburg Metropolitan Municipality was declared a Category A municipality in 1999. It has 11 regions, and the head office of the health district is located in Hillbrow. Soweto falls under region six, together with Doornkop, Dobsonvile, and Protea Glen. The Metro has 26 adult specialised psychiatry clinics, eight of which are in Soweto. A simple random sampling method was done. Zola, Chiawelo, Lillian Ngoyi, and Orlando clinics were randomly selected from eight Soweto clinics using the draw hat method. Soweto clinics serve a large community of psychiatric population in an urban area, that reflects board demographic and a large variety of pathology as an indication of the types of patients seen in our mental health setting.

The clinics are secondary-level specialised units that work on an outpatient basis and operate Monday-Friday from 8h00 to 16h00. The clinics are run by professional nurses, registrars, and medical officers under the supervision of qualified psychiatrists. Patients in these clinics are usually referred from primary health care services, the private sector or are down referrals from surrounding hospitals.

The study population included all patients with schizophrenia seen at the clinics mentioned above in December 2020. For inclusion in the study, participants needed to be:

- Patients seen in the identified community clinics with a documented diagnosis of schizophrenia in the clinic file.

- Age 18 years and above.

The exclusion criteria:

- Children and adolescents below 18 years of age.
- Patients with medical comorbidities as documented in their files.
- Patients with psychotic disorders other than schizophrenia.
- Patients with psychoactive substance dependence.

Files from the patients who met the inclusion criteria were reviewed, and data was captured.

3.3 Data Collection

Schizophrenic patients were identified using a clinic booking register, and their clinical records were retrieved and analysed. The following data were collected: age, gender, illness duration, prescribed antipsychotics and anticholinergics, documented movement disorders, and comorbid psychiatric conditions other than substance use disorders. The collected data were recorded on the data collection sheet (Appendix 1). The rationale for collecting data for only one month was to collect data at a single point. The cross-sectional nature was vital as there are usually medication shortages at the clinics, and prescriptions can change regularly.

3.4 Sample Size

From an assessment of Z scores of expected frequencies, a sample size of 100 will detect statistical significance for each objective at the 5% level. Realistically, statistical significance can be expected with a minimum sample of 70 patients.

Using an estimation of sensitivity and specificity at 85% with 10% precision and a 95% confidence interval, the 58% prevalence of patients on polypharmacy and anticholinergic agents, a sample of size of 84 was required, based on sensitivity and 113 for specificity. The actual sample size of 100 patients was adequate for the study since it is greater than the requirement for sensitivity and corresponds to a precision of 10.7% for specificity.

3.5 Data Analysis

The data collected was captured in a Microsoft Excel spreadsheet. A descriptive analysis of the prevalence and count data was performed. Percentages illustrated variables as bar charts.

The data set for this study was generated from assessments of categorical scores. All statistical analyses were conducted using R software (version 3.5.1; https://www.r-project.org). Tests were two-tailed probability values, and statistical significance was accepted when $\alpha \leq 0.05$.

Statistical analyses used in each of the objectives are outlined below.

Objective 1. A chi-squared analysis contingency table was used to determine the prevalence of anticholinergic use amongst patients with schizophrenia in psychiatric community clinics in the Johannesburg metro. This test determined whether the prevalence of anticholinergic use deviates significantly from chance.

Objectives 2 and 3. Pearson's Chi-square Goodness of Fit test was used to analyse the prevalence of anticholinergic use between patients on monotherapy and those on polypharmacy. Relative risk was calculated for anticholinergic use and polypharmacy by dividing the percentage risk per factor variable by the percentage risk of a reference category (monotherapy).

Objective 4. Crude and adjusted logistic regression models were conducted to assess the association between anticholinergic use and sociodemographic and clinical

characteristics. The association was assessed at a 0.05 level of significance. The Hosmer-Lemeshow Goodness of Fit Test was performed to determine whether the data fit the logistic regression model properly. The test was also performed at the alpha 0.05 level of significance. A Hosmer-Lemeshow test above 0.05 would indicate data fit the model.

3.6 Ethics

Permission to conduct the study was granted by the Research Committee of the Johannesburg Health District (Appendix 2). In addition, unconditional ethics approval was received from the University of the Witwatersrand Human Research Ethics Committee Medical (HREC) (Appendix 4).

- As this was a retrospective record review and patients were not interviewed, individual consent was not needed for the patients whose files were selected and reviewed.
- Data was always kept confidential and anonymous as follows:
    - Numbers were allocated anonymously to the selected patient files to identify them.
    - The use of patients' names or any information that would enable the disclosure or identification of patients was avoided.
    - Information collected from the files was only used for its intended purposes. There was no improper use of information or data in this study.

The principal investigator was the only one who had access to raw data.

Chapter 4 : RESULTS

4.1 Clinical and Demographic Characteristics of the Study Population on Monotherapy and APP

Table 1 presents the clinical and demographic data of the study population. A total of 100 patients in community psychiatric clinics in the Johannesburg Metro region were considered in this study. The average age of patients in this study was 47.6 years old. Significantly more males (n = 73) than females (n = 27) were represented in this study (χ^2 = 21.16, df = 1, p = 0.001). Patients on monotherapy and APP differed in male-to-female ratio but did not differ much in illness duration or average age, as illustrated in Table 1.

Patients in the 30-49 age group comprised 50% of the study population. The duration of psychiatric disorders was recorded in 95 patients and averaged 18.5 years. Only 9 (9%) of the 100 patients had psychiatric comorbidities, significantly less than those without (χ^2 = 67.24, df = 1, p < 0.001). Of those with comorbidities, 7 (78%) had intellectual disability (ID), and one each (11%) had major depressive disorder (MDD) and major neurocognitive disorder (MNCD).

Of the one hundred patients, 35 (35%) were on APP, and 65 (65%) were on monotherapy. The 35% prevalence was significantly more than chance (i.e., the null model; χ^2 = 10.24, df = 1, p = 0.001). The FGA-SGA combinations were the most common form of polypharmacy, with over 68.5% of patients prescribed these drugs, followed by FGA-FGA combinations prescribed to approximately 22.85% of patients. Furthermore, all the patients on polypharmacy were on two antipsychotic agents. Most (91%) of patients on polypharmacy were on drugs that combined long-acting injectables and orals as a method of administration. The remainder (9%) were on oral medication combinations.

