CURRENT PRACTICE OF ANTICHOLINERGIC USE IN CONJUNCTION WITH ANTIPSYCHOTIC AGENTS AT HELEN JOSEPH HOSPITAL PSYCHIATRIC OUTPATIENTS

Dr. Xandri Heydenrych

Student Number: 560882

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Supervisor: Associate Prof. ABR Janse Van Rensburg

MMed, FCPsych(SA), PhD

WITS Department of Psychiatry

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DECLARATION

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

December 2018

DEDICATION

This work is dedicated to my family for their endless support.

ACKNOWLEDGEMENTS

I hereby acknowledge the Helen Joseph Hospital Department of Psychiatry for the opportunity to conduct my research, as well as Professor Janse Van Rensberg for his guidance, teaching and support.

PRESENTATIONS

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ABSTRACT

INTRODUCTION. Antipsychotic agents are used in the management of psychiatric disorders. Anticholinergic agents are co-prescribed for neuroleptic-induced side-effects.

PURPOSE AND STUDY OBJECTIVES. This study reviewed the current practice of antipsychotic and anticholinergic agent co-prescribing. Objectives included describing the study population, comparing subgroups and comparing antipsychotic and anticholinergic agent co-prescribing according to set guidelines. The hypothesis was that such guidelines were not followed.

METHODOLOGY. The study design was a cross-sectional retrospective clinical record review. Patients prescribed antipsychotic agents were identified and screened for concurrent anticholinergic agent use. Statistical analyses consisted of both descriptive and comparative components.

RESULTS. The study included 331 patients, with the majority being middle-aged females prescribed atypical antipsychotic agents for a variety of disorders. 40 patients were co-prescribed anticholinergic agents during the first six-month period, and 44 during the second six-month period, with no dose adjustments during the study period.

CONCLUSION. Guidelines with regards to anticholinergic agent use were not followed. Education surrounding anticholinergic agent use should be promoted.

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CHAPTER 1 INTRODUCTION

1.1 Background

Since its discovery in the 1950's, antipsychotic agents have been used in the treatment of a wide variety of psychiatric disorders. Chlorpromazine, the first antipsychotic agent to be used, was found to be sedating and resulted in the effective management of agitated, restless patients without the need for physical restraints and seclusion.[1] Due to its prominent antipsychotic effect, the use of chlorpromazine for this purpose introduced the pharmacological era in psychiatry.[1] Antipsychotic agents currently form the mainstay of treatment for schizophrenia, but are frequently used off-label and as adjunctive medications.[2]

1.1.1 Typical antipsychotics

Associated with the use of these initial antipsychotic agents, also known as typical antipsychotics, are their neuroleptic-induced side-effects, namely neuroleptic-induced parkinsonism, acute dystonia and akathisia.[3] Tardive dyskinesia, a more long term result, is also a concerning, often irreversible, potential side-effect.[3]

(1) Neuroleptic-induced parkinsonism is phenomenologically identical to the motor deficits seen in Parkinson's Disease. It can present with the triad of rigidity, bradykinesia and a resting tremor.[4] These symptoms need to be differentiated from depressive symptoms and negative symptoms often associated with schizophrenia.[5] Neuroleptic-induced parkinsonism can occur during any time of the course of treatment with antipsychotic agents although, more commonly days to weeks after antipsychotic agent initiation or dose increase.[5]

(2) Neuroleptic-induced dystonia refers to the sustained, involuntary contraction of a muscle group, with the neck, eyes and trunk commonly involved. Laryngeal

dystonia can be a life-threatening condition. Acute dystonia can occur within hours to days of antipsychotic agent initiation or dose increase.[3,4,5]

(3) Neuroleptic-induced akathisia is described as the irresistible urge to move, or the subjective feeling of inner restlessness. This commonly manifests as pacing or the inability to sit still. It is, more often than not, objectively noted rather than subjectively reported. It needs to be differentiated from agitation or worsening of psychotic symptoms. Akathisia commonly occurs during the first few hours to weeks after initiating an antipsychotic agent, or increasing the dose.[3,4,5]

Stahl notes that in schizophrenia, for example, "positive symptoms" of the disorder such as hallucinations and delusions, are caused by dopaminergic hyperactivity in the mesolimbic pathway.[6] Negative symptoms of the disorder, such as anhedonia, a-volition and impaired cognition, are thought to be due to dopaminergic hypo-activity in the mesocortical pathway.[6] The key pharmacological property of typical antipsychotics is their ability to block dopamine-two (D2) receptors in the mesolimbic and mesocortical pathway.[6] They therefore improve these positive symptoms, but exacerbate the negative symptoms of schizophrenia. When D2 receptors are blocked in the nigrostriatal pathway, it can result in subsequent neuroleptic-induced parkinsonism, dystonia and akathisia.[6] When D2 receptors in the nigrostriatal pathway are chronically blocked, this may result in upregulation and increased sensitivity of receptors resulting in a hyperkinetic movement disorder called tardive dyskinesia - this condition is difficult to treat and often irreversible.[6]

1.1.2 **Atypical antipsychotics**

As described by Stahl, atypical antipsychotics are D2-receptor antagonists with rapid dissociation.[6] They treat the positive symptoms of schizophrenia by blocking D2 receptors in the mesolimbic pathway, while rapid dissociation results in a decreased risk of developing tardive dyskinesia.[6] Atypical antipsychotics are also serotonin-2A (5HT2A) receptor antagonists. This action increases dopamine release in the nigrostriatal pathway, thus decreasing the incidence of neuroleptic-induced side-effects. 5HT2A-antagonism also increases dopamine release in the mesocortical pathway, thereby treating the negative symptoms of schizophrenia.[6] Atypical antipsychotics have varying degrees of inherent anticholinergic activity, further decreasing the risk of developing neuroleptic-induced side-effects.[6]

1.1.3 **Anticholinergic agents**

Stahl describes dopamine and acetylcholine having a reciprocal relationship in the nigrostriatal pathway. Dopamine suppresses anticholinergic activity, however, when D2 receptor blockade occurs due to the administration of typical antipsychotics, acetylcholine becomes overly active.[6] Anticholinergic agents diminish excess acetylcholine activity caused by removal of dopamine when D2 receptors are blocked.[6] These agents mitigate the effects of dopamine blockade in the nigrostriatal pathway, and treat neuroleptic-induced parkinsonism, dystonia and akathisia, while also worsening the symptoms of tardive dyskinesia.[6]

According to Sadock, Sadock and Ruiz, the most common and well known anticholinergic agent is atropine, which is extracted from the *Atropa Belladonna* plant.[3] It has a large number of clinical indications, ranging from being an antidote to cholinesterase inhibitors to being used in premedication before general anaesthesia.[3] The two anticholinergic agents that are commonly used in psychiatry in South Africa

are, namely, biperiden and orphenadrine. Most anticholinergic agents are administered orally, reaching therapeutic levels in less than three hours.[3] It is widely distributed and crosses the blood brain barrier, with significant levels in the central nervous system achieved within 30 to 60 minutes.[3] Some anticholinergic agents are available as intramuscular and intravenous formulations, which have a more rapid onset of action. Anticholinergic agents are extensively metabolised, and are excreted in both the urine and bile.[3]

Sadock, Sadock and Ruiz described anticholinergic agents acting through blocking cholinergic receptors, namely nicotinic and muscarinic receptors.[3] Nicotinic receptors are located on striated muscle at the neuromuscular junction, the autonomic ganglia and in the central nervous system.[3] Muscarinic receptors are widely distributed and are found, among others, in the cardiac muscle, the gastrointestinal tract, the urogenital tract, the eye muscles and the salivary glands.[3] They are also located in the central nervous system where five distinct muscarinic receptor types have been identified - M1 and M4 receptors are found primarily in cortical areas, while M2 and M3 receptors are mostly found in the deeper structures of the central nervous system.[3] Anticholinergic agents are therefore commonly co-prescribed with antipsychotic agents for neuroleptic-induced side effects.[3] As atypical antipsychotic agents theoretically produce fewer neuroleptic-induced side-effects, one would deduce that there would be less anticholinergic co-prescribing with atypical antipsychotic agents. However, studies have shown that anticholinergic co-prescribing occurs with both typical and atypical antipsychotic agents.[7]

1.1.4 Side-effects of anticholinergic agents

Sadock, Sadock and Ruiz also discuss anticholinergic agents having side-effects of their own. These can be grouped into peripheral and central side effects.[3] In terms of peripheral side-effects, a variety of anticholinergic side effects can result because of the wide distribution of muscarinic receptors.[3] In the eye, for example, cycloplegia may occur, that is associated with loss of accommodation and blurred vision. Regarding the cardiovascular system, anticholinergic agents can cause a tachycardia via blocking the effect of parasympathetic fibres.[3] In toxic doses, intraventricular conduction block may occur. Anticholinergic agents decrease secretions through its effects on the secretory glands, that commonly presents as a dry mouth. These agents also affect the motility of the gastrointestinal tract through which constipation and even paralytic ileus can occur. They also cause relaxation of the ureter and the bladder wall, leading to urinary retention and urinary hesitancy.[3] These symptoms are often unpleasant and can make anticholinergic agent use intolerable to the patient which impacts on patient compliance to medication. Due to peripheral effects, anticholinergic agents can also precipitate or exacerbate pre-existing medical conditions, which make them contraindicated in a number of medical conditions such as glaucoma, benign prostate hypertrophy and a variety of cardiac conditions.[3, 8,9]

With regards to central side effects, nicotinic and muscarinic receptors are widely distributed in the central nervous system. Acetylcholine is therefore involved in a number of processes in the central nervous system, ranging from motor control and cognitive processing to learning, memory and arousal.[3,] The most common central side effects of anticholinergic agents to note, include delirium and cognitive impairment.[3, 10] Delirium is characterized by a global impairment of consciousness, resulting in a decreased level of arousal, attentiveness and environmental perception. Symptoms and signs of a delirium may vary, and may be related to the underlying

cause.[3] Anticholinergic agents and delirium have mostly been studied in the elderly.[10] Delirium in this population has been linked to an age-related deficit in central cholinergic transmission and deficient drug metabolism. The elderly also have an increased risk of chronic illnesses, thus polypharmacy is not uncommon.[9] The anticholinergic burden of the combination of drugs, rather than of an individual drug, can result in delirious states and is directly linked to the severity of delirium symptoms.[11] Anticholinergic burden in such patients has also been linked to increased mortality.[11]

In one study, anticholinergic agents were found in children and adolescents to have a dose-dependent negative effect on cognition – they impaired verbal learning of new material and declarative memory.[12] Patients with schizophrenia have cognitive impairments involving areas such as executive functioning, attention, processing speed, verbal learning, working memory and memory itself. Only an estimated 15% of patients with schizophrenia have no cognitive impairment.[9] Cognitive functioning has been proven to be a greater predictor of quality of life than both positive and negative symptoms.[9] In one study it was shown that in patients with schizophrenia, receiving anticholinergic medication was a predictor of significant memory impairment, especially with regards to semantic organisation and free recall efficiency.[13] Additionally, another study found that anticholinergic agents impaired both immediate and working memory in patients with schizophrenia, and that their use was associated with decreased global cerebral blood flow. When anticholinergic agents were withdrawn in the study patients, there was an improvement in both immediate and working memory, as well as increased cerebral blood flow.[14]

These findings raised the question as to whether all cognitive impairment due to anticholinergic agents are reversible in schizophrenia on withdrawal of these agents.

Data appears to be scarce. One study reported improved attention and concentration, however impaired long term memory, learning of new information and delayed verbal recall remained.[13] Further studies are required in this aspect with regards to schizophrenia in particular.

Cognitive impairment related to anticholinergic agents has also been studied in the elderly and has been proven in a wide range of clinical settings. Similarly to delirium, the elderly are more vulnerable to cognitive impairment due to their inherent cholinergic physiology, delayed drug metabolism and that they often have a high anticholinergic burden due to polypharmacy.[10] It was shown in a large study that the use of drugs with anticholinergic activity increased the cumulative risk of cognitive impairment and mortality in the elderly.[15]

The abuse potential of anticholinergic agents has also been a topic of interest since the 1980's and has generated wide spread discussion. It is known that in schizophrenia, patients often seek stimulating experiences, most commonly through excessive smoking or excessive caffeine intake.[16] This is related to the negative symptoms of schizophrenia, with patients trying to find transient relief from these symptoms.[16] Such negative symptoms may also be exacerbated through the use of typical antipsychotics. In patients already on antipsychotic agents, parenteral administration of anticholinergic agents can result in euphoric states with abolition of negative symptoms [16] This could result in abuse of these agents in patients already on antipsychotic agents. The abuse potential of anticholinergic agents in patients not on antipsychotic agents, however, is low. In psychiatric practice, a high index of suspicion is required in patients possibly over reporting symptoms of neuroleptic-induced side-effects, without these symptoms being objectively verified.

