The occurrence of hyponatraemia amongst patients with severe mental illness admitted at Solomon Stix Morewa Memorial Hospital, Johannesburg.

Dr. Natsai Marjory Sekai Nhiwatiwa

301920

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DECLARATION

I, Natsai Nhiwatiwa, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Psychiatry at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

……..

Signature of candidate

13 June 2023

DEDICATION

To my aunt: Chipiwa Shava

PRESENTATIONS ARISING FROM THIS STUDY

1. Nhiwatiwa NMS (2021). Medical dilemmas in a mental health care institution. Clinix Hospital Group Webinar.
2. Nhiwatiwa NMS (2022). The occurrence of hyponatraemia amongst patients with severe mental illness admitted at Solomon Stix Morewa Memorial Hospital, Johannesburg. University of the Witwatersrand Department of Psychiatry Research Day 2022.

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My Lord and saviour, Jesus Christ – 1 Peter 5:10-11

ABSTRACT

Background

Morbidity in patients with severe mental illness is known to be higher than in the general population. Numerous factors contribute to this, including the propensity to have comorbid conditions and the effects of long-term treatment with psychotropics. Hyponatraemia is the most common electrolyte abnormality found in hospitalised patients. Patients with severe mental illness are vulnerable to the development of hyponatraemia due to psychogenic polydipsia, comorbid conditions and the long-term use of psychotropics.

Aim

To evaluate the occurrence of hyponatraemia in patients with severe mental illness that are admitted at Solomon Stix Morewa Memorial Hospital and to determine the associations between the hyponatraemia and the patients' demographic and clinical variables.

Objectives

To assess and quantify the occurrence of hyponatraemia in patients with severe mental illness. To establish the cases, grades of severity and the trends of hyponatraemia in the study sample. To make possible associations between the development of hyponatraemia and the various clinical profiles. To analyse the trends of sodium testing in the study participants.

Results

32% of the patients had hyponatraemia on admission to Solomon Stix Morewa Memorial Hospital, significantly higher than that of the general population. Female patients and patients on antihypertensive medications were more likely to have hyponatraemia. Other medical conditions such as hypertension, type 2 diabetes mellitus and chronic obstructive pulmonary disease were significant predictors for the development of hyponatraemia. Patients on combination antipsychotics (first- and second-generation antipsychotics)

were also more likely to develop hyponatraemia than those not on combination antipsychotics.

Conclusion

Hyponatraemia was found in a significant proportion of the study participants. Patients with severe mental illness are more likely to have co-morbid illnesses that can be overlooked. The comorbid illnesses render the patients more likely to develop complications such as hyponatraemia that worsens their outcomes and mortality. More research is required to establish the role of combination antipsychotics as a possible cause of the development of hyponatraemia in psychiatric patients. Definitive monitoring guidelines are required in the long-term management of patients with severe mental illness. More recognition of hyponatraemia as a significant adverse effect of comorbid illness, psychiatric illness and chronic medication is required in patients with severe mental illness.

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NOMENCLATURE

Term	Abbreviation
Antidiuretic hormone	**ADH**
Chronic obstructive pulmonary disease	**COPD**
Cyclic adenosine monophosphate	**cAMP**
Dopamine	**D**
Estimated glomerular filtration rate	**eGFR**
Life Esidimeni	**LE**
Long-acting injectable antipsychotics	**LAI**
Millilitres	**mL**
Millimoles per litre	**mmol/L**
Non-government organization	**NGO**
Selective serotonin reuptake inhibitor	**SSRI**
Serotonin and norepinephrine reuptake inhibitor	**SNRI**

Severe mental illness	**SMI**
Solomon Stix Morewa Memorial Hospital	**SSMMH**
Syndrome of inappropriate antidiuretic hormone secretion	**SIADH**
Urea and electrolytes	**UE**
5-Hydroxytryptamine	**5HT**

Chapter 1: Introduction

1.1 Background

Hyponatremia is defined as the reduction of serum sodium concentrations to levels of 135 millimoles per litre (mmol/L) and below (Rondon and Badireddy, 2022). Hyponatraemia is the most typically encountered electrolyte abnormality in clinical practice and frequently affects hospitalised patients (Adrogue et al., 2022, Spasovski et al., 2014). Hyponatraemia is known to worsen the clinical outcomes of all patients but is frequently unrecognised in patients with severe mental illness (SMI) (Sivaraman and Manivel, 2016, Sawant et al., 2019).

It is estimated that around 20% of patients that present to a hospital, via the emergency department, across the world, are found to have hyponatremia (Spasovski et al., 2014). Hyponatremia is associated with longer hospital stays and worsened morbidity and mortality in patients with various conditions (Asadollahi et al., 2006). Therefore, hyponatraemia is as much a public health concern as it is a common clinical occurrence. Hyponatraemia is of significant interest in the care of patients with SMI as patients with SMI are vulnerable to increased morbidity and mortality due to the mental illness itself, other medical conditions, substance use and various lifestyle choices (Hjorthoj et al., 2017). Despite this knowledge, patients with SMI often die from preventable and treatable conditions such as metabolic disorders (Crump et al., 2013).

In the recent past, in South Africa, the morbidity and mortality in patients with SMI was highlighted by the death of patients in the Life Esidimeni tragedy. This tragedy occurred in 2016 when over 1400 patients who were placed at Life Esidimeni (LE) care facilities in Gauteng Province were rapidly discharged to unlicensed nongovernment organisations (NGOs) (Health Ombud, 2017). 144 patients died in the tragedy with at least one death being linked to hyponatraemia by the Health Ombud (2017). The details around the deaths of the other patients were largely unknown, but the available details suggested that the patients died from treatable and commonly occurring conditions such as dehydration and seizures (Health Ombud, 2017).

As the tragedy evolved, the surviving patients were transferred to allocated hospitals according to the remedial actions proposed by the Health Ombud (2017). One of the hospitals allocated was Solomon Stix Morewa Memorial Hospital (SSMMH), in Johannesburg, where the treating clinicians noted an unusually high occurrence of hyponatraemia in the transferred patients on routine testing.

1.2 Literature review

1.2.1 The epidemiology of hyponatraemia

Hyponatraemia is known to affect up to 1.72% of the general population, and it is greatly associated with older age, prescription medication and comorbid medical conditions (Mohan et al., 2013). It has been found that the majority of the cases of hyponatraemia are mild and asymptomatic (Mohan et al., 2013). Hospitalised patients have been found to have higher prevalence rates of hyponatraemia. Hao et al (2017) found that 17.5% of hospitalised patients had hyponatraemia in their cohort study and the impact of the hyponatraemia on patient mortality rates had been greatly underestimated. In a study that correlated the mortality of patients with acute heart failure to the degree of hyponatraemia on admission to the hospital, it was concluded that hyponatraemia was a crucial independent predictor of mortality regardless of age, sex, haematocrit, left ventricular ejection fraction and prescribed medications (Lu et al., 2016, Hao et al., 2017). This study concluded that this finding could be applied to a variety of different types of patients.

The epidemiology of hyponatraemia in patients with SMI has been sporadically studied with Gleadhill et al (1982) confirming a 5.8% prevalence of hyponatraemia in hospitalised patients with schizophrenia. The study introduced the notion that patients with SMI were at increased risk for hyponatraemia due to psychogenic polydipsia and long-term exposure to psychotropic medications (Gleadhill et al., 1982). Lange-Asschenfeldt et al., (2013) found a similar prevalence (4.9%) of hyponatraemia in admitted psychiatric patients. However, this study concluded that the patients were at risk of developing hyponatraemia because of polypharmacy with non-psychiatric medications (Lange-

Asschenfeldt et al., 2013). When studying outpatients with schizophrenia, it was found that 10% of the patients developed hyponatraemia in a 15 year period and it was closely linked to the long-term use of antipsychotic drugs (Yang and Cheng, 2017).