Table 1: Clinical and demographic profile of the study population (monotherapy and APP).

	Total sample (n=100)	**Monotherapy (n=65)**	**APP (n=35)**
Variables			
Gender			
Male/female	73/27	45/20	28/7
Age ranges	**Average**=47.6		
• 18-29 • 30-49 • 50-69 • 70-85	• 6 • 50 • 42 • 2	• 5 • 32 • 26 • 2	• 1 • 18 • 16
Illness duration	18.5 years	17.5	19.5
Anticholinergic prescription	26	11	15
Characteristics of APP			
FGA-SGA	-	-	24 (68.5%)
FGA-FGA	-	-	8 (22.85%)
SGA-SGA	-	-	3 (8.5%)
Method of admin in APP			N (%)
• LAI +oral	-	-	32 (91.43)
• Oral +oral	-	-	3 (8.6)

******Five patients had undocumented illness duration. MDD-major: depressive disorder, ID: intellectual disability, MNCD: major neurocognitive disorder, LAI: long-acting injectable, admin: administration. FGA: first generation antipsychotic, SGA: second generation antipsychotic

Patients in this study were on eight different prescribed antipsychotic medications, as monotherapy or in combination. Table 2 illustrates the distribution of prescribed antipsychotic drugs in the study setting. Four out of the eight were SGAs (clozapine, olanzapine, risperidone and amisulpride), and four were FGA (haloperidol, flupenthixol decanoate, zuclopenthixol decanoate and chlorpromazine). Two of the four FGAs were long-acting injectables (LAI). Most patients were on flupentixol decanoate (40%) and risperidone (29%) as monotherapy. Further, over 55% of patients were prescribed FGAs, over 49% were on LAI, and 44% were prescribed SGAs.

Table 2: Antipsychotic drugs prescribed at the Johannesburg Metro Health District clinics.

Treatment	Sample size (n)	% of the total sample	% of the monotherapy group
Flupentixol decanoate	26	26	40
Risperidone	19	19	29.2
Zuclopenthixol decanoate	6	6	9.2
Olanzapine	5	5	7.96
Haloperidol	4	4	6.15
Clozapine	4	4	6.15
Amisulpride	1	1	1.5
FGA (total)*	36	36	55.38
SGA (total)*	29	29	44.6
LAI (total)*	32	32	49.32

FGA: first-generation antipsychotic, SGA: second-generation antipsychotic, LAI: long-acting injectable.

The majority (n = 26; 74%) of patients on monotherapy were prescribed the FGA drug flupenthixol decanoate. Men (62%) accounted for the higher proportion of those prescribed this or any drug prescribed as monotherapy. The average age and illness

duration of those prescribed flupenthixol decanoate was over 50 and 38 years, respectively. The most commonly prescribed SGA drug for monotherapy patients was risperidone (29%). Similar to the gender differences observed in the patients on flupenthixol decanoate, men were highly represented in this group accounting for over 84%. Monotherapy patients on risperidone were 45 years old on average and had the illness for over 22 years (Table 3). Therefore, patients on flupenthixol decanoate were older and had longer illness duration than those on monotherapy.

Table 3: Demographic characteristics of patients on monotherapy

Characteristics	**Ami**	**Cloz**	**Fluanxol**	**Clopixol**	**Olanz**	**Risp**	**Halo**
	n=1	**n=4**	**n=26**	**n=6**	**n=5**	**n=19**	**n=4**
% of total sample = 100%	1	4	2	6	5	19	4
Sex (n): male	M=0	M=3	M=16	M=6	M=4	M=6	M=3
	F=1	F=1	F=10	F=0	F=1	F=13	F=1
Average age	71	38.25	50.76	43.5	45.8	45.42	40.5
Average illness duration	46	11.5	23**	15.6	14.5*	22.14**	17

*One patient had an undocumented duration of illness which affected this value. **Two patients had undocumented illness duration. Abbreviations: ami: amisulpride, cloz: clozapine, fluanxol: flupenthixol decanoate, clopixol: zupenthixol decanoate, olanz: olanzapine, risp: risperidone, halo: haloperidol.

Table 4 presents the different antipsychotic combinations prescribed for APP patients. Risperidone + flupenthixol decanoate was the most commonly prescribed combination, accounting for over 25% of APP prescriptions, followed by olanzapine + flupenthixol decanoate (17%), risperidone + zupenthixol decanoate (11%), and haloperidol + flupenthixol decanoate (11%) combinations. Flupenthixol decanoate + amisulpride,

clozapine + risperidone, and flupenthixol decanoate + amisulpiride were the least prescribed combinations. These combinations were prescribed to one patient each.

Table 4: Antipsychotic combinations prescribed at the Johannesburg Metro Health District clinics

Treatment	Sample size(n)	% of total Population	% of the APP group
Clozapine + amisulpiride	2	2	5.71
Clozapine + risperidone	1	1	2.85
Clozapine + zupenthixol decanoate	2	2	5.71
Clozapine + fluphenthixo1l decanoate	2	2	5.71
Fluphenthixol decanoate +amisulpiride	1	1	2.85
Haloperidol + zupenthixol decanoate	3	3	8.57
Haloperidol + Fluphenthixol decanoate	4	4	11.42
Olanzapine + Fluphenthixol decanoate	6	6	17.14
Risperidone + Fluphenthixol decanoate	9	9	25.71
Risperidone + zupenthixol decanoate	4	4	11.42
Zupenthixol decanoate + chlorpromazine	1	1	2.85

4.2 Prevalence of Anticholinergic Use in the Study Population

The rate of anticholinergic use in this study was 26%, and orphenadrine was the only prescribed anticholinergic agent. A similar percentage of patients on polypharmacy (57.7%) and monotherapy (42.3%) were on anticholinergic agents (Figure 1). In contrast, fewer patients on polypharmacy (25.0%) than on monotherapy (75.0%) were not on anticholinergic agents (Figure 1). The proportions of patients on polypharmacy versus monotherapy differed significantly for those using or not using anticholinergic agents (Fisher's exact test p = 0.004).