It is known that patients with first-episode psychosis are more likely to present with extrapyramidal side effects to antipsychotic agents than multi-episode patients. This has raised the question about prophylactic anticholinergic agent use in this population, as such side effects, especially acute dystonia, can influence future adherence to treatment. This would be beneficial, especially with depot antipsychotic preparation use to further promote adherence. However no studies to date have shown evidence for anticholinergic prophylaxis in first-episode schizophrenia. There are significant concerns about their cognitive side-effects in addition to central and peripheral side-effects therefore this practice should be avoided.[9]

1.1.5 **Guidelines for the use of anticholinergic agents**

According to Taylor et al., anticholinergic agents should be administrated intra-muscularly or intravenously in neuroleptic-induced dystonia (Appendix A).[5] A short course of oral anticholinergics should be commenced while the antipsychotic dose is reduced, or while the antipsychotic is switched to another agent.[5] Guidelines are similar in neuroleptic-induced parkinsonism, except that intramuscular or intravenous use of anticholinergic agents may not be necessary.[5] Broekema et al., noted that the risks versus benefits of anticholinergic use should always be assessed.[7]

Because anticholinergic agents are associated with adverse effects, as well as having abuse potential in those patients treated with antipsychotic agents, it can be deduced that these agents should be withdrawn and stopped if and when possible. In psychiatric practice, one would be concerned that neuroleptic-induced side effects may recur if anticholinergic agents are withdrawn. Emphasis has been placed on anticholinergic use, possibly ensuring better adherence on antipsychotic treatment, mainly due to their ability to reduce unwanted side effects.[15] In contrast, unwanted anticholinergic side effects may also influence adherence to both antipsychotic and

anticholinergic agents.[7] Studies looking at successful withdrawal of anticholinergic agents without recurrence of side-effects have been very inconsistent, but methodological difficulties have also been described in some of the studies which resulted in negative findings. One study had a 86% rate of successful withdrawal of anticholinergic agents.[17] Successful withdrawal was also achieved in those studies which gradually withdrew the anticholinergic agent, in contrast to those with abrupt cessation.[5]

The Maudsley Prescribing Guidelines indicate that anticholinergic agents may be used in the treatment of neuroleptic-induced dystonia and neuroleptic-induced parkinsonism. They suggest that after treatment has been initiated with an anticholinergic agent, and neuroleptic-induced side-effects have stabilized, anticholinergic use should be reviewed at least once every three months.[5] It is accepted that the majority of patients do not require long-term anticholinergic treatment. According to these guidelines, anticholinergic agents should also not be prescribed at night as symptoms are usually absent during sleep.[5]

1.1.6 **Typical versus atypical antipsychotics**

Since the introduction of atypical antipsychotic agents, their use has steadily increased due to the theoretical assumption that they produce less neuroleptic-induced side effects than typical antipsychotic agents. The atypical antipsychotic agents, however, carry a much greater metabolic risk profile.[5] This has led to numerous studies that examined whether the one is really superior to the other. For example, the "Cost Utility of the Latest Antipsychotics in Schizophrenia Study Band 1" (CutLass-1) study was a randomized control trial that looked at the clinical and cost-effectiveness of atypical antipsychotics, and whether it would be superior in patients whose treatment with typical antipsychotics was changed, either due to inadequate response or side-effects.

The typical antipsychotics were associated with lower cost and showed a trend towards better outcomes. The investigators made a conservative conclusion that the two classes of drugs were equivocal with the exception of clozapine.[18]

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was a larger, double-blind multisite study in patients with chronic Schizophrenia.[19] The primary outcome was discontinuation of the antipsychotic agent or switching to another antipsychotic agent. Their finding was that atypical antipsychotic agents, with the exception of clozapine, were not significantly superior to typical antipsychotics.[19] CUtLASS shared this finding. A meta-analysis, by Leucht et al., of three other large meta-analyses looking at typical versus atypical antipsychotic agents also showed similar results to both CUtLASS and CATIE.[20] They compared atypical antipsychotics with placebo, with typical antipsychotics and with atypical antipsychotics head-to-head. It showed that atypical antipsychotics are not a homogenous group and suggested that the current classification system should be abandoned. Each has different properties so treatment plans must be individualised.[20] An editorial, by Lewis and Lieberman, suggested that typical antipsychotic agents that are carefully prescribed are as good as atypical antipsychotics in most patients with established schizophrenia.[21] Careful prescribing refers to lower dosage ranges and avoiding high potency drugs. When switching between antipsychotics, one should look at the reason for switching and should keep this in mind when deciding upon a second agent, while a consistent finding was that clozapine remains the most superior antipsychotic agent.[21]

When examining the co-prescribing patterns of anticholinergic and antipsychotic agents, a few studies have been done. In the United Kingdom, it was found that anticholinergic agents were commonly co-prescribed with long-acting injectable

antipsychotics (both typical and atypical). Use of anticholinergic agents increased when these were combined with oral antipsychotic agents.[22] The CATIE trial also assessed concomitant antipsychotic and anticholinergic agent use in patients with schizophrenia: those patients prescribed both a typical and atypical antipsychotic were more likely to be on an anticholinergic agent, followed by typical antipsychotic agents alone, then atypical antipsychotic agents alone. Those patients prescribed an anticholinergic agent also had poorer neurocognitive functioning.[23] A large multi-centre European study that looked at the co-prescribing of antipsychotic and anticholinergic agents found similar results.[6]

A Chinese study, looking particularly at the use of anticholinergic agents in in-patients with schizophrenia, found that nearly half of clinically stable patients in their trial were prescribed an anticholinergic agent with no clear indication for its use. In their out-patient populations, atypical antipsychotics were frequently co-prescribed with anticholinergic agents. They also emphasised that treatment guidelines were not correctly followed, and that anticholinergic agents should gradually be withdrawn where possible.[24] Another large Asian study similarly found that more than half of their stable patients with schizophrenia were on anticholinergic agents, and their use was not reviewed.[25] A study of out-patients in Bahrain found that atypical antipsychotic monotherapy was preferred in up to 70% of patients, yet 57,3% of all patients were also prescribed an anticholinergic agent. They also noted that there was more anticholinergic co-prescribing when more than one antipsychotic was prescribed. They suggested evidence-based prescribing practice.[26]

From the above, it can be noted that in clinical practice, anticholinergic agents use is often overlooked, and prescriptions are renewed without making appropriate dose adjustments. The use of long-term anticholinergic agents has been linked to

deleterious effects. Guidelines suggest that their use should be reviewed every three months as long-term use is not indicated in the majority of patients. It is therefore an important aspect of patient care to investigate, and to address if guidelines are not followed.

1.2 Study purpose and objectives

The purpose of this study was to review the current practice of anticholinergic agent use in conjunction with antipsychotic agents at Helen Joseph Hospital Psychiatric Outpatient Department (HJH POPD).

The objectives for this study were:

(1) To describe the demographic and clinical profile of all patients on antipsychotic agents;

(2) To compare the characteristics of patients treated on typical and atypical antipsychotic agents (including risperidone, haloperidol and depot preparations);

(3) To compare the use of anticholinergic agents in conjunction with antipsychotics at HJH POPD with set guidelines on the use of anticholinergic agents, e.g. the Maudsley Prescribing Guidelines.[16]

1.3 Hypothesis

The hypothesis for this study was that the concurrent use of anticholinergic and antipsychotic agents at HJH POPD was not managed adequately according to set guidelines.

CHAPTER 2 METHODS

2.1 Study design

The study design was a cross-sectional retrospective clinical record review of patients at Helen Joseph Hospital's psychiatric outpatient department (HJH POPD) who were treated with an anticholinergic agent in conjunction with an antipsychotic agent.

2.2 Study population

HJH is a tertiary level hospital situated in Auckland Park, Johannesburg. It offers psychiatric casualty services, consultant liaison and has an acute general psychiatric inpatient unit consisting of 30 beds. As patients are seen in an acute setting, anticholinergic agent use is often necessitated as neuroleptic-induced side-effects may occur in those patients receiving antipsychotic agents. Anticholinergic agents may even be started prophylactically in combination with certain antipsychotics. HJH POPD is where psychiatric patients known to the unit are followed up and where new patients are assessed and managed.

The HJH POPD was regarded as a suitable site, as patients who were commenced on anticholinergic agents in conjunction with antipsychotics agents, either in the POPD itself or during an earlier admission to the HJH acute inpatient unit, are followed up at the clinic and could be identified. The study population consisted of all psychiatric patients on an antipsychotic agent seen at HJH POPD over a one year period, e.g. from 1 January to 31 December 2011. As all patients on an antipsychotic during the study period were screened for co-prescribed anticholinergic agents, this represented a 100% sample of patients seen at HJH POPD.

2.3 Data collection

Patients on antipsychotic treatment were identified using the existing electronic database of all patients seen at HJH POPD. These patients' clinical records, including their discharge summaries, were retrieved. The patients were divided into two groups: the first six-month visit (January to June 2011) and the second six-month visit (July to December 2011). Data was collected according to a data sheet for patients (Appendix B) which included demographic and clinical variables, namely: gender; age; demographic area; diagnosis; co-morbid substance abuse; current antipsychotic treatment (typical or atypical); antipsychotic name; antipsychotic related side-effects (an indication for anticholinergic agent treatment); anticholinergic treatment and anticholinergic agent related side-effects.

The purpose of collecting data for the first six-month visit was for comparison of anticholinergic agent use with the second six-month period, particularly regarding dosing. This allowed for investigation of whether dose reductions, which should have occurred at the second six-month visit according to guidelines, had occurred or not.

Although anticholinergic agent dose reductions should occur at three monthly intervals, six month periods were selected to include those patients given six month follow up dates.

2.4 Data analysis

Data from the data collection form was translated into an Excel spreadsheet. Data analysis was carried out using SAS. Reference: SAS Institute Inc., *SAS Software, version 9.3 for Windows,* Cary, NC, USA: SAS Institute Inc. (2002-2010)

The X^2 test was used to assess the relationships between categorical variables. Fisher's exact test was used for 2 x 2 tables or where the requirements for the X^2 test could not be met. The strength of the associations was measured by Cramer's V and the phi coefficient respectively. For Cramer's V and the phi coefficient, the following scale of interpretation was used: - 0.50 and above: high/strong association; - 0.30 to 0.49: moderate association; - 0.10 to 0.29: weak association; - below 0.10: little if any association. The 5% significance level was used throughout - p-values <0.05 indicated significant results.

2.5 Ethics

This study was approved by the University of the Witwatersrand's Human Research Ethics Committee (HREC) - Appendix C (Ethics Clearance Certificate). Due to the retrospective nature of the study, individual informed consent was not required. The names and personal identifying details of the patients in the study remained anonymous and was not recorded on the data sheets. Written permission from the HJH Head of Department of Psychiatry and the Chief Executive Officer (CEO) at Helen Joseph Hospital was obtained to conduct the research.

CHAPTER 3 RESULTS

A total of 331 patients receiving antipsychotic treatment were identified during the second six-month study period at HJH POPD from 1 July to 31 December 2011. Of these patients, 40 in the first six-month period and 44 in the second six-month period were treated with an anticholinergic agent. The attributes of these patients were first described in terms of: demographic variables (including gender age and geographical area); and clinical and treatment variables (including diagnosis, current antipsychotic agent prescribed, and anticholinergic agent prescribed. There was, however, no information documented for antipsychotic related side effects, as well as anticholinergic agent side effects.

Antipsychotic type refers to typical and atypical classes as well as combination treatment with two or more antipsychotic agents. Anticholinergic agent refers to either orphenadrine or biperiden. Antipsychotic treatment refers to the generic name of the drug.

3.1 Descriptive analysis

3.1.1 Demographic variables

(1) Gender

The study sample (n=331) consisted of 43% (n=142) males and 57% (n=178) females. No records with regards to gender were available for 11 patients.

(2) Age

The mean age for the group (n=229) was 45.9 years (SD=16.0 years), the median age was 45 years (interquantile range 32 to 58 years), with a range in age of 16 to 93 years. For further analysis, age range was categorised into the following groups: 16 to 29 years; 30 to 39 years; 40 to 49 years; 50 to 59 years; and older than 60 years (Figure 3.1). The ages were not recorded for two patients.