The risk factors for the development of hyponatraemia include renal, cardiac and pulmonary disease that impact the fluid balance of the body (Kayar, 2016). Further risk factors include advancing age and the use of medications. Additional risk factors include being female and of smaller body size (Ali and Bazzano, 2018, Viramontes et al., 2016). It is postulated that as patients age, the thirst centre in the hypothalamus and water homeostasis mechanisms become less sensitive to the fluctuations in the serum osmolalities (Ali and Bazzano, 2018). With regards to gender and body size; it has been proposed that females are more vulnerable to developing hyponatraemia due to their relatively smaller body size and the effect of oestrogen on water reabsorption at the level of the level of the renal tubules (Ali and Bazzano, 2018, Nishimura et al., 2019).

1.2.2. The pathophysiology of hyponatraemia

Sodium is a major cation that is the most abundant electrolyte in serum plasma and plays a crucial role in all bodily electrical activities and cell-fluid balance (Adrogue et al., 2022). Neurons and myocardial cells are particularly vulnerable to the changes in serum sodium levels resulting in the typical presentations and complications of hyponatraemia (Adrogue et al., 2022). The control of sodium is, therefore, crucial for optimal functioning of all the cells of the human body.

The control of serum sodium is a complex process involving the hypothalamus and renal filtration. The antidiuretic hormone (ADH) is secreted by the posterior hypothalamus and controls osmoregulation (Barrett et al., 2009). The hypothalamus has osmoreceptors that detect any change in serum osmolality. Any increase in the serum osmolality leads to increased secretion of ADH which leads to fluid retention in the extracellular space (Barrett et al., 2009). ADH also reduces renal filtration and subsequent urine production. Increased serum osmolality also stimulates the thirst centre of the hypothalamus thus, promoting increased water intake (Barrett et al., 2009). The consequent increased

extracellular volume leads to lower concentrations of plasma constituents such as sodium.

Hypotonicity refers to lowered solute concentrations in the plasma, promoting greater fluid influx into the cells (Tzamaloukas et al., 2019). Such fluid shifts occur in hyponatraemia and greatly affect cell functioning. Hypotonicity is potentially fatal as it can cause conditions such as cerebral oedema (Tzamaloukas et al., 2019). On a larger scale, such transcellular shifts can lead to a wide spectrum of disorders affecting the serum osmolality. These include redistributive or hypertonic hyponatremia, hypotonic hyponatremia and pseudohyponatraemia. Pseudohyponatraemia is isotonic and is caused by the increase of osmotically active serum constituents such as lipids or proteins (Tzamaloukas et al., 2019). Hypotonic hyponatremia is the most commonly encountered sodium abnormality caused by increased water retention or increased fluid intake (Tzamaloukas et al., 2019). Hypotonic hyponatraemia is commonly caused by hypervolaemic states caused by conditions that interfere with the renal excretion of water such as cardiac, renal and endocrine abnormalities (Adrogue et al., 2022). Hypovolaemic hyponatraemia is caused by a significant loss in total body water due to vomiting, diarrhea, salt-wasting renal pathology and the use of diuretics (Tzamaloukas et al., 2019).

Euvolaemic hyponatraemia involves no change in the total body water and is often caused by medications, endocrine conditions such as Addison's disease and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH is a condition in which the posterior pituitary secretes excessive ADH despite low serum osmolalities (Yasir and Mechanic, 2022). SIADH is commonly caused by pulmonary disease, malignancy, central nervous system disorders and various medications (Yasir and Mechanic, 2022).

Urine concentration is a process that involves filtration, reabsorption and secretion of various serum constituents in the cortical and medullary collecting tubular cells in the kidneys (Barrett et al., 2009). A reduction in serum osmolality would encourage ADH

inhibition and would prevent water retention at the level of the Loop of Henle and the collecting ducts resulting in hypotonic urine (Barrett et al., 2009).

The severity of hyponatraemia ranges from mild to severe hyponatraemia depending on the serum sodium concentration (Spasovski et al., 2014). Mild hyponatraemia is a serum sodium range from 130 to 135 mmol/L. Moderate hyponatraemia is a sodium range from 125 to 129 mmol/L and severe forms of hyponatraemia are sodium levels below 125 mmol/L (Spasovski et al., 2014).

Mild forms of hyponatraemia are often asymptomatic in patients, and therefore, remain undiagnosed (Joergensen et al., 2019). Very few cases of mild hyponatraemia are known to cause symptoms such as headaches, restlessness, anorexia and dizziness in patients (Giuliani and Peri, 2014). An association between mild hyponatraemia and an increased risk of falls in patients have been reported (Renneboog et al., 2006).

Moderate hyponatraemia results in disorientation, depressed levels of consciousness and seizures (Giuliani and Peri, 2014). Severe forms of hyponatraemia result in respiratory depression, coma and death (Giuliani and Peri, 2014).

In addition to the classification of hyponatraemia according to its severity, hyponatraemia is further classified as acute or chronic. Acute hyponatraemia develops within 48 hours and does not allow for the compensatory mechanisms to be initiated (Verbalis, 2010). Acute hyponatraemia causes a rapid decrease in serum osmolality and a significant fluid shift resulting in fluid influx into the brain tissue that can cause oedema. The swelling of the brain can be significant enough to cause brain herniation (Giuliani and Peri, 2014).

Hyponatraemia is also classified as chronic hyponatraemia if it persists for more than 48 hours. Chronic hyponatraemia is often asymptomatic as it allows for the neurons to compensate for the osmotic pressure changes thereby preventing significant swelling and therefore, minimizing symptoms (Verbalis, 2010). This is achieved by the aquaporin 1 and 4 channels selectively allowing fluid into the cell according to the cell's volume receptors

(Verbalis, 2010). To further reduce the osmotic pressure, the sodium-potassium adenosine triphosphatase pump promotes electrolyte extrusion into the extracellular space to maintain cell volume (Verbalis, 2010).

Both acute and chronic hyponatraemia result in altered intranuclear protein transcription and neuronal firing that impacts the mortality of a range of patients. It is well researched that hyponatraemia can worsen the morbidity of neonates as well as worsen the outcomes of patients in the third stage of labour (Moen et al., 2009, Chalela et al., 2016). Patients with SMI are equally as vulnerable to the negative impacts of hyponatraemia.

1.2.3 Morbidity in patients with SMI and the socio-health vulnerability

The morbidity in patients with SMI is known to be greater than that of the general population (Karim et al., 2019). It is known that the life expectancy of patients with schizophrenia may be reduced by up to ten years, with Hjorthoj et al (2017) concluding that patients with schizophrenia live up to 14.5 years less than the general population. This finding is attributed to the chronic medications, lifestyles and the propensity for comorbid medical conditions in patients with SMI (Hjorthoj et al., 2017).

SMI is understood to consist of a group of psychiatric diagnoses including psychotic, mood and neurodevelopmental disorders that cause significant functional impairment in a patient (Martínez-Martínez et al., 2020, Gaynes et al., 2015). This commonly includes the diagnoses of psychotic and mood disorders that often require life-long treatment with psychotropics. The illnesses often cause significant impairment in the patient's ability to function, often deeming them unable to be gainfully employed and contribute to society. SMI frequently leads to repeated hospitalizations, incarceration and homelessness (Martínez-Martínez et al., 2020).