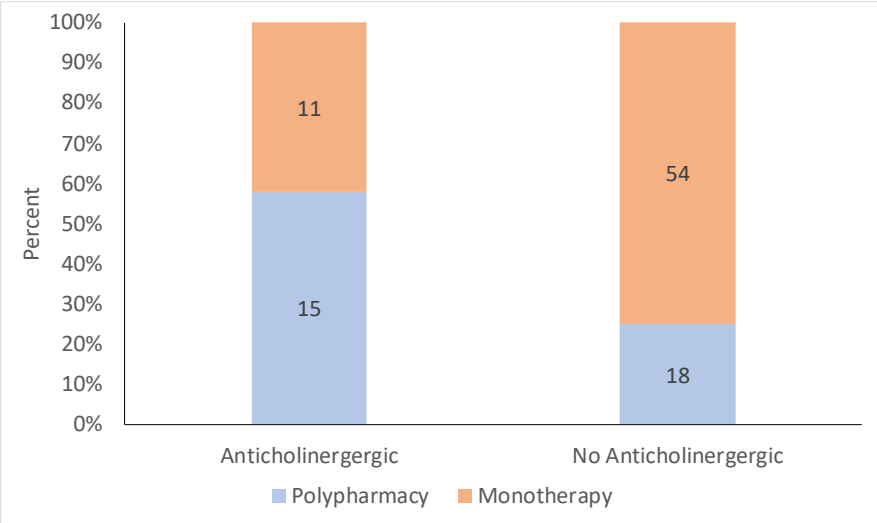

Figure 1: The proportion of polypharmacy or monotherapy patients on anticholinergic agents or not at Johannesburg metro region psychiatric clinics. The number of patients is shown within the bars.

4.3 Demographic and Clinical Characteristics of Patients on Monotherapy and APP Groups on an Anticholinergic Agent

Table 5: Comparison of the clinical and demographic characteristics of patients on monotherapy and APP groups prescribed anticholinergic agents.

	Monotherapy Group	APP Group
Variables		
Sex		
Male	7	15
Female	4	0
Average age (years)	49.7	44
Illness duration (years)	21	17.8
Prescribed antipsychotics		
FGA	8	-
SGA	3	-
LAI (monotherapy or combination)	6	16
FGA-FGA combination	-	5
FGA-SGA combination	-	10
SGA-SGA combination	-	0

FGA: first generation antipsychotic, SGA: second generation antipsychotic.

More men than females in this study were prescribed an anticholinergic agent. About 85% of males were prescribed an anticholinergic agent compared to 15% of females. All females prescribed an anticholinergic agent received a single antipsychotic agent, and all males were on APP.

The anticholinergic prescription rates were further divided in the monotherapy group into FGA and SGA monotherapy. Only three patients on SGA were prescribed an anticholinergic agent, two on risperidone, and one on clozapine. About 85% of patients on an anticholinergic agent were prescribed an LAI either as monotherapy or in combination with other agents. Of the patients on LAI, 61% were receiving it in

combination with another agent. The FGA-SGA combination was the commonest at 66.6%.

4.4 Associations Between Demographic and Clinical Characteristics of Patients on Monotherapy and APP and Anticholinergic Use

There were fewer patients on polypharmacy (16.7%) than on monotherapy (83.3%) that had a documented EPSEs (Figure 2). Similarly, fewer patients on polypharmacy (35.1%) than on monotherapy (64.9%) had no movement disorder (Figure 2). The proportion of patients on polypharmacy versus monotherapy did not differ significantly for the presence or absence of EPSEs (Fisher's exact test p = 0.661). EPSEs were recorded in only six patients, significantly less than the 94 patients without EPSEs (χ^2 = 77,44, df = 1, p < 0.001). Significantly fewer patients (n=26) were on anticholinergic agents than those who were not (n-72) (χ^2 = 21.59, df = 1, p < 0.001). All 26 patients were on orphenadrine.

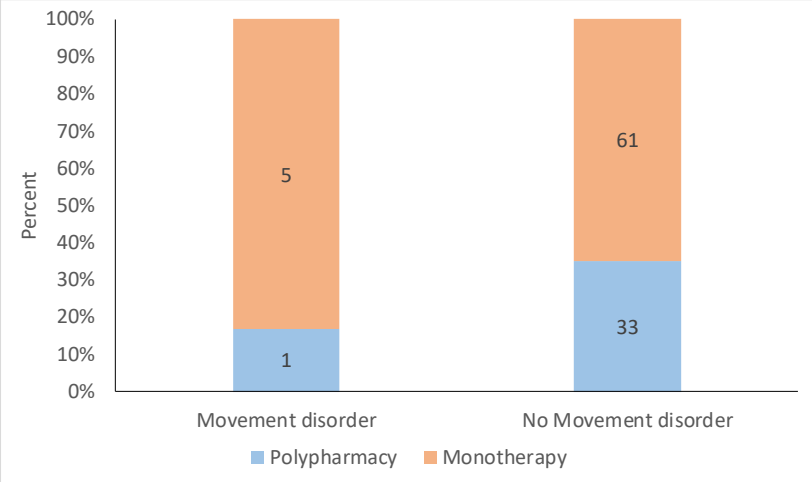

Figure 2: The percentage of polypharmacy or monotherapy patients with or without movement disorders at Johannesburg metro region psychiatric clinics +the number of patients is shown within the bars.

Table 6 presents the crude and adjusted logistic regression model examining the relationship between anticholinergic use and other factors listed below. The crude model found an association between anticholinergic use and the explanatory variables, polypharmacy, and FGA combination drug classification. The results indicated that patients on polypharmacy and FGA combinations of polypharmacy were four and five times more likely to use anticholinergic agents than patients on monotherapy and FGA monotherapy, respectively. A marginal association between anticholinergic use and patients on FGA/SGA combination was also observed, showing more odds of anticholinergic use amongst patients on FGA/SGA (Odd Ratio=3.09, 95% CI: 0.99 – 9.64, p-value = 0.051) compared to patients on just FGA drugs. After adjusting for all other factors that may introduce bias in the adjusted model results, no association was found between anticholinergic use and the variables mentioned above or any other. In post-estimation, the Hosmer-Lemeshow showed data fit the model correctly; that is, the logistic regression model was the sensible model to perform given the data presented.

Table 6: The crude and adjusted logistic regression model assessing the association between anticholinergic use and sociodemographic and clinical characteristics.