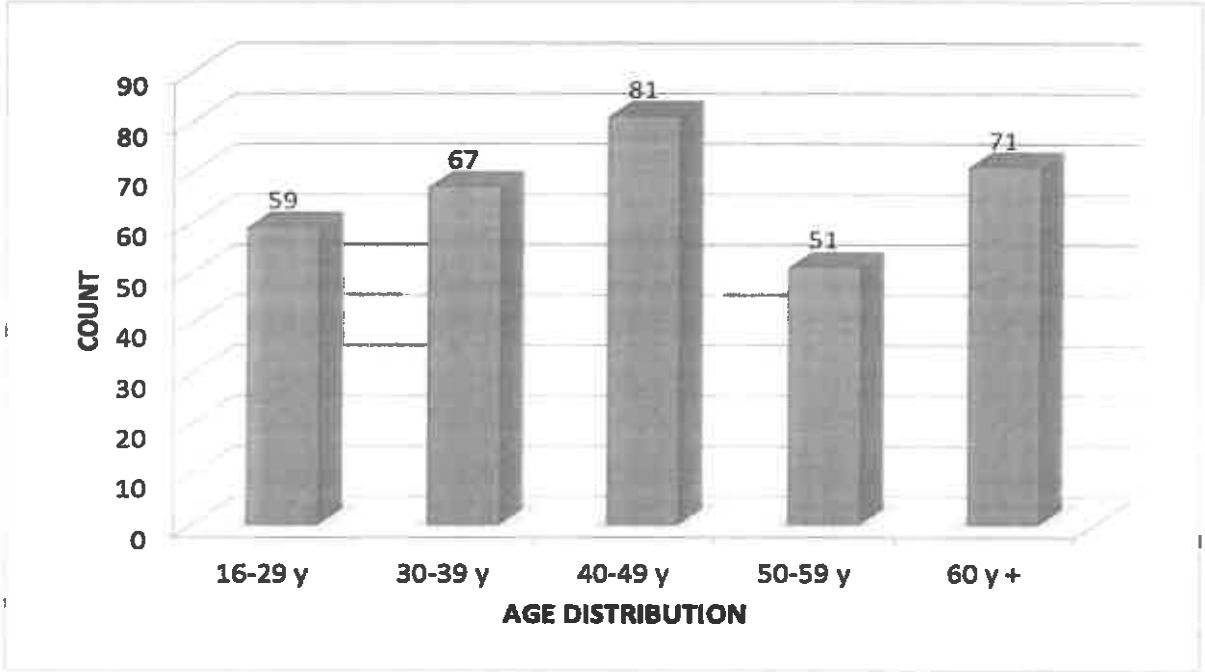


Figure 3.1: Age distribution of patients treated with antipsychotic agents at HJH POPD from July to December 2011, n=229

(3) Geographical area

HJH is situated in the Johannesburg Metro District Area, but serves patients from various regions across the city (Figure 3.2). The majority of patients in the study groups came from the Johannesburg Metro District Area (64%; n=213) area, while other patients (15%; n=51) were from the West Rand. The remainder (5%; n= 17) of the patients, originated from: Ekurhuleni District (3,3%; n=11), Midrand (0,3%; n=1),

Sedibeng (0,6%; n=2), North West Province (0,3%; n=1) and from other countries (0,6%; n=2). Data on patient's geographical area was not available for 50 patients.

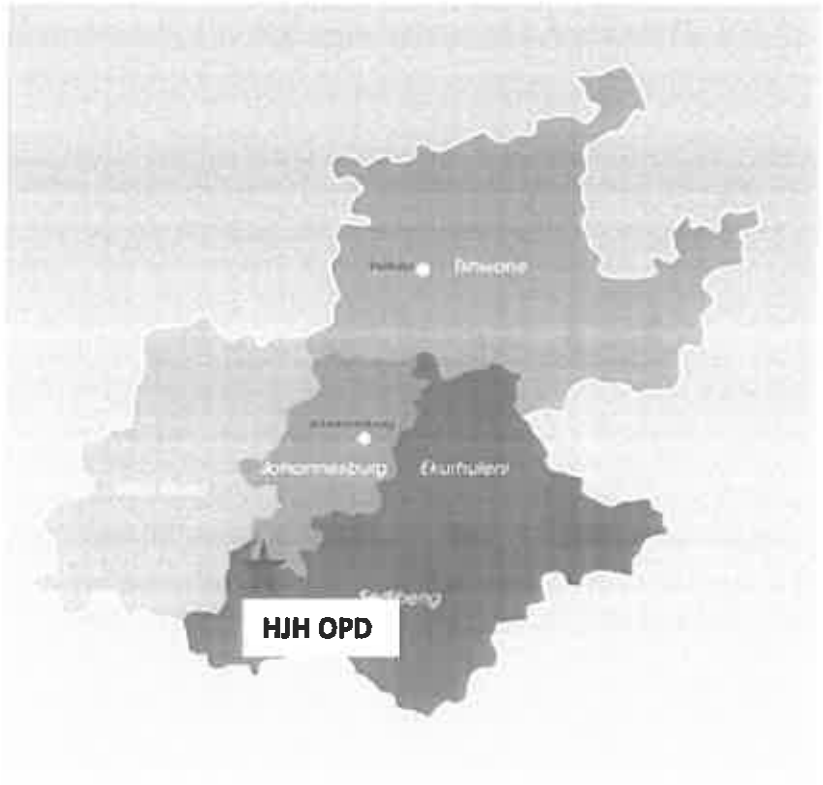


Figure 3.2: Map of health district regions in Gauteng Province

3.1.2 Clinical and treatment variables

Variables assessed included documented diagnosis, current antipsychotic treatment prescribed, and anticholinergic agent prescribed both in the first and second six-month periods.

(1) **Psychiatric Diagnosis**

The psychiatric diagnoses of the patients are shown in Figure 3.3. Percentages, however, do not consistently add up to 100% in this summary as more than one diagnosis was frequently documented. Diagnoses included Behavioural Related

Disorders (n=123; 37,2%),[1] Psychotic Disorders (n=99; 29,9%), Mood Disorders (n=83; 25,1%), Disorders due to a General Medical Condition (GMC) (n=58; 17,5%), Substance Related Disorders (n=36; 10,9%) and Other Disorders (19; 5,7%).

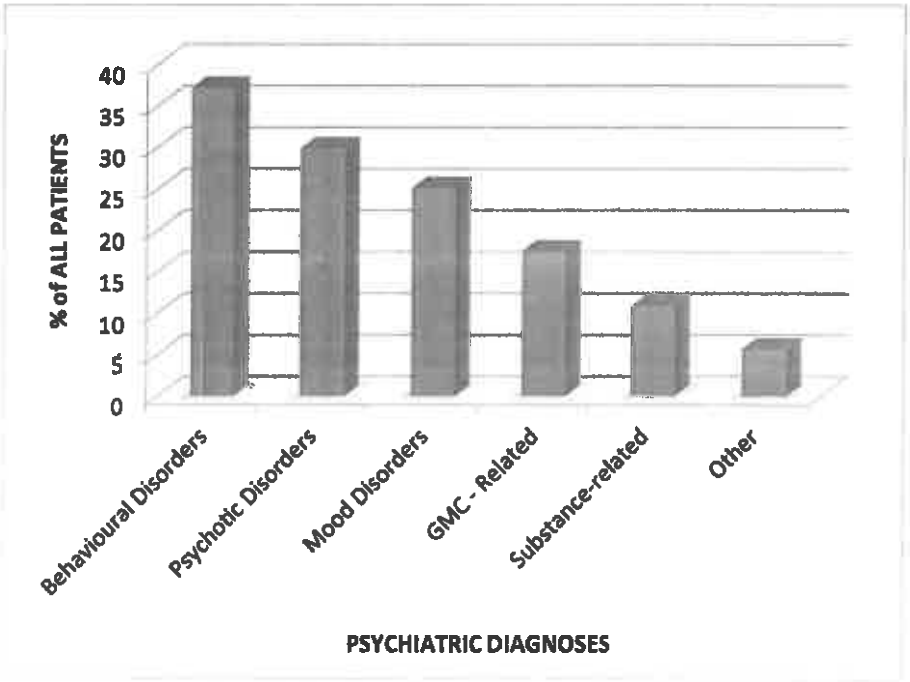
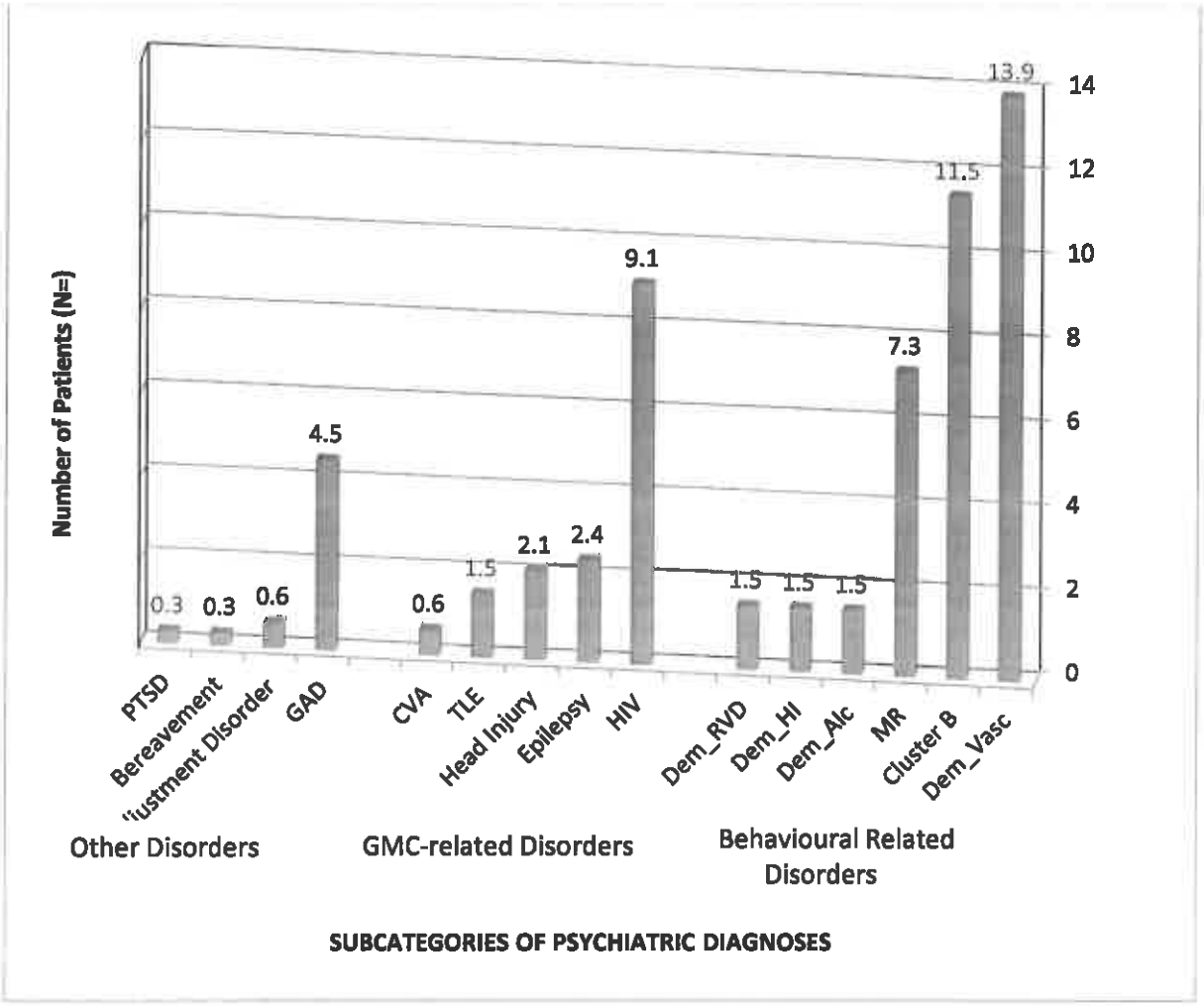


Figure 3.3: Psychiatric diagnoses of patients treated with antipsychotic agents at HJH POPD from July to December 2011

Diagnoses included in the subcategories of "Behavioural related Disorders", "General Medical Condition (GMC) related Disorders" and "Other Disorders" are shown in Figure 3.4.

[1] Behavioural related disorders included developmental related disorders (e.g. mental retardation/intellectual impairment and personality disorders) and dementia



Other Disorders: PTSD – Post Traumatic Stress Disorder; GAD – Generalized Anxiety Disorder
GMC - General medical condition) related Disorders: CVA – Cerebrovascular Accident; TLE – Temporal Lobe Epilepsy; HIV – Human Immunodeficiency Virus
Behavioral related DIsorders: Dem_RVD – Dementia due to Retroviral Disease, RVD – Retroviral Disease; Dem_HI – Dementia due to head injury; Dem_Alc – Alcohol induced Dementia, MR – Mental Retardation,[2] Cluster B – Personality Disorder; Dem_Vasc – Vascular Dementia

Figure 3.4: Subcategories of psychiatric diagnoses of patients treated with antipsychotic agent at HJH POPD from July to December 2011

[2] Mental Retardation, a DSM-IVR diagnostic term, was changed to Intellectual Impairment in DSM-5 (2013)

(2) Antipsychotic agents prescribed

For a total of 84% of patients (n=279) an atypical antipsychotic agent was prescribed during the second six-month period, followed by 13% of patients (n=43) for whom a typical antipsychotic agent was prescribed. For 2.7% of patients (n=9), a combination of both a typical and atypical antipsychotic agent were prescribed. Atypical antipsychotics prescribed included oral risperidone, long acting depot risperidone, quetiapine, olanzapine and clozapine. Typical antipsychotics included haloperidol, flupenthixol decanoate, zuclopenthixol decanoate and chlorpromazine. The different antipsychotic agents prescribed are described below (Figure 3.5). Oral risperidone was used in treating the majority of the patients (n=204, 62%).