Substance use, such as alcohol and tobacco smoking, is highly prevalent amongst patients with SMI (Asharani et al., 2020, Abeysena and Bandara, 2018). Smoking, in particular, is known to impair water excretion and has been positively correlated with hyponatraemia in previous studies, rendering patients with SMI vulnerable to the development of hyponatraemia and other metabolic complications (Allon et al., 1990).

While the need for screening for metabolic and cardiovascular diseases in patients with SMI may seem obvious, Saloojee et al (2014), in a Durban-based cross-sectional study, found that less than one percent of their study sample was adequately screened for metabolic and cardiovascular diseases, once diagnosed with a mental illness. It is evident that patients with SMI remain socially and medically vulnerable and may not be adequately screened and managed for commonly occurring comorbidities including hyponatraemia.

Patients with SMI are more likely to have undiagnosed cases of metabolic and cardiovascular diseases despite their increased contact with health care services (Crump et al., 2013, Saloojee et al., 2014). They are two to three times more likely to die from cardiovascular diseases than individuals who do not have a mental illness (Crump et al., 2013). In addition to the increased mortality due to suicide and accidents, patients with SMI also experience a disproportionately higher mortality due to preventable medical conditions such as type 2 diabetes mellitus and obesity (Mauer, 2006). This increased mortality due to other medical conditions may be indicative of poor medical assessment and management of patients with mental illness. Common, treatable medical conditions are more likely to be overlooked in patients with SMI due to diagnostic overshadowing (Shefer et al., 2014). Furthermore, factors such as stigma towards mental illness and resource constraints also impact on the quality of the clinical assessments of patients with SMI (De Hert et al., 2013).

1.2.4 Medication-induced hyponatraemia

Patients with SMI are at risk for various metabolic and endocrine complications such as hyponatraemia, due to the long-term treatment with psychotropic medications (Sailer et al., 2017, Bojdani et al., 2019).

Medications are a well-established cause of hyponatraemia (Kim, 2022). Cytotoxic drugs, analgesic medications, antidepressants, mood stabilisers, anticonvulsants and antipsychotic medications are the classes of medications most commonly associated with hyponatraemia (Shepshelovich et al., 2017).

1.2.4.1 Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are postulated to cause hyponatraemia by increasing ADH secretion (De Picker et al., 2014). It is suggested that the increased serotonin activity increases the osmoreceptor sensitivity and causes increased ADH secretion as in SIADH (De Picker et al., 2014, Mannesse et al., 2013). Hyponatraemia is a life-threatening and significant complication of treatment with SSRIs especially in the elderly (Viramontes et al., 2016). Mannesse et al (2013) reported that 9.3% of elderly patients developed hyponatraemia while on SSRI treatment. Patients over the age of 65 years are most at risk for developing SIADH due to SSRIs (Tomar et al., 2021). The hyponatraemia often remains undetected until the patient develops physical symptoms such as nausea and vomiting, indicating moderate hyponatraemia. There are documented cases of elderly patients developing delirium due to the antidepressant-induced hyponatraemia (Bouman et al., 1998). This indicates the need for close monitoring of elderly patients for the development of hyponatraemia caused by SSRIs.

Despite the risk of hyponatraemia, there is a lack of consensus regarding the monitoring of electrolytes in patients on SSRIs (Dodd et al., 2011). Dodd et al (2011) recommends more frequent monitoring of urine and serum osmolality in patients on SSRIs should be implemented in addition to frequent serum sodium monitoring.

1.2.4.2 Antipsychotic medication

Antipsychotic medications are widely used in the treatment of SMI and are known to cause hyponatraemia (Dixon et al., 2009, Yang and Cheng, 2017). It has been researched that antipsychotic-induced hyponatremia emanated from SIADH, leading to reduced water clearance and resulting in hyponatremia (Hariprasad et al., 1980, Meulendijks et al., 2010). Introductory studies, conducted in the 1970s, piloted the notion that haloperidol and thiothixene impaired the patient's ability to excrete excess water (Ajlouni et al., 1974, Peck and Shenkman, 1979). Since these initial studies, cases of hyponatraemia have been associated with first generation antipsychotics and second generation antipsychotics such as risperidone, aripiprazole, olanzapine, ziprasidone and clozapine (Ali and Bazzano, 2018). Long acting injectable antipsychotics have also been linked to hyponatraemia (Chowdhury et al., 2018, Faizan et al., 2020). The mentioned

antipsychotics, besides thiothixene and clozapine, are amongst the first-line treatment in the management of psychotic disorders in South Africa (Emsley et al., 2013). This alone qualifies the need for surveillance of hyponatraemia in patients with SMI.

Although antipsychotics are well-known to cause hyponatraemia, the prevalence of antipsychotic-induced hyponatraemia is not well studied (Shepshelovich et al., 2017, Mannesse et al., 2010). The mechanism by which antipsychotics cause hyponatraemia is not clearly understood. The literature suggests that there may be a tri-directional relationship between psychosis, hyponatraemia and psychotropic medication. Patients with severe psychosis are more likely to develop psychogenic polydipsia (Shinkai et al., 2008) which results in euvolaemic hyponatraemia (Sivaraman and Manivel, 2016). Patients on antipsychotics are also vulnerable to the development of hyponatraemia (Ranga et al., 2014, Ali and Bazzano, 2018). Hyponatraemia, itself, worsens psychosis, through altered neuronal firing (John et al., 2017).

The several mechanisms by which antipsychotics can cause hyponatraemia are related to the mechanism of action of antipsychotics. The primary mechanism of antipsychotics includes dopamine antagonism (Kaplan and Sadock, 2015). It has been shown that ADH continues to be secreted despite relatively low serum osmolalities when the dopamine receptors are blocked (Wells and Forsling, 1992). This suggests that dopamine antagonism reduces the sensitivity of the osmoreceptors in the supraoptic nucleus which then promotes ADH secretion despite low serum osmolalities (Wells and Forsling, 1992).

First-generation antipsychotics have a higher affinity to dopamine (D) 2 receptors, with some second-generation antipsychotics rapidly dissociating from the D2 receptors (Taylor et al., 2018). Second-generation antipsychotics also interact with various other receptors including dopamine D3, D4 and 5-hydroxytryptamine (5-HT) receptors (Brunton et al., 2010). In addition to the effect on dopamine antagonism on the osmoreceptor sensitivity, it is postulated that antipsychotics increase the receptor sensitivity to angiotensin 2, which increases the secretion of ADH and the sensation of thirst (de Leon et al., 1995).

Second-generation antipsychotics can cause hyponatraemia through their action at 5-HT receptors (Mazhar et al., 2021). Antagonism at the 5-HT1c and 5-HT2c receptors

increase serotonergic activity which leads to increased ADH secretion (Madhusoodanan et al., 2002). Antipsychotic medication can also induce hypotension through alpha 1 adrenergic blockade. The baroreceptor reflex is then activated, thus stimulating ADH secretion (Ranga et al., 2014). Antipsychotic use can also increase ADH secretion by potentiating the baroreceptor reflex that is activated by the hypotension caused by the antipsychotics. Antipsychotics can induce hypotension through the antagonism of alpha-1 adrenergic receptors, promoting further fluid retention at the level of the renal tubules (Ranga et al., 2014).

LAIs are generally considered as an alternative to oral antipsychotics and are recommended as monotherapy (Doshi et al., 2015). However, the evidence suggests that there are increasing numbers of patients treated concurrently with both oral antipsychotics and LAI resulting in polypharmacy (Doshi et al., 2015). It can be deduced that the combination of both oral antipsychotics and LAI would increase the risk of adverse effects such as the development of hyponatraemia. However, no studies have been published on this subject. Evidence regarding LAI-induced hyponatraemia currently consists of case reports, indicating that long-acting risperidone and paliperidone may be positively associated with the development of hyponatraemia (Chowdhury et al., 2018, Faizan et al., 2020).