	Crude Model		**Adjusted Model**	
Variable	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	1.01 (0.97 – 1.05)	0.802	1.01 (0.95 – 1.06)	0.820
Gender				
Male	1 (Reference)		1 (Reference)	
Female	0.41 (0.13 – 1.34)	0.141	0.42 (0.09 – 1.82)	0.246
Polypharmacy				
No	1 (Reference)		1 (Reference)	
Yes	4.10 (1.59 – 10.51)	0.003	1.90e-07 (95% CI = 0)	0.992
Prescribed antipsychotic drug classification				
FGA	1 (Reference)		1 (Reference)	
FGA combination	5.63 (1.10 – 28.83)	0.038	3.97e+07 (95% CI = 0)	0.991
FGA/SGA combination	3.09 (0.99 – 9.64)	0.051	1.68e+07 (95% CI = 0)	0.992
SGA	0.25 (0.05 – 1.29)	0.097	0.19 (0.03 – 1.15)	0.071
SGA-SGA combination	**predicts outcome perfectly		**predicts outcome perfectly	
Movement disorder				
No	1 (Reference)		1 (Reference)	
Yes	2.91 (0.39 – 21.86)	0.298	8.06 (0.80 – 80.89)	0.076
Psychiatric comorbidities				
No	1 (Reference)		1 (Reference)	
Yes	0.37 (0.04 – 3.17)	0.366	0.16 (0.01 – 1.92)	0.150
Hosmer-Lemeshow goodness of fit for multivariable (adjusted) logistic model run = 0.522				

Chapter 5 : DISCUSSION

5.1 Demographic Characteristics of the Study Population

5.1.1 Gender

The male-to-female ratio of patients with schizophrenia is reported to be equal, with the only difference being the age of onset of the illness (Sadock, 2014). However, the Diagnostic and Statistical Manual of Mental Disorders indicates differences in male: female ratios with different samples. For example, negative symptoms, chronicity of the illness, and poor prognosis are more common in males, and equivalent ratios occur with mood symptoms and brief presentations (American Psychiatric Association, 2013). This study found a male: female ratio 3:1 (n=73 males and 27 females), which significantly deviates from the literature. The deviation may be attributed to differences in environmental risk factors associated with schizophrenia in South and sub-Saharan Africa. For instance, a South African study by Koen et al. (2008) found that men (83.5%) were highly represented in patients with schizophrenia compared to women (16.5%). Our study and the study by Koen differ from universal standards; however, this might be due to the nature of context and environmental differences.

In addition to environmental differences, the above findings may be explained by diagnostic bias as female patients with schizophrenia present with more mood symptoms, are less disorganised, and are more functional (American Psychiatric Association, 2013). Therefore, females might have been more likely to be given another diagnosis rather than schizophrenia. Another variable could be that there are high rates of cannabis use disorder amongst men, which might increase their likelihood of developing schizophrenia and explain its high prevalence in men in this study. An American study by Cuttler (2016) found that men reported higher cannabis use compared to women. Similarly, Ramalgan (2021) observed the likelihood of daily cannabis use in young South African men was 11 times when compared to women. Longitudinal studies, such as the Swedish cohort studies of cannabis use and the risk of developing schizophrenia by Andreasson (1987) and Zammit (2002), presented a dose-

response relationship between the two variables. These findings might mean males are more predisposed to schizophrenia than their female counterparts. As such, it is plausible to hypothesise that the high prevalence of schizophrenia in South African men may be attributable to a high prevalence of cannabis use in this demographic (Ramalgan, 2021). The reduced level of disorganisation in women may result in a disease presentation that families can cope with. Hence, there is less family pressure for regular follow-ups and less frequent clinic attendance. There is also a possibility that most female patients were excluded due to medical comorbidities or because of reviewing patients seen in one month only.

5.1.2. Age and duration of illness

The average age of the study population was 47.6 years, with an average illness duration of 18.5 years. In this study, 50% of the participants fell within the 30-49 years of age category. This age category is usually expected to be economically active, and having many patients in this age range is a concern. A Nigerian study by Igbinomwanhia (2017) found that 40% of schizophrenic patients were aged 31- 40.

Stable patients from tertiary and surrounding hospitals are usually referred to community-based specialised psychiatry clinics for follow-up. There is a high possibility that young patients might be following up at hospitals as they might not have achieved clinical stability. The exclusion of patients using substances might have seen many young patients being excluded from the study, leaving older patients. Young patients might also have poor insight into their illness, directly affecting their attendance at follow-up appointments. Most studies do not show a relationship between sociodemographic variables and compliance with medication in patients with schizophrenia. However, there is a positive relationship with older age, which can be related to improved insight as patients get older (Higashi, 2013).

There is an elevated risk of relapse associated with the discontinuation of antipsychotics, so long-term prescriptions of antipsychotics are recommended (Taylor, 2018). The age and duration of illness in this study highlight the chronicity of schizophrenia and the long-term prescriptions associated with the illness. Despite

remission, clinicians are still wary of weaning patients off medication because of relapse-related worries (Moncrieff, 2020). Fears of stopping medication might explain the chronic prescription of antipsychotic agents and the average duration of illness of 20 years.

5.2 Prevalence and Characteristics of Patients on APP vs Monotherapy

Shenoy (2020) found that at least 43.9% of participants in their study were on APP. A study by Koen (2008) in Stellenbosch found South African prevalence rates of APP were about 28.6%. In the current study, the prevalence of APP was 35%, much higher than Koen and colleagues observed. The increased prevalence might be due to a general increase in polypharmacy prescribing practices over time, and our study also included patients with schizoaffective disorder. The rate of monotherapy in a study by Park (2014) was 10.53%, significantly less than our finding of 65%.

Two Nigerian studies have shown a high prevalence rate of APP. Anozie (2020) found that 50.9% of patients with schizophrenia were on APP, and Igbinomwanhia (2017) found a prevalence of 70.4% (the highest prevalence rate thus far). Most literature reports prevalence rates of about 10-50%, and our study was well within universal norms. The pharmacoepidemiologic study had APP prevalence rates of approximately 24.6% in 2012, which was lower than the prevalence rates in this study (Sneidera, 2015).

One of the reasons why APP rates do not decline is due to difficulties or hesitancy by clinicians in converting patients back to antipsychotic monotherapy. Other factors include treatment resistance, switching arrests, long acting injectables, illness severity, inpatients' family, and patient resistance to converting to monotherapy once stabilised on APP (Igbinomwanhia, 2017).