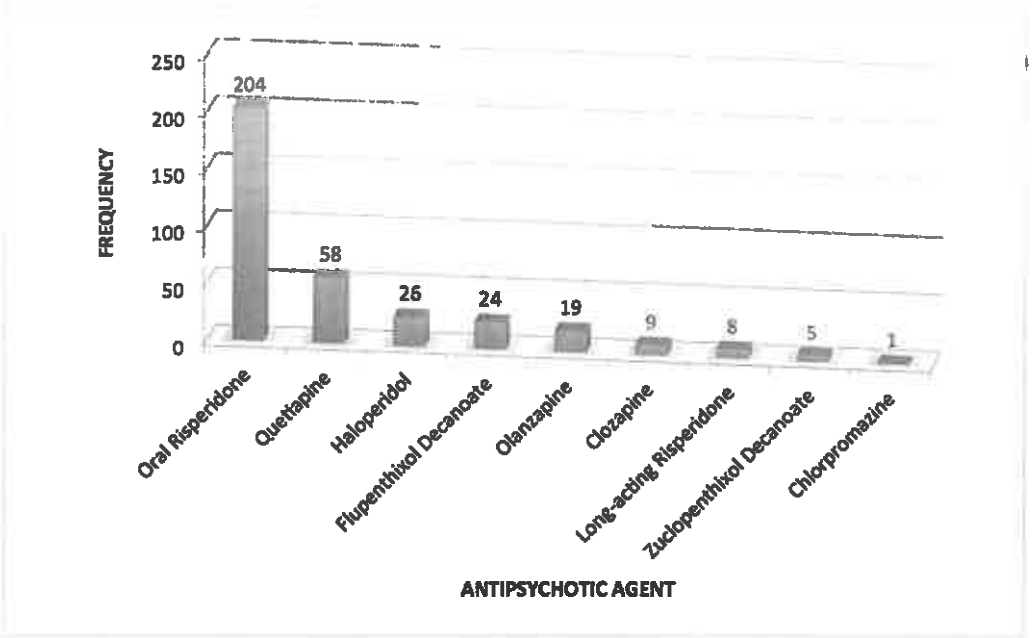


Figure 3.5: Frequency of antipsychotic agents used to treat patients at HJH POPD from July to December 2011

(3) Concurrent anticholinergic agent prescribed

During the first six-month period, anticholinergic agents were concurrently prescribed with antipsychotic agents in 12.1% of patients (n=40). All patients were prescribed only one anticholinergic agent with the majority of patients prescribed orphenadrine

(n=31). Similarly, during the second six-month period, anticholinergic agents were prescribed in 13.3% of patients (n=44). All patients were prescribed one anticholinergic agent with the majority of patients prescribed orphenadrine (n=33).

3.2 Comparative analysis

A comparative analysis of different variables were done by: (1) type of antipsychotic agent; (2) anticholinergic agent at both first and second six-month period; (3) anticholinergic agent use compared to guidelines; as well as (4) looking at the association between antipsychotic agent and anticholinergic agent co-prescribing.

3.2.1 Analysis by type of antipsychotic agent

In terms of the comparison between the type of antipsychotic agent used in the second six-month visit:

- There was no significant associations found between:
    - antipsychotic agent type and gender (p=0.16) , or age category (p=0.51) – See Figures 3.6 and 3.7

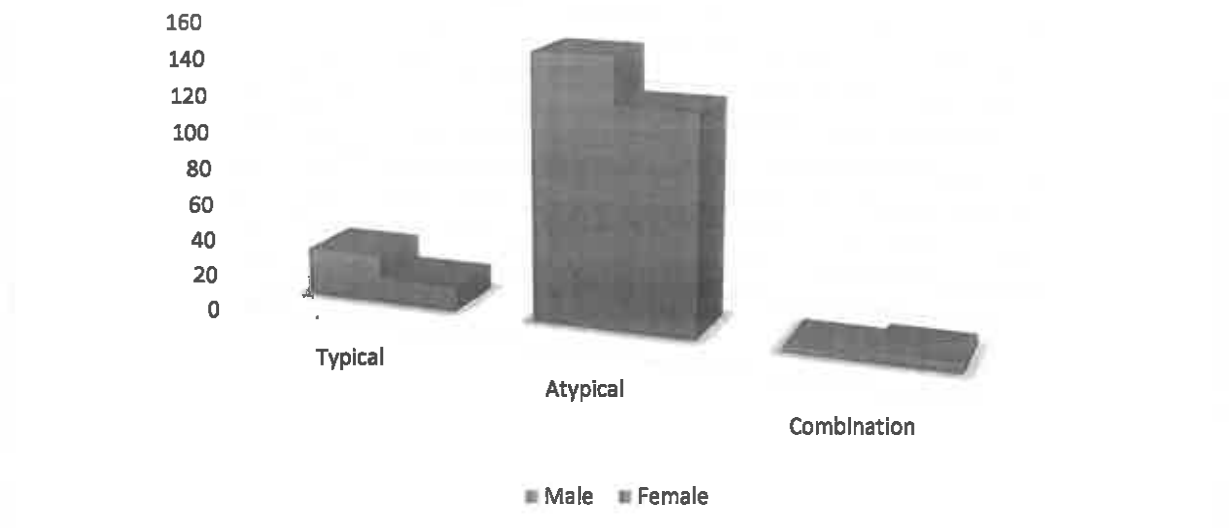


Fig 3.6: Antipsychotic type and gender in patients treated with antipsychotic agents at HJH POPD from July to December 2011, n=320

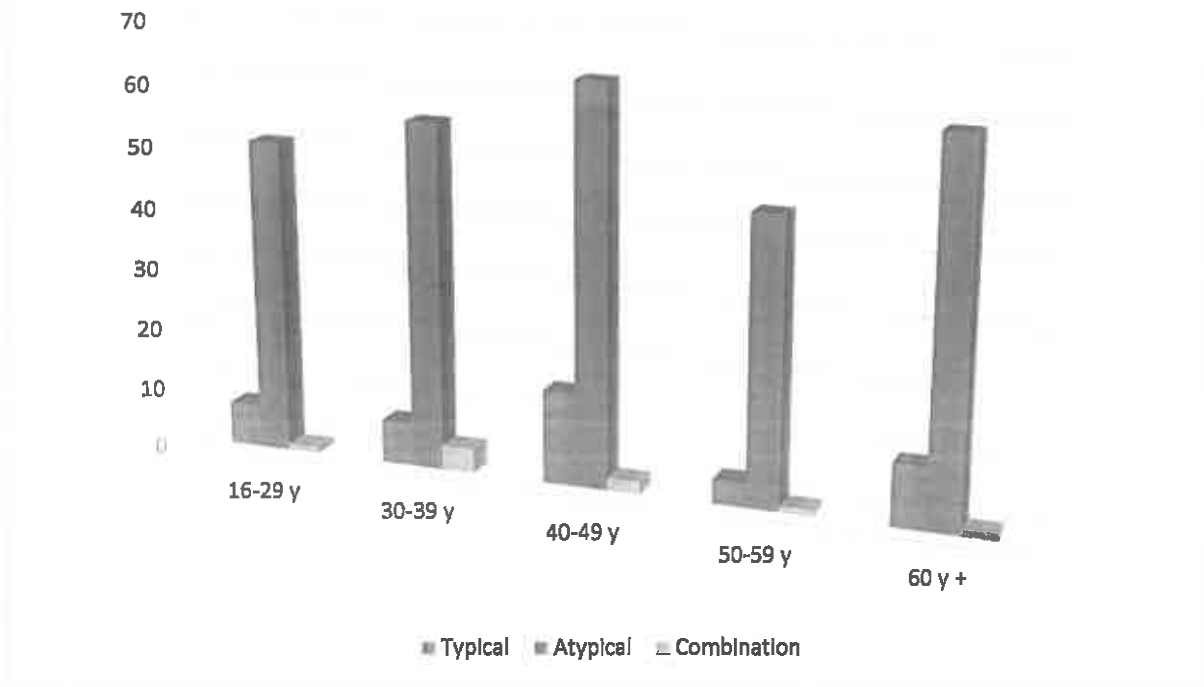


Fig 3.7: Antipsychotic type and age in patients treated with antipsychotic agents at HJH POPD from July to December 2011, n=329

- antipsychotic agent type and any of the diagnostic disorders (Table 3.1)

Table 3.1: Antipsychotic agent type and diagnoses in patients treated with antipsychotic agents at HJH POPD from July to December 2011

DISORDER	TYPICAL	ATYPICAL	COMBINATION
Mood	13	69	1
Psychotic	15	79	5
Behavioural	19	102	2
GMC	5	51	2
Substance-related	4	30	2
Other	2	17	0

- Considering only those patients prescribed an anticholinergic agent, there was no association between:
  - antipsychotic type and the anticholinergic agent prescribed at either the first six-month visit (p=0.32), or the second six-month visit (p=0.53) – See Table 3.2

Table 3.2: The association between antipsychotic type and anticholinergic agent prescribed at the first and second six-month visit at HJH POPD, n=44

Period	AC Agent	Typical	Atypical	Combination
First 6-month visit	Orphenadrine	11	18	2
	Biperiden	1	7	1
Second 6-month visit	Orphenadrine	11	20	2
	Biperiden	2	8	1

AC – Anticholinergic agent

- antipsychotic agent type and anticholinergic agent dose for either anticholinergic agent at either visit

- There was a weak significant association found between:
  - antipsychotic type and anticholinergic agent use at the first six-month visit ($p<0.0001$; Cramer's $V=0.22$), as well as
  - anticholinergic agent use at the second six-month visit ($p<0.0001$; Cramer's $V=0.21$)

As shown in figure 3.8, the proportion of patients co-prescribed an anticholinergic agent, was lower for those on atypical antipsychotic regimes than for the typical antipsychotic and combination antipsychotic regimes.

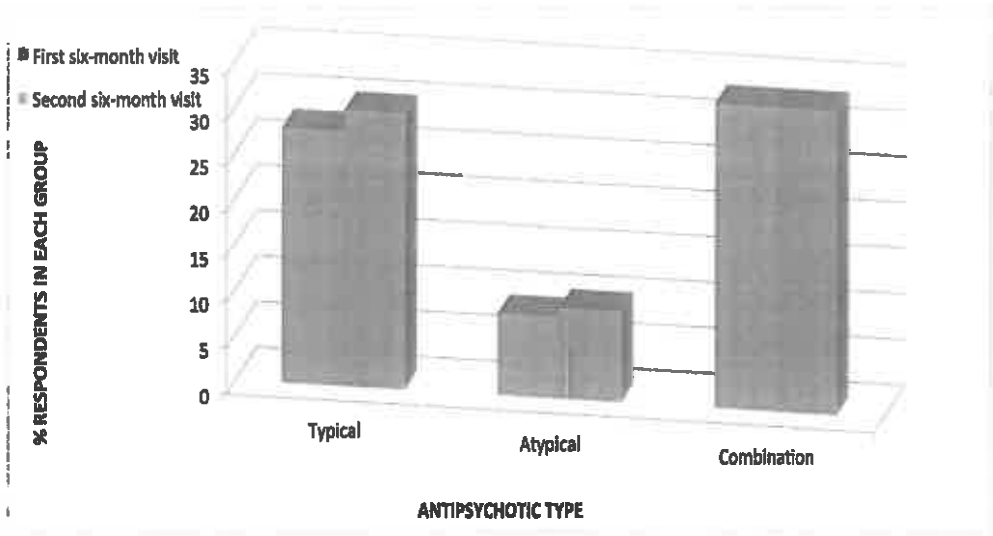


Figure 3.8: Antipsychotic type and anticholinergic agent use at HJH POPD from January to December 2011

3.2.2 Analysis by anticholinergic agent use at first six-month visit

- There was no significant association between anticholinergic agent use and gender (p=0.39) or age category (p=0.84).