1.2.4.3 Anticholinergic medication

Anticholinergic medications are often used in the treatment of patients with SMI, as adjunct medication to manage the extrapyramidal side effects caused by antipsychotic medication (Toto et al., 2021). The dopamine antagonism caused by the antipsychotics depletes dopamine in the striatum and causes extrapyramidal side effects and subsequent movement disorders (Toto et al., 2021). A retrospective longitudinal study found that anticholinergic medications were widely used in the acute management of patients with SMI with 35.4% of patients being treated with at least one anticholinergic medication during their stay at a psychiatric hospital (Toto et al., 2021). To date, there is no research into the direct relationship between anticholinergic medication and the development of hyponatraemia.

1.2.4.4 Mood stabilisers

Sodium valproate, lamotrigine and carbamazepine are commonly used anticonvulsants that are utilised for their mood stabilising properties. Anticonvulsants have been well-studied as a cause of hyponatraemia (Intravooth et al., 2018). Of the anticonvulsants, carbamazepine has the most evidence as a cause of hyponatraemia (Bragança et al., 2010, Lu and Wang, 2017).

Carbamazepine acts as a sodium channel blocker and this has been proven to alter the sensitivity of the osmoreceptors in the hypothalamus (Bragança et al., 2010). Along with the increased circulation of ADH, it is proposed that the renal tubules also become increasingly sensitive to ADH in carbamazepine treatment (Bragança et al., 2010). The two mechanisms lead to increased water retention and continued ADH secretion despite relatively low serum osmolalities. The incidence of carbamazepine-induced hyponatraemia ranges from 4.8 to 41.5% in patients on carbamazepine for various conditions (Sahoo and Grover, 2018).

There have been numerous cases of severe hyponatraemia due to treatment with sodium valproate (Beers et al., 2010). In addition to increasing the kidney's sensitivity to the ADH, the sodium valproate also inhibits the enzymatic break down of the ADH by inhibiting vasopressinases. This would result in the prolonged half-life of the ADH and further fluid retention (Miller, 2006). It is also postulated that the sodium valproate causes heightened sensitivity of the osmoreceptors in the hypothalamus leading to SIADH (Miller, 2006).

Research regarding lamotrigine-induced hyponatraemia is limited to case studies at this stage. Mewasingh et al (2000) reported two cases that demonstrated a probable relationship between lamotrigine and hyponatraemia. It is also theorised that lamotrigine increases the sensitivity of the osmoreceptors to the action of ADH (Mewasingh et al., 2000). A case report published in 2019 described a middle-aged female patient who developed Takotsubo cardiomyopathy, also known as an apical ballooning syndrome, due to severe hyponatraemia caused by lamotrigine. The hyponatraemia and cardiomyopathy resolved spontaneously on cessation of the lamotrigine (Nakamura and Nagamine, 2019). The case report concluded that the lamotrigine either acted as the ADH

or increased the sensitivity of the renal tubules to the ADH significantly enough to cause severe hyponatraemia.

Lithium's relationship with water homeostasis is the opposite of all the previously described drugs. The administration of lithium can increase both urine production and plasma sodium levels potentially resulting in hypernatraemia (Kazama et al., 2007). Lithium has been proposed as a treatment modality for hyponatraemia; however, this has not been further studied due to concerns of tubule-interstitial nephritis and lithium toxicity (Zietse et al., 2009).

A case-control study published in 2020 established that lithium treatment was associated with reduced hospitalizations due to hyponatraemia (Falhammar et al., 2020a). This occurrence was likely due to the adverse effects of lithium that include polyuria and polydipsia which are caused by the reduced renal response to ADH.

The development of lithium-induced diabetes insipidus is thought to be due to several mechanisms including the reduced renal response to the ADH, resulting in the production of large quantities of hypotonic urine resulting in severe dehydration and hypernatraemia (Blevins and Wand, 1992). Lithium-induced diabetes insipidus can result in the production of over 4000mL of urine in a day (Bendz and Aurell, 1999). Lithium is postulated to reduce the renal tubule response to ADH, thus reducing the kidney's ability to concentrate urine. Lithium is proven to work through second messenger systems including the reduction of adenylate cyclase production as well as cyclic adenosine monophosphate (cAMP) (Bendz and Aurell, 1999, Kaplan and Sadock, 2015). cAMP plays a pivotal role in the formation of aquaporin storage vesicles which in turn allow luminal walls to become permeable to water and aid water reabsorption in the kidneys.

1.2.4.5 Antihypertensive medications

Antihypertensive medications are known to cause hyponatraemia (Falhammar et al., 2020b). Thiazide diuretics are most commonly associated with hyponatraemia. It is postulated that the thiazide diuretics increase permeability of the luminal membranes of the collecting ducts, thus reducing the serum osmolality (Falhammar et al., 2020b). There is less evidence confirming the association between hyponatraemia and the other

antihypertensive drug classes such as calcium channel blockers. This is theorized to be due to the differing mechanisms of actions that do not influence renal filtration, as do thiazide diuretics (Falhammar et al., 2020b).

1.2.5 Psychogenic polydipsia

Psychogenic polydipsia, or primary polydipsia, is a condition characterized by excessive, self-induced water intake and, if prolonged, can result in complications such as hyponatraemia (Dundas et al., 2007). Psychogenic polydipsia was first described in patients with schizophrenia and remains closely linked to patients with SMI (Dundas et al., 2007). Psychogenic polydipsia is a result of dysfunction in the hypothalamic thirst mechanism and subsequent water intake. Abnormalities of the hypothalamus, hippocampus and the surrounding entorhinal cortex are theorized as the cause of psychogenic polydipsia (Verbalis, 2010). It has also been postulated that patients on antipsychotic medications often increase their water intake due to the anticholinergic effects of some antipsychotics which include a dry mouth and constipation (Taylor et al., 2018). Severe cases of psychogenic polydipsia can result in hypervolaemic hyponatraemia with subsequent irreversible neuronal damage (Giuliani and Peri, 2014). Excessive water intake can result in the daily production of over 50 millilitres per kilogram (mL/kg) of urine. This would result in the production of over 3000 mL of urine per day for a person who weighs 60 kilograms (Rennke and Denker, 2013). The normal range of daily urine production in the average adult is 1000-2000 mL per day. Psychogenic polydipsia is generally associated with normal urine concentrating abilities (Atsariyasing and Goldman, 2014).

Mercier-Guidez and Loas (2000) found that 10.7% of the inpatients had psychogenic polydipsia in a French cross-sectional study that monitored the drinking habits of patients with schizophrenia. It was further noted that one third of the patients with psychogenic polydipsia were at risk of developing water intoxication and subsequent hyponatraemia (Mercier-Guidez and Loas, 2000). Patients with schizophrenia are vulnerable to developing psychogenic polydipsia due to the presence of psychosis and the impairment in the functioning of the thirst centre (Alexander et al., 1973, Dundas et al., 2007). The MDR1 gene, which has been linked to more severe cases of schizophrenia, has also

been linked to the development of psychogenic polydipsia in patients with schizophrenia (Shinkai et al., 2008). Patients with SMI and psychogenic polydipsia have worse long-term outcomes than patients who have SMI without the comorbid psychogenic polydipsia (Hawken et al., 2009). Patients with comorbid psychogenic polydipsia suffer increased mortality due to the SMI and additional mortality due to the hyponatraemia caused by the psychogenic polydipsia (Hawken et al., 2009). Hawken et al (2009) demonstrated that patients with psychogenic polydipsia lived nine years less than patients without psychogenic polydipsia.