This study did not show significant statistical differences in the ages between the two groups, with an average age of 47.4 in the monotherapy group and 47.5 in the polypharmacy group. This was in keeping with the average age of the total sample of

47.6 years (Table 1). Therefore, it can be assumed from these findings that APP is unrelated to the patient's age, but other factors play a role in the prescribing patterns.

Shenoy (2020) found that the population on APP had an average age of 35.6 years, ten years younger than this study population. Shenoy's study was conducted in India, which shares economic development characteristics with South Africa. The age differences are statistically significant. A local study by Koen (2008) showed related results to Shenoy, with an average age of 35.0 years. The Nigerian study by Igbinomwanhia (2017) found results consistent with Koen and Shenoy, with a mean age of 37.85. The age differences noted might be related to the exclusion criteria in this study because excluding patients with psychoactive drug dependence eliminated young patients and left the study with an older population. In addition, younger patients may have poorer adherence to treatment, fewer clinic visits, or not be stabilised sufficiently to receive treatment at the clinic level.

Of the patients on APP, 68.57% were on FGA-SGA combinations. Of all the patients on APP, 32 (91.43%) were on a long-acting injectable (LAI). LAI has better tolerability, improves adherence, and prevents relapses. Patients should not be labelled as treatment-resistant if LAI has not been used (Kane, 2021). The total proportion of long-acting injectable use across the population was 65%. All the long-acting injectables were FGA, possibly due to a lack of second-generation LAIs at the clinics. Only 8.5 % were on SGA-SGA combinations, and 22.85% were on FGA-FGA combinations. FGA-SGA combinations are generally associated with long-acting injectables (Sneider, 2015).

Sneider (2015) found the use of long-acting injectable agents was 34.3%, with an FGA-SGA drug combination rate of 56.8%. The high use of long-acting injectables in this study might be attributed to high non-adherence rates in the study population. The preference for a long-acting injectable over a short-acting AP is that it bypasses first-pass metabolism and achieves stable plasma concentration, thereby reducing the risk of relapse (Kane, 2021).

Koen (2008) found the use of depot preparations at Lentegeur Hospital to be 52.2%, 46.2% at Stikland Hospital and 59.9% at Valkenberg Hospital. Both this study and Koen show increased rates of depot antipsychotic use, which might be related to high rates of non-adherence in this population. An Indian study by Shenoy (2020) found FGA-SGA combinations at 54.4% and 85.7% of patients on two compared to 14.3% on three agents. All patients on APP in this study were on two agents. Twenty-seven out of 35 (77.14%) of these patients were on flupenthixol decanoate, and the prescription rate in the monotherapy group was 40%. The total rate of flupenthixol decanoate prescribed across the study population was 53%. The Metro Health District only has two FGA LAIs, and SGA depot preparations are unavailable, leaving clinicians with little to work with. With that said, flupenthixol depot was still a preferred LAI over zupenthixol decanoate. The 2020 edition of the standard treatment guidelines and essential medicine list for South Africa at the primary health care level only has two LAI in their list, namely, zupenthixol decanoate and flupenthixol decanoate. This explains why all the patients on LAI were only on these two agents.

A Chinese study by Wang (2021) found the most common drug combinations were SGA-SGA oral combinations, and none of the participants was on depot preparations. The prescription rates of clozapine (24%) in this study are inconsistent with the literature, where most prescribers shy away from prescribing clozapine. The high percentage of SGA-SGA combinations might be due to the social status or cardio-metabolic profile of the study participants in China or the availability of second-generation drugs. The controversies surrounding long-acting injectables are responsible for their low prescription in a clinical setting, e.g., limited use to non-adherent populations (Kane, 2021).

Significant differences existed between the Chinese study and the study at Soweto clinics. In the former, no depot preparations were used, but other agents not readily available in the Johannesburg Health District, like aripiprazole, ziprasidone, sulpiride, perospirone, perphenazine, and quetiapine, were prescribed. Overall, clozapine use in this study was 11% in both groups. The low prescription rates of clozapine may reflect a lack of monitoring guidelines and facilities for patients on clozapine. There is a

possibility that clinicians are apprehensive about starting patients on clozapine due to concerns about fulfilling the requirements of a monitoring strategy.

5.3 Anticholinergic Use in the Study Population

5.3.1 Prevalence of anticholinergic use

The rate of anticholinergic use in this study was 26%, and orphenadrine was the only prescribed anticholinergic agent. The 2020 edition of the standard treatment guidelines and essential medicine list for South Africa has only two anticholinergic agents listed for use at the primary healthcare level: oral orphenadrine and parenteral biperiden. This explains why all patients were prescribed orphenadrine only, as the biperiden would not be given to an outpatient population.

A Japanese study in 2022 found that 30.5% of the patients discharged from 77 hospitals were prescribed an anticholinergic agent (Zhang, 2022). The difference between this and the Japanese study was that biperiden was the commonly prescribed anticholinergic agent. However, in their study, multiple anticholinergic agents were available, unlike the study in the Johannesburg metro district, where all patients were prescribed orphenadrine.

Chong (2000) found that almost 64% of the patients in a Chinese study were on anticholinergic agents. In that study, most patients were on prophylactic prescriptions of anticholinergic agents. It was also highlighted that patients not on anticholinergic agents during the study period had been on one in the past.

A REAP (the Research on Asia Psychotropic Prescription pattern) study found an average of 63.4% of elderly patients with schizophrenia were prescribed an anticholinergic agent (Xiang, 2011). These findings are almost double the prevalence rate of the current study and are concerning because of the increased risk of side effects in older patients. The anticholinergic burden in patients with schizophrenia is

high, mainly from anticholinergic prescriptions, but also because some antipsychotic agents have anticholinergic properties.

The Johannesburg metro district has maintained a lower rate of anticholinergic agent prescription. Unfortunately, there is no clear documentation in the patient's records about why an anticholinergic agent was prescribed. These low prevalence rates in the Johannesburg metro district might be underestimated because patients with medical comorbidities and psychoactive drug dependence were excluded.

5.3.2 Gender

Most patients on anticholinergics were male (84.6%), equating to a ratio of almost 5.5:1, which is higher than the male-to-female ratio in the study population of 3:1. A United Kingdom study by Paton in 2003 investigating antipsychotic and anticholinergic prescription patterns found that 59% of their study population comprised males. A Chinese study found 77% of males were on anticholinergic agents (Chong, 2000). The gender ratio in this study population of 3:1 differs significantly from the literature, where schizophrenia affects males and females equally.