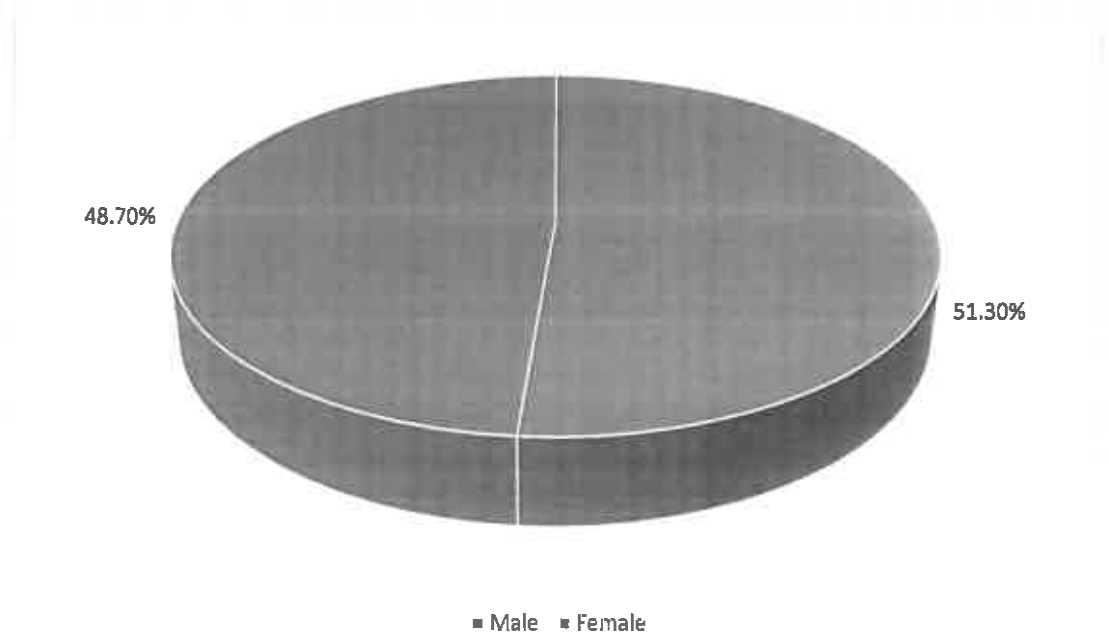


Fig 3.9: Anticholinergic agent use and gender from January to June 2011 at HJH POPD, n= 39

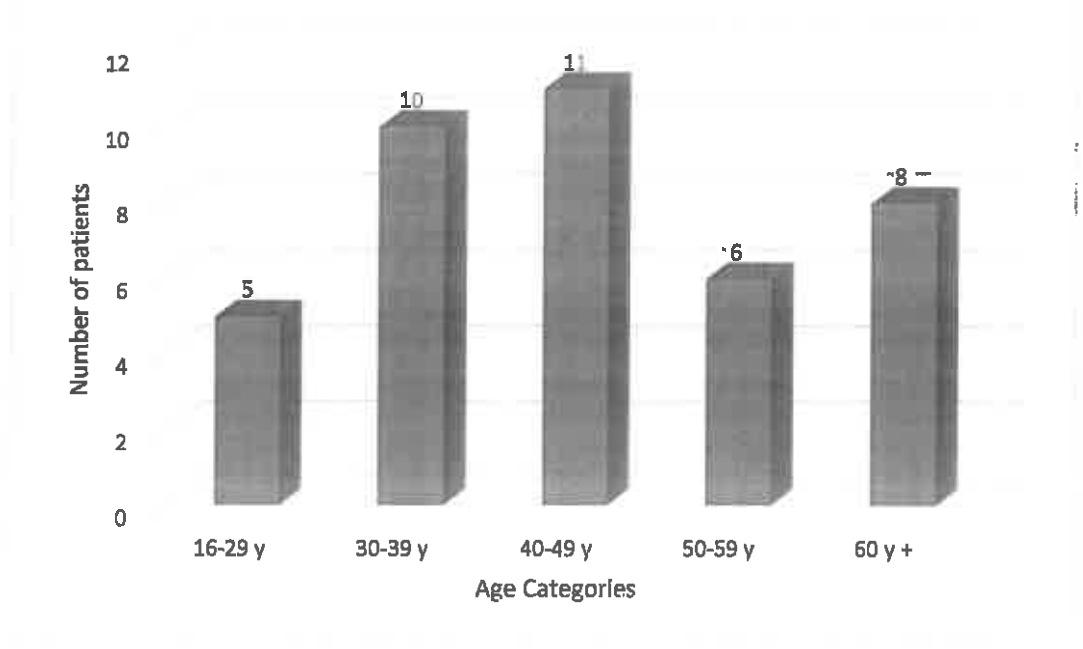
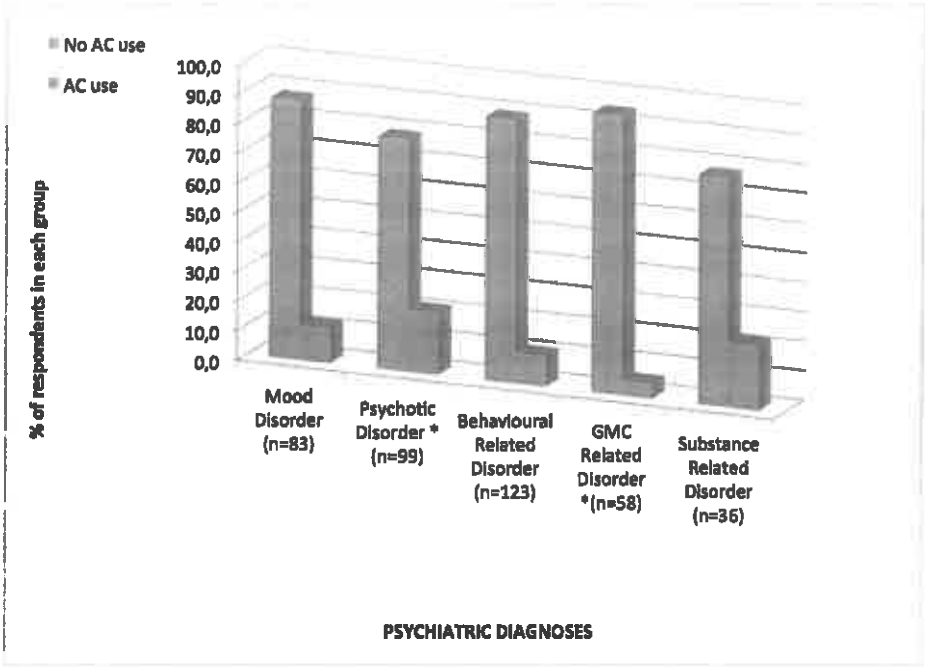


Fig 3.10: Anticholinergic agent use and age distribution from January to June 2011 at HJH POPD, n= 40

- There were weak significant associations between anticholinergic use and the following disorders:
  - psychotic disorders (p=0.016, Phi coefficient=0.14)
  - GMC-related disorders (p=0.026, Phi coefficient=0.12

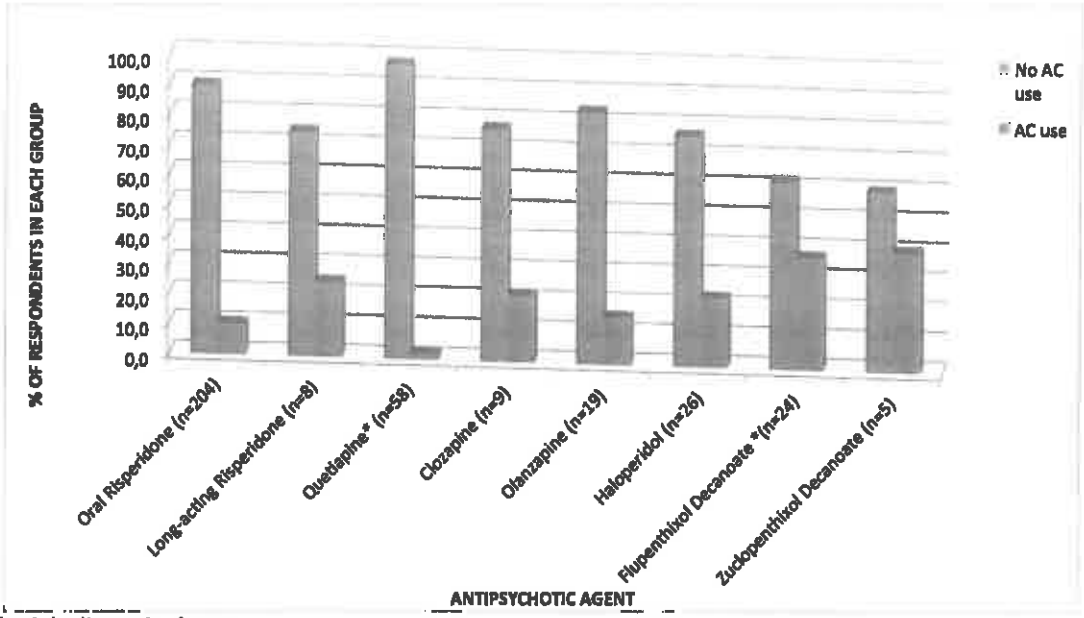
The graph below shows that patients with a diagnosis of a psychotic disorder had a higher proportion of anticholinergic use, compared to a patient with a GMC-related disorder had a lower proportion of anticholinergic use (Figure 3.11).



AC- Anticholinergic Agent, GMC – Disorders due to a General Medical Condition
* - weak significant associations between disorder and AC use

Figure 3.11: Anticholinergic agent prescribing and diagnoses from January to June 2011 at HJH POPD

- There were also weak significant associations between anticholinergic agent use and the following antipsychotic agents:
  - quetiapine and lower use (p=0.0063, Phi coefficient=0.15)
  - flupenthixol decanoate and higher use (p<0.0001, Phi coefficient=0.22). (Figure 3.8)

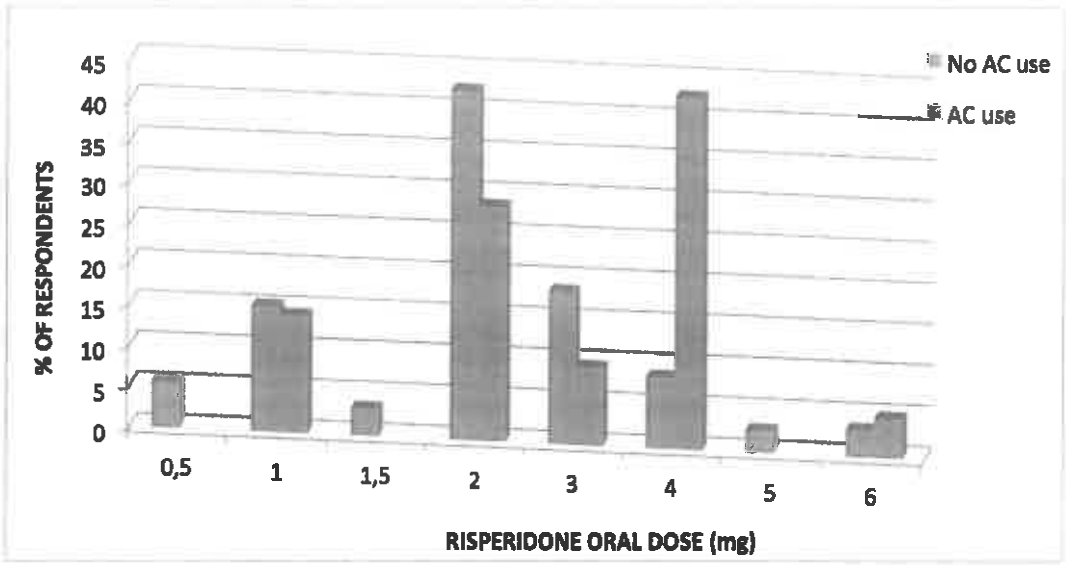


AC- Anticholinergic Agent

*-indicates weak significant associations between antipsychotic and AC use

Figure 3.12: Anticholinergic agent use associated with antipsychotic agents prescribed to patients from January to June 2011 at HJH POPD

- There was a moderate significant association between anticholinergic use and risperidone oral dose (p=0.16, Phi coefficient=0.33). Although the trend was not very clear, it appears that anticholinergic agent use was associated with higher doses of this (atypical) antipsychotic agent compared to non-use of anticholinergic agents (Figure 3.13).



AC- Anticholinergic Agent

Figure 3.13: Risperidone oral dosages and anticholinergic agent use at HJH POPD from July to December 2011

- There were no other significant associations between anticholinergic agent use and any of the antipsychotic agent dose levels.