1.2.6 The effects of hyponatraemia and the impact on SMI

Hyponatraemia causes several neurological symptoms that worsen the prognosis of patients admitted to the hospital (Lu et al., 2016). The osmotic changes cause fluid influx into the neurons and result in neuropsychiatric sequelae, such as irritability, confusion, seizures and changes in consciousness. New-onset depressive symptoms and decline in cognitive functioning have been directly linked to hyponatraemia in patients with no previous psychiatric diagnosis (Fan et al., 2019). However, in patients with SMI, features of hyponatraemia may be misidentified as new-onset psychiatric symptoms and behaviour changes, resulting in under-management of the hyponatraemia (Sivaraman and Manivel, 2016). Due to the overlap between psychiatric symptoms and the manifestations of hyponatraemia, the diagnosis of hyponatraemia in patients with SMI may be overlooked (Guirguis et al., 2013).

Significant neurological symptoms, caused by hyponatraemia, emerge when serum sodium levels fall below 130mmol/L (Smith et al., 2000). Untreated hyponatraemia results in cerebral oedema, seizures, confusion and eventual death (Sivaraman and Manivel, 2016, Mohan et al., 2013). As noted, seizures, confusion and sudden death were of great concern in the investigation into the cause of death of the patients in the LE tragedy (Health Ombud, 2017). The lack of monitoring guidelines for the electrolyte profile in patients with SMI is a possible contributing factor to this often-concealed condition and the subsequent demise of patients with SMI (DeHert et al., 2011).

1.2.7 Monitoring of hyponatraemia in patients with SMI

Monitoring guidelines regarding the management of patients with SMI emphasize the routine monitoring of electrocardiograms, weight and abdominal circumference, cholesterol levels, serum glucose, prolactin levels and extrapyramidal side effects (Marder et al., 2004, Keepers et al., 2020). No routine electrolyte (or sodium) monitoring, except at baseline, is recommended unless clinically indicated (Keepers et al., 2020). This lack of routine monitoring could result in mild or asymptomatic cases of hyponatraemia being undetected. The most conclusive monitoring guidelines available are those recommended for patients on SSRIs which recommend that serum sodium levels be measured at baseline, one month then at three months after SSRI initiation (Mannesse et al., 2013, Taylor et al., 2018).

The LE tragedy resulted in the death of patients with SMI and hyponatraemia was attributed to at least one of the patients' deaths. The details surrounding the deaths of the other patients also highlight the possible under-monitoring, under recognition and underdiagnosis of complications, such as hyponatraemia, in patients with SMI. This brings to the foreground, the need for the study of hyponatraemia in the South African psychiatric context.

Research into the morbidity of patients with SMI continues to be relevant as patients with SMI often succumb to the phenomenon of diagnostic overshadowing and inadequate screening for co-morbid medical conditions (Saloojee et al., 2014). In addition there remains a lack of clear guidance on monitoring of hyponatraemia in patients with SMI (DeHert et al., 2011). This current study is motivated by the mortality in the LE tragedy and the subsequent observations of hyponatraemia by the treating clinicians.

1.2 Hypothesis

There is a significant occurrence of hyponatraemia in patients with SMI which may be due to chronic medications or psychogenic polydipsia.

1.3 Aim of the study

1.3.1 To determine the occurrence of hyponatraemia in the patients admitted at SSMMH with SMI

1.3.2 To establish the possible associations in the cases of hyponatraemia with the demographic and clinical variables of the study participants.

1.4 Study Objectives

1.4.1 To establish the number of cases, trends and severity of hyponatraemia in patients with SMI admitted at SSMMH.

1.4.2 To establish demographic and clinical profiles of the patients who were found to have hyponatraemia.

1.4.3 To determine possible associations between the demographic and clinical variables such as age, gender, diagnosis and medication use with the development of hyponatraemia.

1.4.4 To analyse the trends of sodium testing in the study participants.

Chapter 2: Methods

2.1 Study design

This study was a retrospective records review of the patients with SMI admitted at SSMMH. The sample consisted, largely, of patients transferred to SSMMH between March 2017 and March 2018 from various NGOs following the LE tragedy. The study examined the patient's clinical details including age, gender, diagnosis and prescribed medications. The patients' initial renal function (urea, creatinine and glomerular filtration rates) was recorded. In addition, all the results of the serum sodium levels of each patient that were done by the time of the records review were recorded to assess for the occurrence of hyponatraemia.

2.2 Study population

The study population consisted of all the patients admitted to the psychiatric wards at SSMMH from March 2017 to March 2018. SSMMH is a designated medium to long-stay facility for patients with SMI. The participants in the study were the patients who were previously placed at various LE centres and were discharged to different NGOs in 2016. The admissions to SSMMH began in March 2017 in compliance with the Health Ombud's recommendations following the investigation into the deaths of the patients that occurred at the NGO facilities. In addition to the former LE patients, there were a few patients who were admitted from various acute hospitals and psychiatric hospitals in Gauteng province.

The total number of participants was 398 which included patients who were in the wards during the study period as well as patients who had since died in that period. The sample included nine deceased patients whose records could be retrieved. The remainder of the deceased patients were not included in the study as their records could not be retrieved. The (recordable) deceased patients were included in the study because hyponatraemia is known to worsen mortality, and this may have contributed to the patients' morbidity and mortality. The study included data that was captured across thirteen different wards at SSMMH. Four wards were designated female wards and nine wards were designated male wards. The sample included a total of 332 males and 66 females.

2.3 Data collection

The required information was obtained from each patient's file. The patients' files were stored in each ward where the patients were admitted. The records of the deceased patients were stored in the records department of the hospital.

The following data was collected from each patient's file:

- Patient age and gender
- Date of admission
- Medical diagnosis
- Psychiatric diagnosis
- Medications prescribed, including both psychiatric and medical treatment
- Renal function- urea, creatinine and estimated glomerular filtration rate
- Results of all sodium readings recorded in the patients' files

The information was collated into an excel spreadsheet that contained the fields of the categories described above (Appendix A). Each patient was assigned a patient number and the information was collected from each file systematically. For the purpose of this study, non-psychiatric diagnoses were recorded as "medical diagnosis" to delineate between psychiatric and other medical conditions.

2.4 Data analysis

2.4.1 Sample size calculation

The sample size included all the patients that were admitted in the psychiatric wards at SSSMMH as well as the deceased patients whose records could be retrieved. However, a sample size calculation was still performed in order to ascertain that the size of the study population (398 patients) was adequate to meet the objectives of the study.

The sample size for the study was calculated using the following calculation which is recommended in health prevalence studies:

$$n = \frac{z^2\, p(1-p)}{e^2}$$

n = Calculated sample size

Z = Z- statistic for the chosen level of a confidence interval

P = Proportion or expected prevalence

e = margin of error

With the above formula, the adequate sample size was calculated as 146 (Daniel, 1999).

In this study, the above was calculated with a 99% confidence interval and a proportion of 5.8% as per the 1982 study that established the prevalence of hyponatraemia in patients with schizophrenia (Gleadhill et al., 1982). The margin of error was set at 5 %.

The study population of 398 participants was therefore sufficient to draw definite conclusions with an increased confidence level.

2.4.2 Statistical analysis

A quantitative analysis was performed on the collected data. The data were analysed by both the researcher and a University of the Witwatersrand biostatistician in a collaborative effort.

The patient data were collected and entered into Microsoft's Excel™. Each patient was assigned a patient number and the data was collated and captured according to the patient number. The data was then entered into R Software ™ (R version 3. 4. 2) and used to perform descriptive statistics on the various collected parameters.