This finding suggests that the male gender is associated with high anticholinergic rates, mainly because they have high rates of APP, use of LAI and FGA. It is unclear why this particular group has a high prevalence of the prescriptions above; however, it can be hypothesised that they may have poor symptom control, non-adherence, or severe illness.

5.3.3 Age and illness duration

The average age of patients on an anticholinergic was 47.2 years which was not statistically different from the rest of the study population at 47.6 years. Most literature has found that anticholinergic use is more common in younger patients, while most patients in this study were middle-aged. Abouzaid (2014) found that patients with EPSEs were younger males, with a mean age of 36.5 years.

Chong (2000) found a mean age of 50.4 in recipients of anticholinergic agents, which was lower than that of patients not on anticholinergic agents, who had a mean age of

58.4 years. Based on their demographic profile, younger patients were a risk factor for prescribing anticholinergic agents.

The difference in the mean age of anticholinergic users across the above studies may result from different ethnicity, sociodemographic environment, and prescribing patterns across different settings. Excluding patients with medical comorbidities and psychoactive substance use in this study might have excluded many young patients, thus leaving the sample with an older population.

The average illness duration in the anticholinergic group was 19.3 years, similar to that of the whole study sample. This highlights the chronicity of schizophrenia. No literature was found on the illness duration of patients prescribed anticholinergic agents.

5.3.4 Antipsychotic prescription pattern (APP vs monotherapy)

Of the clinic patients, 57.6% on anticholinergics were also prescribed APP, and only 38.4% were on monotherapy. A Chinese study found that patients on APP were prescribed anticholinergics more than monotherapy, with prevalence rates of 7-36% for monotherapy and 20-63% for APP (Zhang, 2022). The Chinese study was done comparing anticholinergic prescriptions across different hospitals, and although this study was done across four clinics, comparisons were not made on their individual prescription rates (Zhang, 2022).

FGA antipsychotics were the most prescribed agents in the monotherapy group. Of the patients on monotherapy, 72% were prescribed FGAs, and 75 % were on LAI. These findings reinforce that FGA prescription is associated with anticholinergic use in patients on antipsychotic monotherapy. The high anticholinergic prescription in patients on FGAs is related to their pharmacological properties, with a more likely risk of inducing EPSEs.

Of the patients on APP, 66.6% were on FGA-SGA combinations, and FGA-FGA combinations accounted for the rest. The majority on APP were on a combination of an LAI and another agent accounting for 61% of the patients on APP. LAI was prescribed to 84.2% of patients in both groups. Paton (2003) found equal rates of anticholinergic prescription between FGA-FGA and FGA-SGA combinations at 40%. Reasons for using

FGA-SGA combinations may include using LAIs to improve symptom control and adherence or to cover symptoms in patients with features of a mood disorder. In addition to greater total antipsychotic dosages associated with APP, the FGA-SGA combination also has added side effects, such as cardio-metabolic and EPSEs.

5.4 Anticholinergic Use in Patients on Monotherapy and APP

5.4.1 Prevalence

In the APP group, 45.7% were on an anticholinergic agent, and 2.85% (n=1) had tardive dyskinesia as a documented movement disorder. Although only one movement disorder was documented, it is assumed that 45,7% of patients in the APP group have a neuroleptic-induced movement disorder. In this study, an anticholinergic prescription was used as a marker for the presence of a movement disorder. However, a study by Shenoy found a prescription rate of 54.4% for FGA-SGA combinations, and anticholinergic use of 13.8%, which was lower than this study.

The hypothesis that APP is more likely to result in EPSEs, leading to high rates of anticholinergic use, is consistent with the literature. APP is associated with high anticholinergic use, as Sneidera and colleagues (2015) found that over 57% of patients who use anticholinergic agents are on polypharmacy. APP is also associated with the male gender and the use of LAIs. Sneidera and colleagues found that, of the males prescribed APP, 34.3% were on an LAI compared to 10.9% on monotherapy, and 13.8% were prescribed an anticholinergic drug compared to 3.0% on monotherapy (Sneidera, 2015). Barnes et al. (2011) further highlighted that patients on APP were usually male and had more significant anticholinergic use.

5.4.2 Types, class, and routes of antipsychotic administration

Twenty-four out of 26 (92%) patients on anticholinergic agents were on FGA, either prescribed as monotherapy or combined with other agents. The typical combinations were FGA-SGA at 68.57%, FGA-FGA at 22.85%, and SGA-SGA combinations being

the least used at 8.5%. Only two patients were on SGA monotherapy, one on clozapine and one on risperidone.

Su (2017) reported that patients on FGA-SGA combinations were likely to be prescribed anticholinergic agents at the same rate as patients on FGA monotherapy, and anticholinergic prescriptions were high in outpatients due to a lack of regular monitoring of EPSEs. Comparison with patients in surrounding hospitals would have assisted with prevalence rates between the different settings. This highlights that anticholinergic use is mainly associated with FGA rather than APP. Only 25% of the patients without anticholinergics were on APP, and 75% were on antipsychotic monotherapy.

5.4.4 Extra pyramidal side-effects in the study population

The overall rate of documented EPSEs was 6%. It is likely due to omissions in the documentation of EPSEs in the patient records. Since anticholinergic prescriptions were used as a marker of EPSEs, the assumption is that 26% of patients in this study had some EPSE. The difficulty with this assumption is that the high numbers could also be due to the prophylactic prescription of anticholinergics, despite this not being recommended practice.

Of those with documented EPSEs, 66.6% were male, and 33.3% were female. The most documented EPSE was tardive dyskinesia at 50%. However, anticholinergic medication is not indicated for the management of tardive dyskinesia. The high prevalence of tardive dyskinesia reflects the chronicity of schizophrenia as the patients in this study were older with a long duration of illness. It is likely that other EPSEs were not documented, or since EPSEs are reversible, they might have resolved on anticholinergic treatment without concomitant prescription change.

A study by Haddad (2008) found that 72% of patients with schizophrenia had EPSEs, but when reviewing their records, only nine had a treatment plan for them. Furthermore, only one patient out of the 25 had a documented physical examination. These findings highlighted that clinicians might not be screening for EPSEs.