3.2.3 Analysis by anticholinergic agent use at second six-month visit

- There was no significant association between anticholinergic agent use and gender (p=0.62) or age category (p=0.75) at the second six-monthly visit. See Figures 3.14 and 3.15

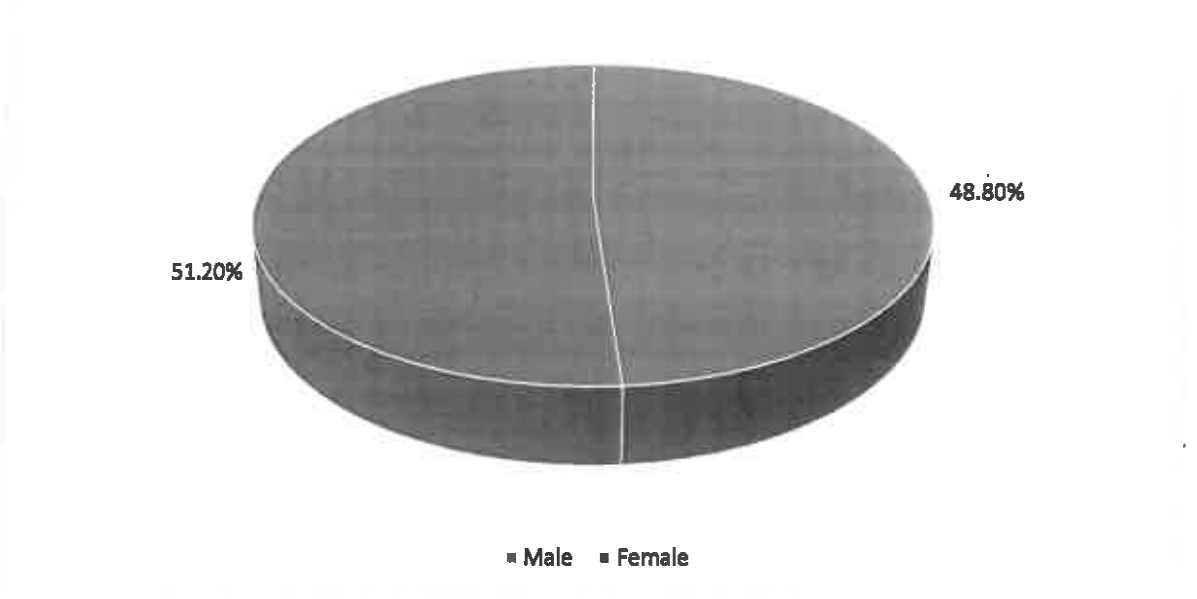


Figure 3.14: Anticholinergic agent use according to gender from July to December 2011 at HJH POPD, n=43

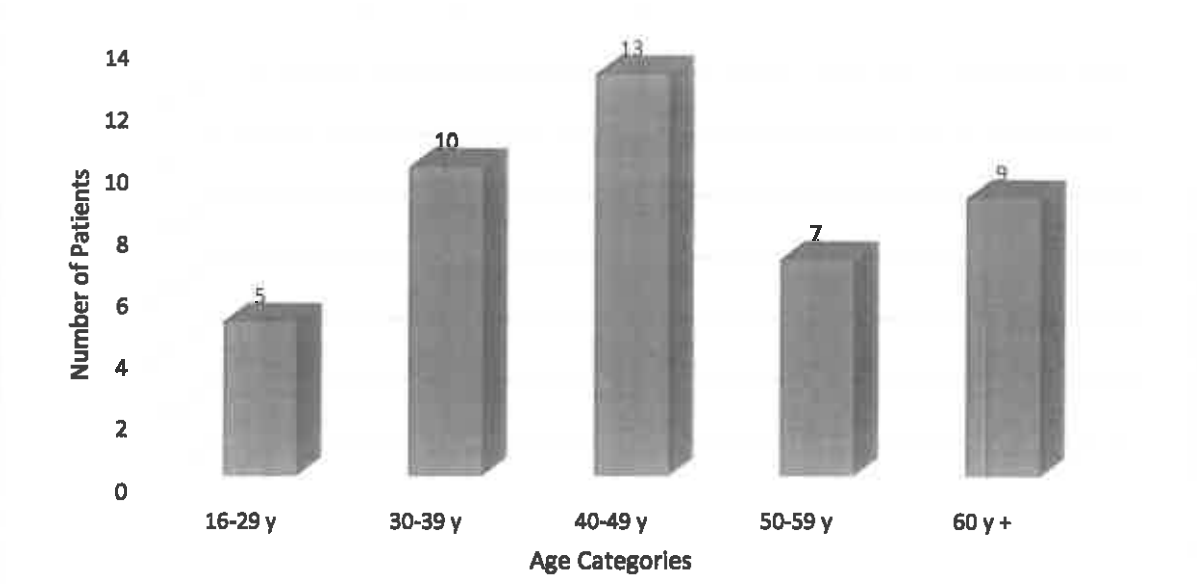
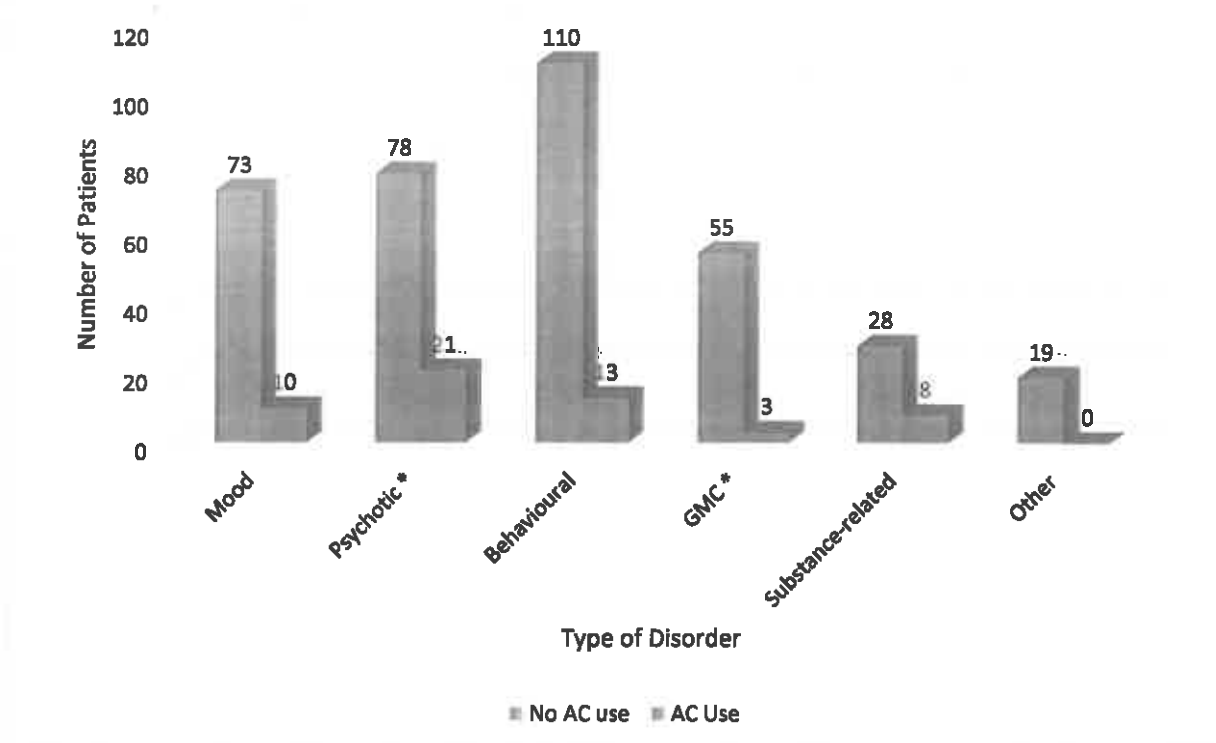


Figure 3.15: Anticholinergic agent use and age categories from July to December 2011 at HJH POPD, n=44

- There were weak significant associations between anticholinergic agent use and the following disorders:
  - psychotic (p=0.0078, Phi coefficient=0.15)
  - GMC-related (p=0.054, Phi coefficient=0.11) (marginally significant only: p is just above 0.05)
  - Similarly to the first six-month visit, patients that had a diagnosis of a psychotic disorder had a higher proportion of anticholinergic agent use, while patients with a GMC-related disorder had a lower proportion of anticholinergic agent use.



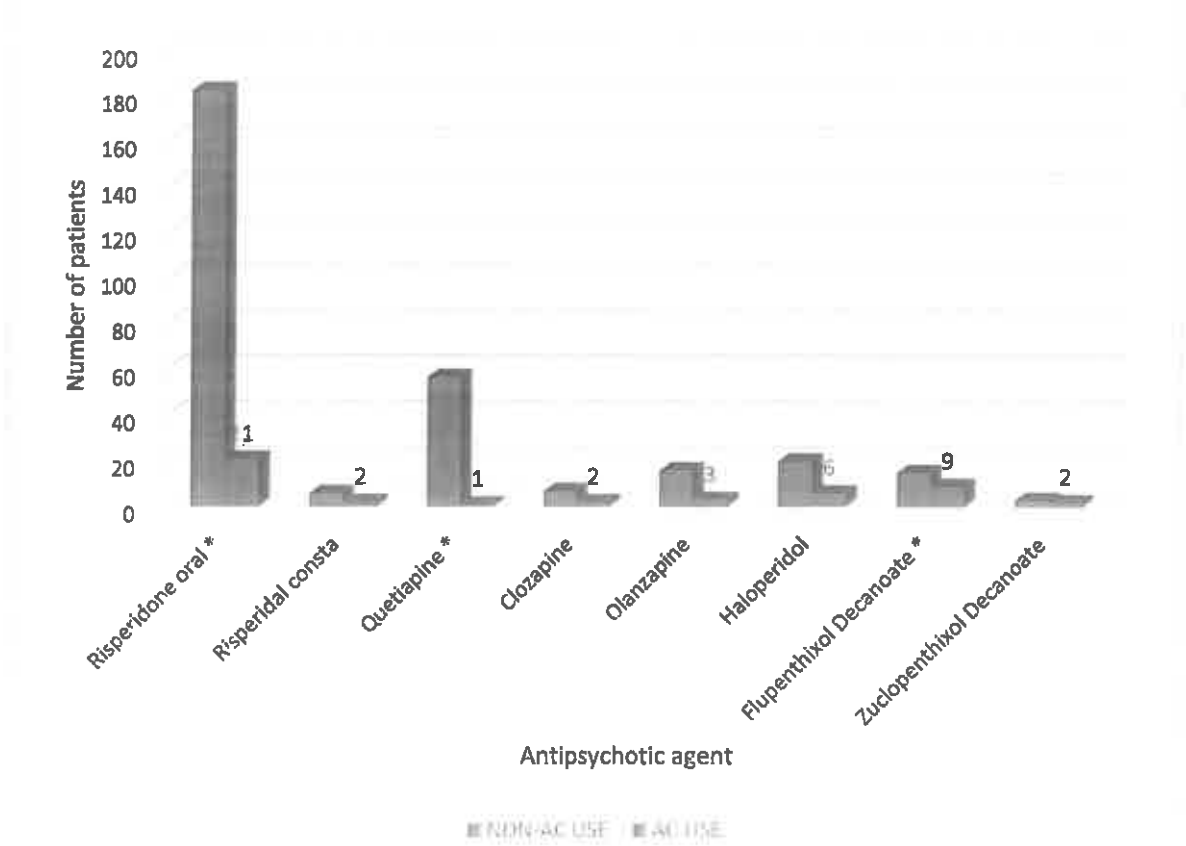
AC – Anticholinergic agent, GMC – General Medical Condition

* - weak significant associations between disorder and AC use

Fig 3.16: Anticholinergic agent use and type of disorder from July to December 2011 at HJH POPD

- There were weak significant associations between anticholinergic agent use and the following antipsychotic agents:
  - quetiapine and lower use (p=0.0023, Phi coefficient=0.15)
  - flupenthixol decanoate and higher use (p=0.0016, Phi coefficient=0.20)
  - Similarly to the first six-month period findings, patients on quetiapine had a lower proportion of anticholinergic agent use, while patients on flupenthixol decanoate had a higher proportion of anticholinergic agent use.

- At the second six-monthly visit, there was also a moderate significant association between anticholinergic agent use and risperidone oral dose (p=0.16, Phi coefficient=0.33). Although the trend was not very clear, it appears that anticholinergic agent use was associated with somewhat higher doses of this antipsychotic agent compared to non-use of anticholinergic agents.
- There were no other significant associations between anticholinergic agent use and any of the antipsychotic agent dose levels.



AC – Anticholinergic agent
*-indicates weak significant associations between antipsychotic and AC use

Fig 3.17: Antipsychotic agent use and antipsychotic agents from July to December 2011 at HJH POPD

3.2.4 Comparison of anticholinergic agent use to guidelines

Only those patients were considered who were on anticholinergic agents at either the first six-month visit (n=40), or the second six-month visit (n=44), or both. The anticholinergic agent use pattern is described below.

From the comparison, it was evident that:

(1) four patients who were not on an anticholinergic agent at the first six-month visit, were subsequently initiated on an anticholinergic agent;

(2) no patients who were on an anticholinergic agent at the first six-month visit were discontinued; and

(3) the 40 patients first noted were on an anticholinergic agent at both occasions

This was a significant finding that there was no change in the anticholinergic use pattern (Bowker's test of symmetry: p=0.046; i.e. the change in pattern between starting/discontinuing the anticholinergic agent was significant.) In addition, possible changes in the nature of the anticholinergic agent were also assessed.

Apart from the four "new" patients on anticholinergic agents, there was only one change noted in a prescribed anticholinergic agent (from orphenedrine to biperiden). Considering only the 40 patients who were on anticholinergic agents at both visits, this change in anticholinergic agent pattern was not significant (Bowker's test of symmetry: p=0.32). Comparing the changes in dosing for the 39 patients who were on the same anticholinergic agent at both visits, there were no changes in dose for either agent.

3.2.5 Anticholinergic and antipsychotic agents

- Amongst the 40 patients who were on an anticholinergic agent at the first six-month visit, only one significant association between any of the antipsychotic agents and the two anticholinergic agents was found
  - zuclopenthixol decanoate (p=0.046, Phi coefficient=0.43; moderate effect size)

- those not on zuclopenthixol decanoate were more likely to be prescribed orphenadrine, while those on zuclopenthixol decanoate (although few in number) were more likely to be prescribed biperiden.