The data is presented in tables and graphs. The continuous variables, such as patient age, are reported as mean values ± standard deviation. The categorical variables (such as various medications and diagnoses) are reported as frequencies and percentages.

The data set for this study was generated using mainly categorical scores and analysed using non-parametric tests such as the Chi-squared test. The categorical points included patient gender, medication and clinical diagnosis. The age of the patients was analysed using parametric tests, as it was normally distributed in the sample.

Each serum sodium result collected for each patient was scored as one of four grades. The four recorded grades were either normal (indicating a serum sodium level of 136 mmol/L and above), or mild (sodium level between 130-135 mmol/L), moderate (sodium level between 125-129 mmol/L) and severe (sodium level below 125mmol/L) hyponatraemia for each patient. The scores were further divided into serum results “on admission” and then “post-admission”. The patients were scored as either normal or hyponatraemic post admission. This was to delineate the patients that were admitted to SMMHH with established hyponatraemia and the patients that subsequently developed hyponatraemia during their hospital stay.

The relationship between the cases of hyponatraemia on admission and the sociodemographic variables (gender, medications and clinical diagnosis) was analysed using Pearson’s chi-squared tests. For significant outcomes, Fisher's exact tests were used to compare the number of patients with mild, moderate and severe hyponatraemia against the number of patients without hyponatraemia.

The relationship between the various grades of hyponatremia on admission and the age of patients was analysed using analysis of variance (Anova).

The relationships between the grades of hyponatremia post-admission and gender, psychiatric medication and medical disorders were analysed using Fisher’s exact tests. The relationship between the grades of hyponatremia on admission and the age of the patients was analysed using Welch’s t-test. For all the results, odd ratios were provided for any significant results on Fisher’s exact test results.

To analyse the various clinical entities, the medications and diagnoses of the study sample were grouped according to drug class and type of diagnosis.
The clinical entities were grouped as follows:

Table 1: The medication groups according to the drug class

Drug class	Medications
First-generation antipsychotics	Haloperidol Zuclopenthixol decanoate Chlorpromazine Flupenthixol decanoate
Second-generation antipsychotics	Risperidone Olanzapine Clozapine Quetiapine Amisulpiride
Antidepressants	Citalopram Fluoxetine
Anticonvulsants/mood stabilisers	Sodium Valproate Carbamazepine Lamotrigine Lithium
Sedatives/benzodiazepines	Promethazine Clonazepam Lorazepam
Anticholinergic medication	Orphenadrine Biperiden
Antihypertensives	Enalapril Amlodipine Hydrochlorothiazide
Other medications	Aspirin Simvastatin Thyroxine Antiretroviral therapy Metformin Glimepiride

Clinical diagnosis:

Table 2: The diagnoses groups according to clinical diagnosis

Diagnosis group	Clinical diagnosis
Psychotic disorders	Schizophrenia Schizoaffective disorder Psychotic disorders due to another medical condition Substance induced psychotic disorders
Mood disorders	Bipolar 1 disorder Bipolar 2 disorder Mood disorder due to another medical condition Major depressive disorder
Medical conditions	Hypertension Type 2 diabetes mellitus Epilepsy Human immunodeficiency virus Dyslipidaemia Chronic obstructive pulmonary disease (COPD)
Other psychiatric conditions	Generalized anxiety disorder Post-traumatic stress disorder Antisocial personality disorder Borderline personality disorder Intellectual disability Major neurocognitive disorder
Other medical conditions	Inguinal hernia Pulmonary tuberculosis Previous cerebral vascular accident Deep vein thrombosis

In addition, the testing trends were analysed. To quantify how often the patients were monitored for possible hyponatraemia, the total number and an average number of sodium tests were analysed using the Kruskal-Wallis tests in which the grades of hyponatraemia and the normal levels were used as the fixed factors.

2.5 Ethics

This study was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) (Appendix B). Authorisation to access the patients' records was permitted by SSMMH's hospital manager (Appendix C).

Written consent was obtained by proxy for each patient by the hospital manager. In addition, consent was obtained from the families of the study participants. The patients' details remained confidential. Each of the patient's files was given a number to ensure that a patient's details were not collected more than once. Once the collection of the details was complete, the data sheet contained only patient numbers from 1 to 398.
No names or identifiable data were used in the subsequent analysis, reporting and presentations of the study.

The principal investigator was not involved in the management of the patients in the study sample.

Chapter 3: Results

3.1 Sample overview

A total of 398 patients with SMI admitted at SSMMH were included in this study. There were significantly more males (n=332; 84%) than females (n=66; 16%)($\chi^2 = 182.36$, df = 1, $p < 0.001$). The mean age of patients was 50.3 years (SD $\pm$ 11.24, range 23-78).

Figure 1 displays the distribution of the age range of the patients. The age range with the highest distribution of patients was between ages 51 and 60 years, with 128 (38%) patients of the sample being within this age range. This was followed by the 41- 50 years age range (n=110; 28%).

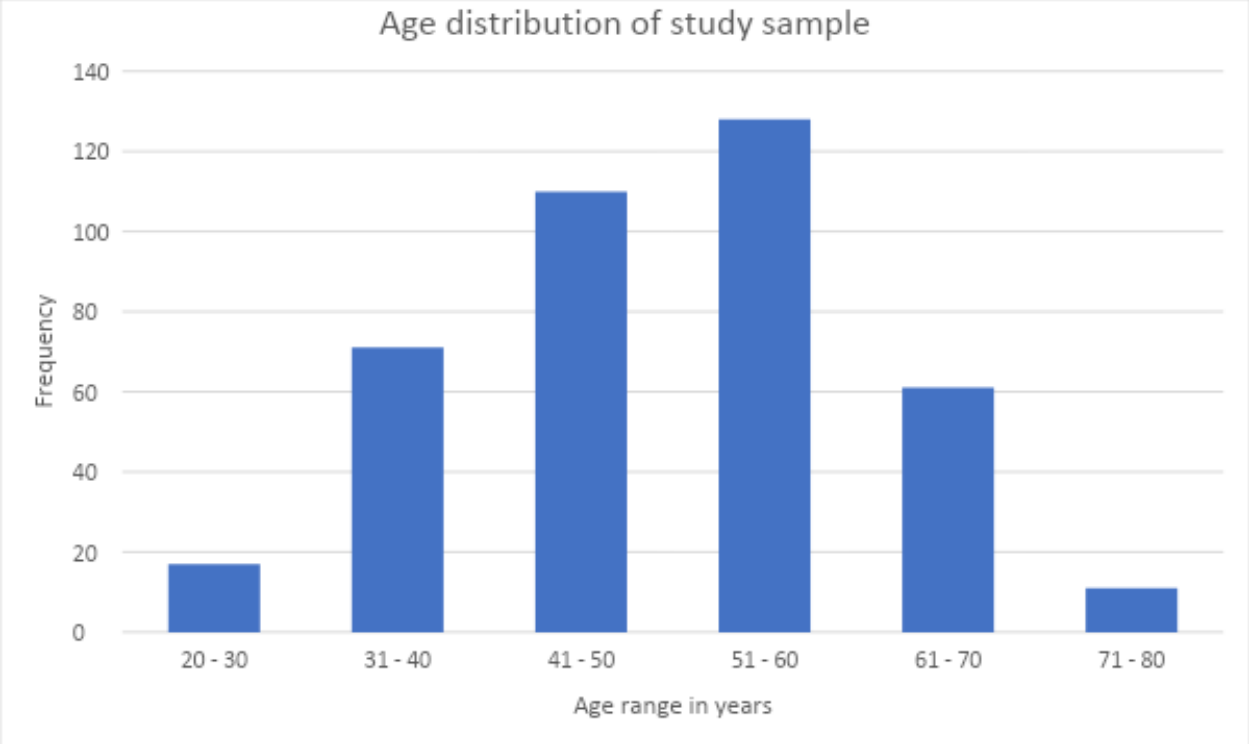

Figure 1: The age distribution of the study sample in years

3.2 Cases of hyponatraemia on admission

Sodium levels were routinely measured for each patient on admission to SSMMH by means of a serum urea and electrolyte panel. As a result, all patients in the sample had urea and electrolytes (UE) done on admission to SSMMH. Each patient's sodium on admission was graded according to the following values:

- Normal serum sodium was recorded for sodium results that ranged from 136 to 146 mmol/L
- Mild hyponatraemia was recorded for values that ranged from 130 to 135 mmol/L
- Moderate hyponatraemia was recorded for serum sodium levels that ranged from 125 to 129 mmol/L
- Severe hyponatraemia was recorded for serum sodium levels that ranged from below 125 mmol/L

Of the 398 patients admitted to SMMHH, 127 patients (31.9%) were found to have hyponatraemia (Figure 2).

These cases of hyponatraemia were graded according to severity (Figure 3). Significantly more patients had normal serum sodium levels on admission (n=271; 68%) compared to those with hyponatraemia ($\chi^2 = 385.21$, $df = 3$, $p < 0.001$). 64 patients (16%) with hyponatraemia on admission had mild hyponatraemia. 51 patients (13%) had severe hyponatraemia on admission. 12 of the patients (3%) had moderate hyponatraemia (Figure 3).

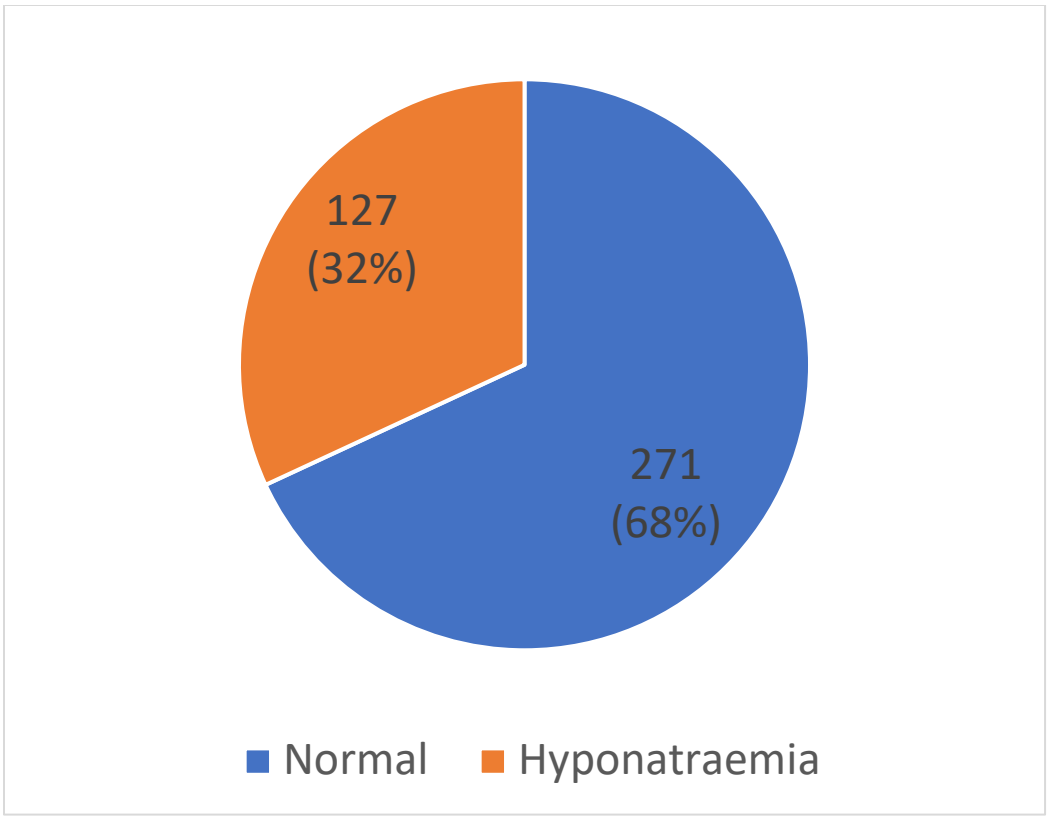

Figure 2: The proportion of the sample admitted to SSMMH with hyponatraemia on admission compared to the patients without hyponatraemia

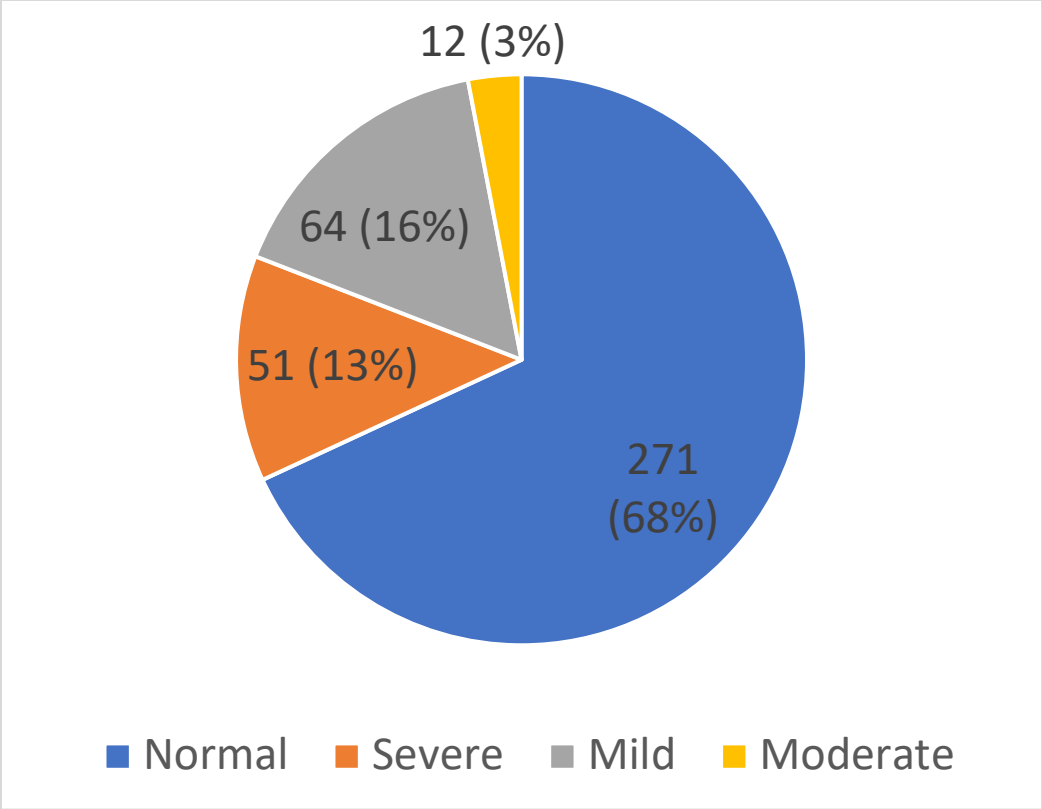

Figure 3: Cases of hyponatraemia on admission according to severity

3.3 Cases of hyponatraemia – post admission

The patients had subsequent UE tests during their hospital stay at SSMMH depending on the clinical indication and their previous sodium levels. This resulted in the post-admission sodium levels being taken on more than one occasion for each patient. For the purpose of this study, the post-admission sodium levels were classified as either normal or hyponatraemic, regardless of the severity. The patients were classified as hyponatraemic if they had at least one reading of hyponatraemia in the post-admission period.