This study found that five of the six patients with documented EPSEs were on a single antipsychotic, and only one was on polypharmacy. These findings are inconsistent with the rates of anticholinergic use of 26% in this study. This may be related to poor record-keeping. It can also be assumed that there might be a high prescription of prophylactic anticholinergics in the Johannesburg Metro district. Nevertheless, since the anticholinergic prescription was used as a marker of movement disorder in the study population, it would appear that 26 % of patients had EPSEs.

5.5. Strengths of the Study

Johannesburg Metro Health district clinics offer specialist outpatient psychiatric services, manned by doctors training at the university affiliated to department of Psychiatry. Hence, the setting provided a homogenous population on specialist-prescribed treatment regimens. Both registrars and medical officers under the supervision of psychiatrists see patients (large in number). This ensures that data collected based on treatment regimens have academic rigor and provide reliability.

5.6 Limitations of the Study

The data in this study at the Johannesburg health district must be interpreted with caution due to several limitations:

The sample size was relatively small compared to other studies on schizophrenia. The study's cross-sectional design was a significant limitation as it did not demonstrate medication switching or discontinuations. The limited area from which the study population was taken makes it difficult to generalise findings to the rest of the population. Also, due to the small sample size, the logistic regression model returned results with wide confidence intervals and miniscule odds ratios, indicating imprecision.

Using anticholinergic prescription as a marker of the presence of movement disorder was a significant limitation of this study. The large difference between the numbers of patients taking anticholinergics and those with documented EPSEs demonstrates that this was not an accurate method of determining the presence of movement disorder in

patients with schizophrenia. The retrospective and cross-sectional nature of the study did not allow the evaluation of successful treatment of EPSEs or if patients on anticholinergics consistently had EPSEs.

Data collected relied on records from the patient's files, and if the presence of EPSEs was not documented, valuable information was not captured. The value of data collected in a record review depends on the quality and integrity of the clinical record. In several cases, poor documentation of clinical decisions may have led to misrepresentation. The study design precluded the examination or interview of patients.

Dosages of antipsychotics were not documented in this study. It is clear from the literature that EPSEs are strongly related to the dose of antipsychotics, especially high doses (Hori, 2022). Without this information, it cannot be concluded that the use of APP alone was specifically associated with anticholinergic use. The dosage of the medication is a significant confounding variable.

The broad exclusion criteria, substance dependence and medical comorbidity, might have excluded the patients at the most significant risk of developing EPSEs.

5.7. Recommendations

- A larger sample size and a more extended period of record review might provide more meaningful results**.**
- A prospective study in which patients are examined, using rating scales, would provide a far more accurate estimation of the prevalence of EPSEs.
- The inclusion of dosages and duration of use of antipsychotic agents in the data would have allowed for a determination of the impact of medication dose on anticholinergic use.
- Prescription of anticholinergic agents for patients in whom EPSEs have not been documented should be reviewed, and, where possible, prescribe one antipsychotic agent.
- Increased use of clozapine may reduce the need for APP.

Chapter 6 : CONCLUSION

Anticholinergic prescription rates are still high in this outpatient clinical setting. They are primarily associated with using FGAs, APP, male gender, and young age. The average age of the sample population was middle-aged; consequently, the age of the patients on anticholinergics was higher than expected. This finding may be due to excluding patients with medical comorbidities and psychoactive drug use. The use of FGAs is more likely to be associated with anticholinergic prescriptions. Su (2017) found that older patients, use of FGA, high doses, and longer duration of illness are some risk factors associated with anticholinergic agent use. Unfortunately, this study did not examine the doses of prescribed antipsychotics, which would have provided important information on the pattern of use of anticholinergic agents.

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APPENDIX 1: PERMISSION TO CONDUCT RESEARCH

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

Research Committee of Johannesburg Health District

Joburg
a world class African city

12TH February 2021

27
Limonient Road
Croydon Kempton Park
1619

Email: japisa1.mn@gmail.com

Enquiries: Ms. Busisiwe Sikhosana
Tel: 011 684 3909
Email :Busisiwe.Sikhosana@gauteng.gov.za
Hillbrow CHC: Administration Building,
Cnr Smith Str. & Klein Street
Private Bag X21, Johannesburg,
South Africa, 2017

Dear: Dr Marcia Ntimani

TITLE: ***A comparison of anticholinergic use between schizophrenic patients on polypharmacy and those on monotherapy***

DRC Ref: 2020-06-007

NHRD Ref no: GP_202006_021

OFFICIAL APPROVAL

The Johannesburg Health District Research Committee (DRC) has reviewed your application. This letter serves as approval to access the Districts Health facilities (mentioned below) for the above research.

The following conditions must be observed:

- The facilities in which the research will be conducted are: CHIAWELO CHC, LILLIAN NGOYI CHC, ORLANDO PROV CLINIC, ZOLA CHC
- These facilities will be visited from: 12/02/2021 to 12/02/2022
- Participants' rights and confidentiality will be maintained all the time.
- No resources (Financial, material and human resources) from the above facilities will be used for the study. Neither the District nor the facility will incur any additional cost for this study.
- The study will comply with Publicly Financed Research and Development Act, 2008 (Act 51 of 2008) and its related Regulations.
- You will submit a copy (electronic and hard copy) of your final report. In addition, you will submit an annual progress report to the District Research Committee.
- Your supervisor and the University of Witwatersrand will ensure that these reports are being submitted timeously to the District Research Committee.

- The District must be acknowledged in all the reports/publications generated from the research and a copy of these reports/publications must be submitted to the District Research Committee.
- You will liaise with the manager/s before initiating the study.

Contact	Sub District	Sub District Manager/ Area Manager	Contact No.	Cell phone
	ABCEF	Ms Lombuso Matlala	011 440 1259	082 307 0267
X	D	Ms Maria Mazibuko	011 674 1200	082 781 9919
	G	Mr Peter Mathole	011 213 9603	072 483 6839
	CoJ A	Ms Nelly Shongwe	011 237 8010	082 467 9276
	CoJ B	Ms Zanozuko Mbane	011 718 9656	082 551 5804
	CoJ C	Mr Tebogo Motsepe	011 761 0200	084 655 5420
X	CoJ D	Ms Busi Phiri	011 986 0164	082 467 9316
	CoJ E	Mr Vusi Mazibuko	011 582 1504	082 464 9547
	CoJ F	Mr M Monyamane	011 681 8130	082 467 9423
	CoJ G	Ms Olga Kruger	011 211 8936	083 286 0388

We reserve our right to withdraw our approval, if you breach any of the conditions mentioned above. Please feel free to contact us, if you have any further queries.