- Similarly, amongst the 44 patients who were on an anticholinergic agent at the second six-month visit, only one marginally significant association between any of the antipsychotic agents and the two anticholinergic agents was found (Figure 3.10).
- Zuclopenthixol decanoate (p=0.058, phi coefficient=0.38; moderate effect size): those not on zuclopenthixol decanoate were more likely to be prescribed orphenadrine, while those on zuclopenthixol decanoate (although few in number) were more likely to be prescribed biperiden.

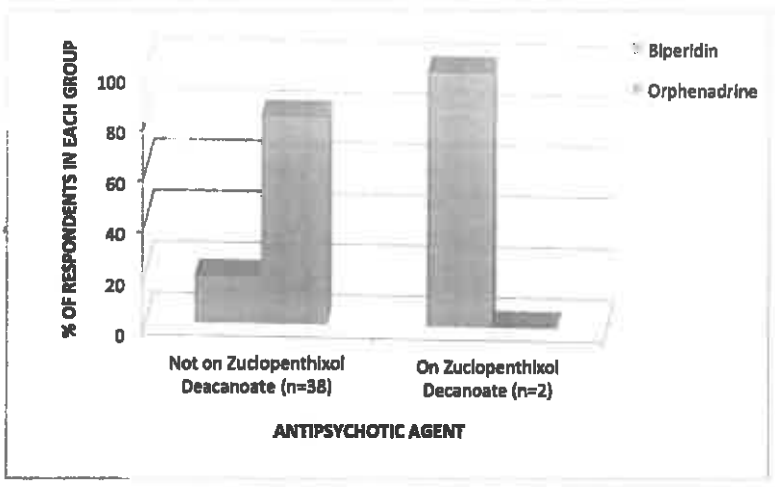


Figure 3.18: Association between zuclopenthixol decanoate and biperiden use from July to December 2011 at HJH POPD

Chapter 4 DISCUSSION

The patients in this study group had a mean age of 45.9 years, they were mostly female and resided in the Johannesburg Metro Area. The mean age was not unexpected, as psychiatric disorders occur throughout the lifespan, despite the time of diagnosis, and is also in keeping with similar international studies.[7,25] Some other studies, where the majority of study participants were male, focused on schizophrenia which may account for this gender disparity.[7] It must be noted that women in general are more likely to access health care systems, and are more likely to be compliant with treatment and follow up.[27] It was expected that the majority of patients would reside in the Johannesburg Metro Area, as this is where Helen Joseph Hospital is situated.

Antipsychotic agent use

Disorders in this study which were associated with antipsychotic agent treatment were behavioural-related disorders; psychotic disorders; mood disorders; general medical condition (GMC) related disorders; substance related disorders and "other" disorders. No similar studies were found that looked at anticholinergic co-prescribing in the context other than schizophrenia. Comorbid disorders were at times documented, but whether these were casually related could not be identified in most patients. [7, 28]

Patients with behavioural-related disorders were most commonly prescribed an antipsychotic agent. These included (in order of occurrence): Vascular Dementia, Cluster B Personality Disorders, Mental Retardation and Dementia due to Other Causes.

Dementia. Behavioural and psychological symptoms of dementia represents a group of "non-cognitive" symptoms and behaviours that can occur in patients with dementia.[29] These symptoms affect between 50-80% of patients.[30] Their management

is important as they strongly correlate with cognitive as well as functional impairment.[29] Its exact pathogenesis remains unknown, but it seems to be due to a combination of biological, psychological and social factors.[29] Off-label use in the elderly with dementia is common with atypical antipsychotic agents, , despite the FDA "Black Box Warning" for their use in this population. It is mostly used for dementia-related psychosis and agitation. The FDA stated increased risk of "cerebrovascular adverse events including stroke" in patients treated with risperidone versus placebo in this population in 2003. Since then, a cascade of warnings regarding other atypical antipsychotic agent use has emerged, with similar "black box warnings" for aripirazole and olanzapine. [31] Pharmacotherapy is only one modality of treatment of which atypical antipsychotic agents are frequently used.[29] According to the Maudsley Guidelines, increased mortality is associated with their use in dementia therefore cautions apply.[5]

Personality Disorders. In this study, the majority of the Cluster B related disorders consisted of patients documented to have Borderline Personality Disorder. There is evidence to show that atypical antipsychotic agents, as well as mood stabilisers can be effective in treating the core symptoms of borderline personality disorder.[32] However, there is no evidence for their use influencing the overall severity of the disorder.[31] It is estimated that a third of patients with borderline personality disorder are prescribed antipsychotic agents, and that prescriptions are on the increase.[33] A meta-analysis found that found that low dose olanzapine was most effective in reducing the risk of neuroleptic-induced side-effects compared to other atypical antipsychotic agents. The safety of their long-term use still needs to be established.[32]

Mental Retardation. Patients diagnosed with mental retardation may present with behavioural difficulties as well as an associated functional psychosis.[34] With regards to behavioural difficulties, aggression is most common. This poses a risk to both the

patient as well as others, including caregivers. It also significantly impairs quality of life.[35] Antipsychotic agents are the most frequently prescribed class of drug in the management of these patients[33]. Risperidone is the only medication with multiple trials documenting its efficacy for behavioural difficulties as well as psychosis in mental retardation.[33]

Psychotic and Mood Disorders. Antipsychotic agents are used in the treatment of first episode and multi episodes of psychosis. According to the Maudsley Guidelines, an antipsychotic agent should be tailored to the need of the patient in terms of overall efficacy, tolerability and the antipsychotic agent's particular side effect profile.[5] As evident in The Maudsley Guidelines, antipsychotic agents are also used in the management of mood disorders. Antipsychotic agents such as aripiprazole are antimanic agents and quetiapine are antidepressant agents.[5] They also treat associated psychotic symptoms if present.[5] Gao et al reported that patients with bipolar disorder, especially when depressed, are more susceptible to neuroleptic-induced side-effects than patients with schizophrenia.[36]

General Medical Conditions. The most common general medical condition (GMC) in patients treated with antipsychotic agents in this study was HIV/AIDS. This finding is made in the context of the local HIV prevalence of 12.2%,[37] and the common co-occurrence of psychiatric disorders and HIV/AIDS. A co-occurring psychiatric disorder may have preceded the HIV infection, or it may be related to HIV infection itself.[38] In this study, patients with a psychiatric disorder secondary to HIV infection was documented, as well as the antipsychotic agents used to treat psychotic as well as mood symptoms related to these disorders. Atypical antipsychotics were preferred as these patients are known to be prone to develop neuroleptic-induced side effects. Consideration should be taken of interactions with antiretroviral treatment on choosing

an antipsychotic agent.[37] With regards to HIV-associated dementia, it is the leading cause of dementia in South Africa and these patients also present with behavioural and psychological aspects of dementia as discussed previously. They may benefit from antipsychotic treatment as one modality of their management.[39]

Other GMC treated with antipsychotic agents included epilepsy, head injury, temporal lobe epilepsy (TLE) and cerebrovascular accidents (CVAs). Epilepsy and TLE are associated with psychotic symptoms in up to 4% of patients. Peri-ictal psychosis should be managed by optimising anticonvulsants, while inter-ictal psychosis is more likely to require treatment with an antipsychotic agent.[5] Fujii and Fujii, in an analysis of case studies in the literature of psychosis and head injury, found that antipsychotic agents are the most effective treatment modality in this population.[40] Patients with Cerebrovascular Accidents can present with both psychotic symptoms and behavioural problems. This is due to the high probability of developing vascular dementia.

Substance Disorders. In this study, antipsychotic agents were used to treat substance-related disorders. Although not specified, it is likely that these included substance-induced psychotic disorders, substance-induced bipolar disorders and substance-induced depressive disorders. Zhornitsky et al., showed that atypical antipsychotics have been effective in treating substance related psychotic and mood symptoms, as well as decrease substance use in patients with such symptoms.[41] Epidemiologically the life–time prevalence of comorbid substance use disorders is up to 50% in patients with schizophrenia, with alcohol and cannabis, after nicotine, being the most commonly used.[41] Potvin et al., reported that the former two have a negative impact on disease progression, with more frequent non-adherence, hospitalisations, impulsivity, violent and aggressive behaviours and poor socioeconomic outcomes.[42]

A large meta-analysis by Potvin and Blanchet found that substance use disorders can both precipitate and exacerbate neuroleptic-induced side-effects.[41] It could not be ruled out that patients with neuroleptic-induced side-effects had increased substance use in an attempt to self-medicate their symptoms.[41] This is an area that will need further study.

Other Disorders. The "Other" category comprised of Generalised Anxiety Disorder (GAD) followed by Adjustment Disorder, Bereavement and Post Traumatic Stress Disorder (PTSD). The literature has shown an increasing trend in the prescription of atypical antipsychotics in the management of anxiety related disorders.[43] The indication of antipsychotic agents specifically related to bereavement and adjustment disorder in this study is not clear - the management of comorbid disorders or as a sedative as an indication has been queried.

Anticholinergic agent use

Suspected or confirmed anticholinergic agent abuse was not documented. Although it has been identified in a wide variety of clinical settings, its overall prevalence is low.[44] It may be that, with absent documentation possibly inferring nil suspicion or confirmation of abuse, that this may be in keeping with standard prevalence rates.

The vast majority of patients were on an atypical regime, with the minority receiving a typical antipsychotic or a combination of antipsychotic agents. Looking specifically at psychotic disorders, similar findings were found in The Second Australian National Survey of Psychosis conducted in 2012.[45] As mentioned, partial or non-adherence is a known predictor for relapse of symptoms. As risperidone is available as a long acting injectable, there has been interest in its use in both first episode psychosis and in multiple episode psychosis. It has also been shown to be cost-effective when compared to non-adherence of oral treatment. In two South African studies, it was

found that neuroleptic-induced side effects were less frequent with the long-acting injectable risperidone than with oral risperidone, and that the former was generally well tolerated.[46, 47] As generic oral medications are used in the state sector, where these studies were conducted, and the risperidone long-acting injectable is the original product generic versus original medications can be a confounding factor relating to oral risperidone's efficacy.

Concurrent anticholinergic agent use with an antipsychotic agent was lower for atypical antipsychotics when compared to typical and combination regimes. Similar findings were found with regards to antipsychotic agent type in studies in Asia[25], Bahrain[26] as well as China[24]. The percentage of co-prescribing of anticholinergic agents in this study, however, was lower compared to these studies. A large European study conducted by Broekema[7] et al also found a lower percentage of patients receiving both agents. Helen Joseph Hospital offers tertiary level psychiatric services in an academic setting, unlike some of the studies quoted. There may therefore be more awareness about the possibility of neuroleptic-induced side-effects, which can influence the choice of antipsychotic agent, or early detection of side effects with resultant switching to a more suitable antipsychotic agent.

With regard to anticholinergic agent use, a weak association was found with increased use in psychotic disorders, and decreased use in those with a general medical condition. As with those studies focusing specifically on anticholinergic agent prescribing in schizophrenia, there is a much higher co-prescribing frequency than found in our study.[25,26] In an academic setting, emphasis is placed on the vulnerability of patients with general medical conditions developing neuroleptic-induced side effects. This should theoretically lead to more judicious prescribing of antipsychotic

agents with the least propensity to result in side effects. Anticholinergic agent co-prescribing in the latter group would therefore be less likely to occur.

It was found that quetiapine was associated with decreased use of anticholinergic agents, while flupenthixol decanoate was associated with an increased use of anticholinergic agents. Quetiapine is a low potency atypical antipsychotic agent with inherent anticholinergic properties, which accounts for this. In contrast flupenthixol decanoate is a high potency typical long acting injectable antipsychotic with a high propensity to produce neuroleptic -induced side effects. However, in a South African study investigating the treatment efficacy and tolerability of flupenthixol decanoate in first episode psychosis, it caused minimal neuroleptic-induced side effects limiting the need for anticholinergic agent use.[48] This is in direct contrast to this study's findings. Another study finding was that zuclopenthixol decanoate use was associated with higher use of biperiden compared to orphenadrine. Given the very small number of patients taking zuclopenthixol decanoate together with an anticholinergic agent, the clinical significance of this result is questionable.

As no indications for anticholinergic agent use was documented, the possibility of its prophylactic use is a possibility. The demographic of patients may differ, which can also impact on inter-individual tolerability among different geographical populations.

Off-label prescribing is common in clinical psychiatric practice, A study conducted at a psychiatric outpatients department in a tertiary level teaching hospital in Gujarat, India, investigated this through a prospective trial – 79,2% of patients received at least one off-label drug, with an inappropriate indication being the most common category.[49] When looking at atypical antipsychotics specifically, although they are in many ways

favourable to typical antipsychotic agents, they themselves have an adverse risk profile. As some atypical antipsychotics, such as olanzapine and clozapine, are histamine-1 receptor antagonists, they are sedative in nature. Queries surrounding their off-label use for insomnia has been raised, as well as their subsequent abuse potential.[50]

Rating scales for neuroleptic-induced side-effects are used in numerous settings. The Extrapyramidal Symptom Rating Scale (ESRS) is a standardised rating scale which has verified sensitivity and reliability in a numerous settings. These include clinical settings with oral antipsychotics, long acting injectable antipsychotics, various central nervous system drugs as well as placebo.[51] Training and implementation of its use could lead to more accurate diagnosis and treatment of neuroleptic-induced side-effects, and therefore also adherence. If its use had been implemented at HJH POPD, clinical data specifically related to anticholinergic agent use would have been available to further assess anticholinergic agent co-prescribing patterns.