On behalf of the District Research Committee, we would like to thank you for choosing our District to conduct such an important study.

Regards

Prof S. Moosa
Chairperson: District Research Committee
Johannesburg Health District
Date: 12th February 2021

Mrs M.L Morewane
Chief Director
Johannesburg Health District
Date: 16/02/2021

Dr Baski Desai
Executive Director (Acting)
City of Johannesburg
Date: 15/02/2021.

APPENDIX 2: DATA COLLECTION SHEET

Case number --------

Demographic data

Age in years		Gender	Male		Female	

Illness duration

Duration in years	Unknown

Psychiatric comorbidities

Comorbidities	Yes	No	Unknown

If yes, condition:

Mood Disorder	
Substance Use	
Neurocognitive Disorder	
Other (Specify)	
Unknown	

Movement disorder documented

Yes		No	

If present specify ……..

Anticholinergic agent used

Orphenadrine	
Biperiden	

APP present

yes	
no	

Prescribed

Haloperidol	
Risperidone	
Olanzapine	
Quetiapine	
Clozapine	
Amisulpride	
Flupenthixol decanoate	
Zuclopenthixol decanoate	
Other, specify	

APPENDIX 3: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

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

TO: Dr M Ntimani
School of Clinical Medicine
Department of Psychiatry
Medical School
University

E-mail: japisa1mn@gmail.com

CC: Supervisor: Dr W Friedlander <Wendy.Friedlander@wits.ac.za>
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: 2020/10/05

REF: *R14/49*

PROTOCOL NO: **M200762** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *A comparison of anticholinergic use between schizophrenic patients on polypharmacy and those on monotherapy*

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.

MS#Works2000\Iain\0007\Clearscan.wps

UNIVERSITY OF THE
WITWATERSRAND
JOHANNESBURG

R14/49 Dr M Ntimani

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200762

NAME: (Principal Investigator)	Dr M Ntimani
DEPARTMENT:	School of Clinical Medicine Department of Psychiatry Medical School University
PROJECT TITLE:	A comparison of anticholinergic use between schizophrenic patients on polypharmacy and those on monotherapy
DATE CONSIDERED:	2020/07/31
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr W Friedjander
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/10/05

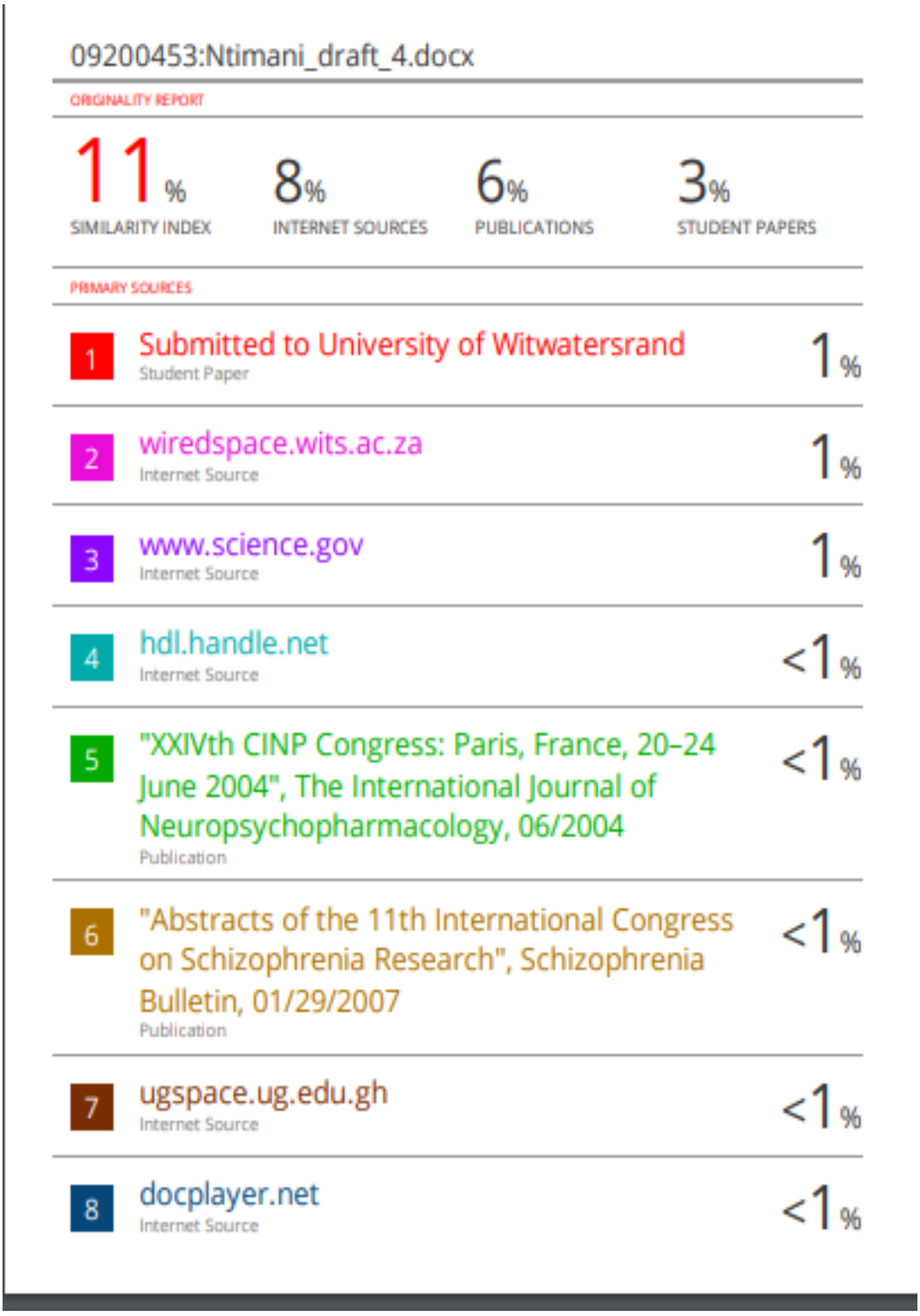
This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized 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 submit details 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 when the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore reports and re-certification will be due early in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

APPENDIX 5 TURNITIN REPORT



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