The objectives of the study were met, and are outlined in the results section. The hypothesis of this study, that the concurrent use of anticholinergic agents and antipsychotic agents are not managed according to set guidelines at HJH POPD, was fulfilled. No patients on an antipsychotic agent and co-prescribed anticholinergic agent had a dose adjustment in anticholinergic agent during the study period. This finding is in keeping with other international studies investigating such co-prescribing patterns.[25, 26]

LIMITATIONS

As this study is a retrospective record review, a significant limitation of this study is missing data. Not only were some demographic variables missing, but more importantly specific data with regards to the indication for anticholinergic agent use and their side effects were also not available. The latter could have influenced compliance and impaired patients who may already have been cognitively vulnerable. The index of suspicion for abuse potential was also not documented. Although the study had a 100% sample size of those attending HJH Psychiatric OPD who met the inclusion criteria, the number of records that could be included in this review was very small.

The study was conducted at HJH POPD, which offers tertiary level psychiatric care. The results cannot be generalised to primary, secondary and quaternary centres, even within the same geographical area treating the same demographic of patients. This limitation is also due to Essential Drug List constraints.

The HJH POPD has psychiatric medical officers and registrars managing both new and existing patients, with supervision by a consultant psychiatrist if needed. Depending on the registrar's seniority and expertise, the management of anticholinergic agent prescribing may not be a focus of attention. This may have biased results.

Chapter 5 CONCLUSION

This study found that numerous diagnoses were associated with the prescribing of antipsychotic agents. Of concern, especially with the use of typical antipsychotics as well as combination antipsychotic use, is the risk of neuroleptic-induced side effects.

In international studies, there was a much higher rate of anticholinergic agent co-prescribing with antipsychotic agents than in our setting. This may be due to differing settings, especially related to academics and access to medication. Most patients in this study were on oral risperidone – associated with this atypical antipsychotic agent was anticholinergic agent co-prescribing. There has been controversy with regards to oral risperidone since the release of generic agents – no studies thus far have investigated the risk of neuroleptic-induced side effects with regards to the original and generic products.

Adequate management of neuroleptic-induced side effects and treatment with anticholinergic agents should be highlighted as an important aspect of patient care. Patients are at risk of anticholinergic side effects, of which central is the most concerning. Peripheral side effects may also influence patient compliance.

Anticholinergic agent use should be monitored regularly. Different hospitals may have different approaches when it comes to anticholinergic agent co-prescribing – similar studies in different settings for comparative reasons are recommended.

Education surrounding anticholinergic agent use should be promoted, especially in academic training centres.

The need for uniform treatment guidelines in South Africa is underway, yet remains challenging due to constraints with psychotropic medication availability.

Practically, a uniform rating scale such as The Extrapyramidal Symptom Rating Scale should be performed on every patient at baseline when starting an antipsychotic agent, then at every visit. All clinicians at HJH POPD should receive training in this regard.

A predesigned chart should be kept in every patient file documenting rating scale scores and the indication for initiating anticholinergic agent. The anticholinergic agent and dose should be recorded. On subsequent visits monitoring ofr both peripheral and central side effects, plus response to treatment must be documented. A high index of suspicion should be had for abuse of anticholinergic agents. Once stable with regards to neuroleptic-induced side effects, the patient should be reviewed in this regard with dose reduction and monitoring for remergence of symptoms. Dose reduction should be attempted every three months with no anticholinergic agent prescribed at night, until the anticholinergic agent has been completely withdrawn. The latter, according to Maudsley Guidelines, is achievable in 80% of patients.

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APPENDICES

CURRENT PRACTICE OF ANTICHOLINERGIC USE IN CONJUNCTION WITH ANTIPSYCHOTIC AGENTS AT HELEN JOSEPH HOSPITAL PSYCHIATRIC OUTPATIENTS

1. Appendix A. Maudsley Prescribing Guidelines
2. Appendix B. Data sheet
3. Appendix C. WITS HREC Ethics Clearance Certificate
4. Appendix D. Turnitin Report Results

1. Appendix A. Maudsley Prescribing Guidelines[51]

ACUTE DYSTONIA

Signs and symptoms:	Muscular spasm in any part of the body example oculogyric crisis and torticollis.
	The patient may be unable to swallow or speak clearly. In extreme cases the back may arch or the jaw may dislocate.
	Acute dystonia may be both frightening and painful.
Prevalence:	Approximately 10%, but more common in young males, in the neuroleptic-naive and with high-potency drugs such as haloperidol.
	Dystonic reactions are rare in the elderly.
Time taken to develop:	Acute dystonia can occur within hours of starting antipsychotics.
	Tardive dystonia occurs after months to years of antipsychotic treatment.
Treatment:	Anticholinergic drugs given orally, IMI or IVI depending on severity.
	Remember the patient may be unable to swallow.
	Response to IV administration will be seen within 5 minutes.
	Response to IM administration takes around 20 minutes.
	Tardive dystonia may respond to ECT.
	Where symptoms do not respond to simpler measures including switching to an antipsychotic with a low propensity for EPS, botulinium toxin may be effective.

PSEUDO-PARKINSONISM

Signs and symptoms:	Tremor and/or rigidity
	Bradykinesia – decreased facial expression, flat monotone voice, slow body movements, inability to initiate movement.
	Bradyphrenia - slowed thinking.
	Salivation
	Pseudo-parkinsonism can be mistaken for depression or the negative symptoms of schizophrenia.
Prevalence:	Approximately 20%, but more common in elderly females and those with pre-existing neurological damage.
Time taken to develop:	Days to weeks after the antipsychotic drugs are started, or the dose is increased.
Treatment:	Several options are available depending on the clinical circumstances.
	Reduce the antipsychotic dose.
	Change to an atypical antipsychotic as monotherapy.
	Prescribe an anticholinergic. The majority of patients do not require long-term anticholinergics. Use should be reviewed at least every 3 months. Do not prescribe at night (symptoms usually absent during sleep).

AKATHISIA

Signs and symptoms:	A subjectively unpleasant state of inner restlessness where there is a strong desire or compulsion to move.
	Foot stamping when seated.
	Constantly crossing/uncrossing legs, rocking from foot to foot.
	Constantly pacing up and down.
	Akathisia can be mistaken for psychotic agitation, and has been (weakly) linked with suicide and aggression towards others.
Prevalence:	Approximately 25%, less with atypicals.
	In decreasing order: aripiprazole, risperidone, olanzapine, quetiapine and clozapine.
Time taken to develop:	Acute akathisia occurs within hours to weeks of starting antipsychotics or increasing the dose.
	Tardive akathisia takes longer to develop and can persist after antipsychotics have been withdrawn.
Treatment:	Reduce the antipsychotic dose. Change to an atypical drug. A reduction in symptoms may be seen with: propanolol, clonazepam and 5HT2 antagonists. All are unlicensed for this indication.
	Anticholinergic agents are generally not helpful.

2. Appendix B. Data sheet

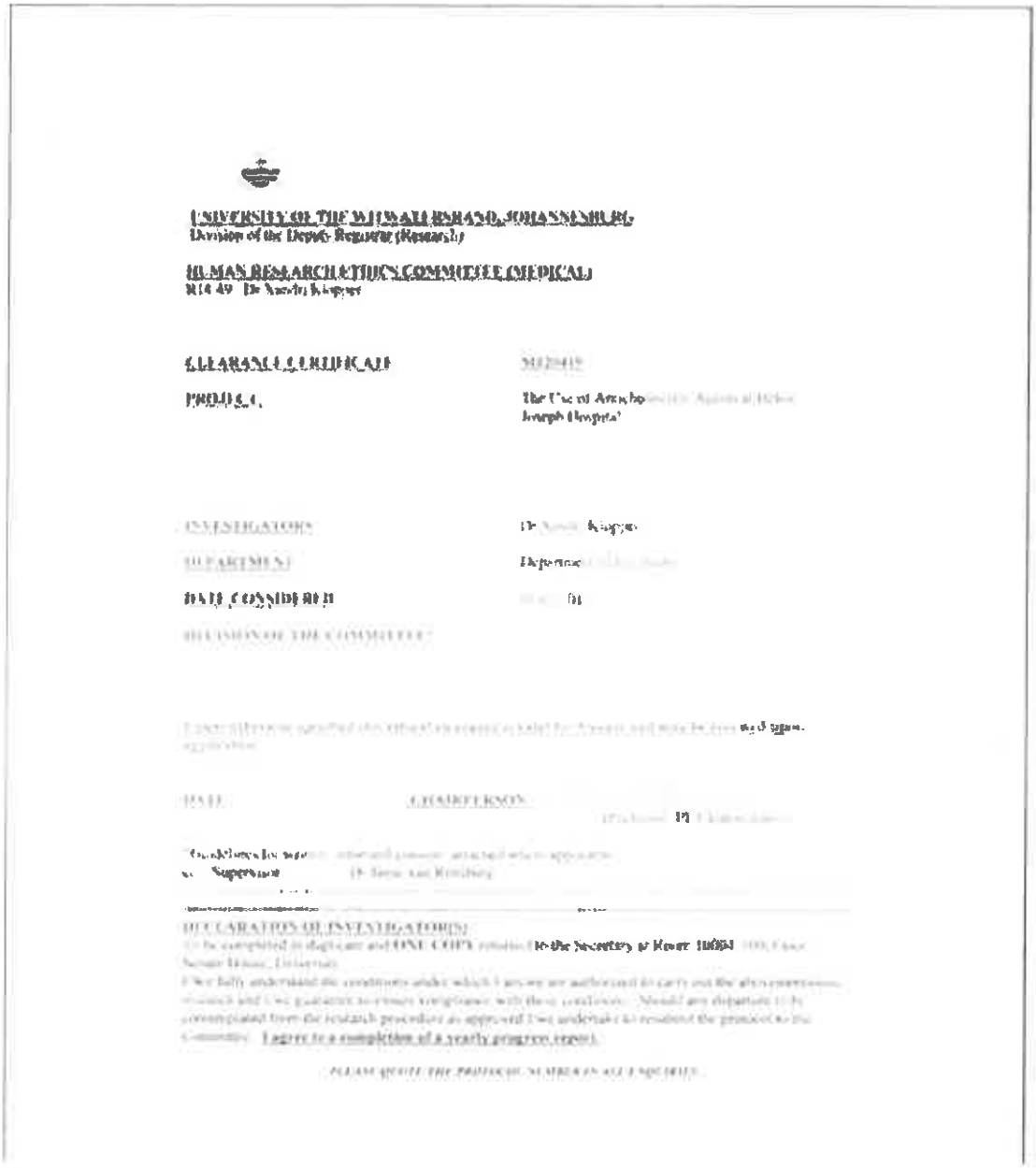
Gender	Male			Female	
Age					
Geographical area					
Diagnosis	**Psychotic Disorders**				
	Mood disorders				
	Bipolar Disorder Type I or II	*MDD* with psychotic features*			
	Substance related disorders mood/psychosis				
	Behavioral related Disorders				
	Mental Retardation+	*Personality disorders*		*Dementia*	
	GMC related disorders				
	Epilepsy	*HIV*		*Other*	
Substance abuse	Cannabis	Heroin	Methaqualone	Stimulants	Anticholinergics

Current AP* Treatment	**Class**	**Agent**	**Dose**	**Route**
	Typical antipsychotic	Haloperidol		
		Chlorpromazine		
		Zuclopenthixol		
		Flupenthixol		
	Atypical	Risperidone		
		Olanzapine		
		Quetiapine		
		Clozapine		
		Sulpiride		
		Amisulpiride		
Antipsychotic related side-effects an indication for anticholinergic treatment (specify period)	Dystonia	Parkinsonism	Akathisia	NMS*

Current treatment with or dose adjustment of anticholinergic agent	Agent	Route	Dose
Preceding 6-months treatment with or dose adjustment of anticholinergic agent	Agent	Route	Dose
Side-effects related to anticholinergic agent (Specify current/ preceding 6-months)	Peripheral (current)	Delirium (current)	Cognitive (current)
	(previous 6months)	(previous 6months)	(previous 6months)

*** AP – Antipsychotic; MDD – Major Depressive Disorder; NMS – Neuroleptic malignant syndrome; + Mental Retardation (DSM-IVR, changed to Intellectual Impairment in DSM-5)**

3. Appendix C. WITS HREC Ethics Clearance Certificate



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Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Nandi Kruger

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PROJECT

INVESTIGATORS

DEPARTMENT

DATE CONSIDERED

DECISION OF THE COMMITTEE

DATE

CHAIRPERSON

Supervisor

DECLARATION BY INVESTIGATORS

To the Secretary at Room

I fully understand the conditions under which I am/we are authorised to carry out the above mentioned research and I undertake to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the proposal to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

4. Appendix D. Turnitin Report Results.

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