Figure 4 demonstrates how significantly more patients (n=237; 59%) were classified as hyponatraemic during their admission compared to the patients who did not have hyponatraemia throughout their hospital stay (n= 161; 41%) ($\chi^2 = 26.71$, df = 3, $p < 0.001$).

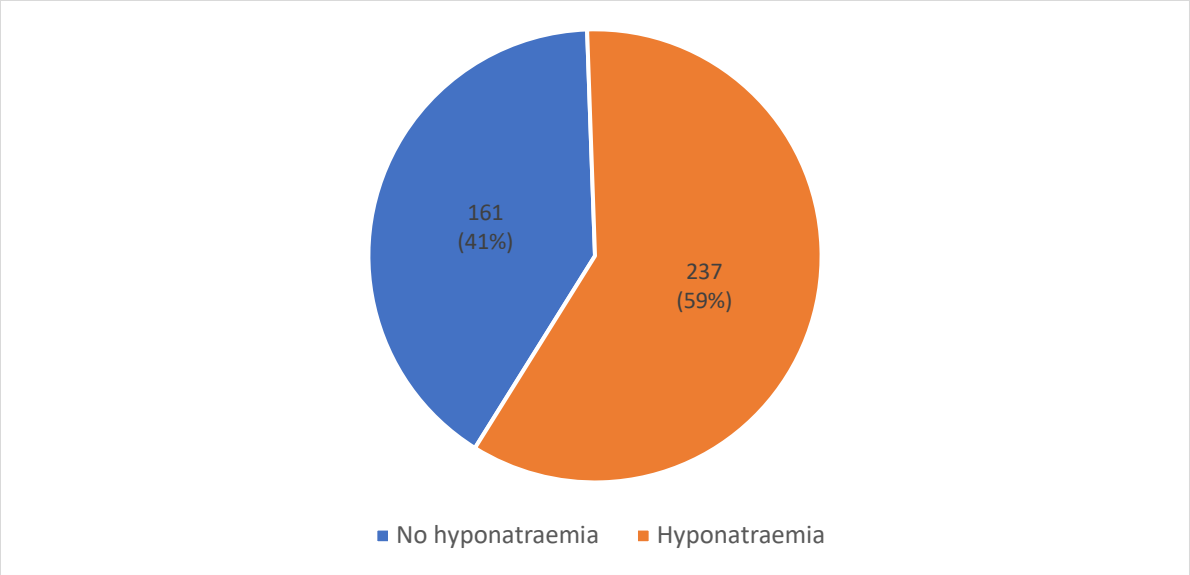

Figure 4: The number and percentage of patients who had hyponatraemia during their hospital stay compared to the patients without hyponatraemia.

The various trends of the occurrence of the hyponatraemia were categorized into four groups:

- Hyponatraemia to normal: this group was designated for the patients who were admitted to SSMMH with hyponatraemia and then subsequently improved to normal sodium levels during their hospital stay.
- Hyponatraemia to hyponatraemia: This group was designated for the patients who had hyponatraemia on admission to SSMMH and continued to have hyponatraemia during their hospital stay.
- Normal to hyponatraemia: This group was designated for the patients who were admitted to SSMMH with normal sodium levels and subsequently developed hyponatraemia during their hospital stay.
- Normal to normal: This group was designated for the patients who were not found to have hyponatraemia on admission to SSMMH or during their hospital stay (Figure 5).

Significantly more patients (n=237; 59%) were recorded to have hyponatraemia at least once during their hospital stay. 27% of the patients (n= 109) were in the normal to

hyponatraemic group, meaning that the patients were admitted with normal sodium levels but subsequently developed hyponatraemia during their hospital stay. 64 of the patients (16%) were in the hyponatraemic to normal group. 64 patients (16%) were in the group that stayed hyponatraemic from their admission and throughout their hospital stay.161 patients (41%) had normal sodium levels on admission to SSMMH and throughout their hospital stay ($\chi^2 = 26.71$, df = 3, $p < 0.001$) (Figure 5).

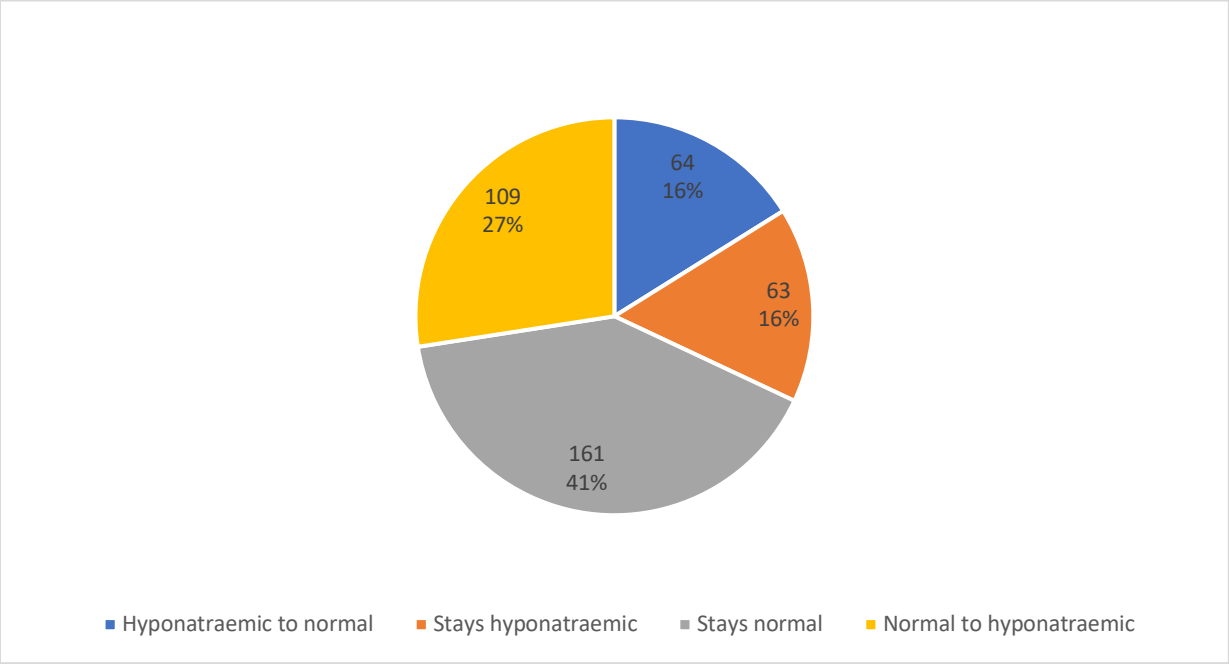

Figure 5: The number and percentage of patients comparing pre and post admission sodium levels

3.4 The trends in sodium testing

All the study participants had a sodium test on admission to SSMMH. This is represented in figure 6. The trends in sodium testing of the patients are demonstrated by the whisker graphs which represent the upper extreme of number of tests and the lower extreme. The graphs also demonstrate the upper and lower quartiles which demonstrate the range in which the majority and the minority of the tests were taken. The patients with the most tests on average were the patients who had moderate hyponatraemia (median = 5 tests). The median number of tests for the patients who had normal sodium levels and those with mild and severe hyponatraemia had the same median number of test of 4.85 (H =

4.47; df = 3, p = 0.215) (Figure 6). In addition, patients with moderate sodium levels had the greatest average number of sodium tests per year at 4 tests per year (H = 8.92; df = 3, p = 0.032; Figure 6).

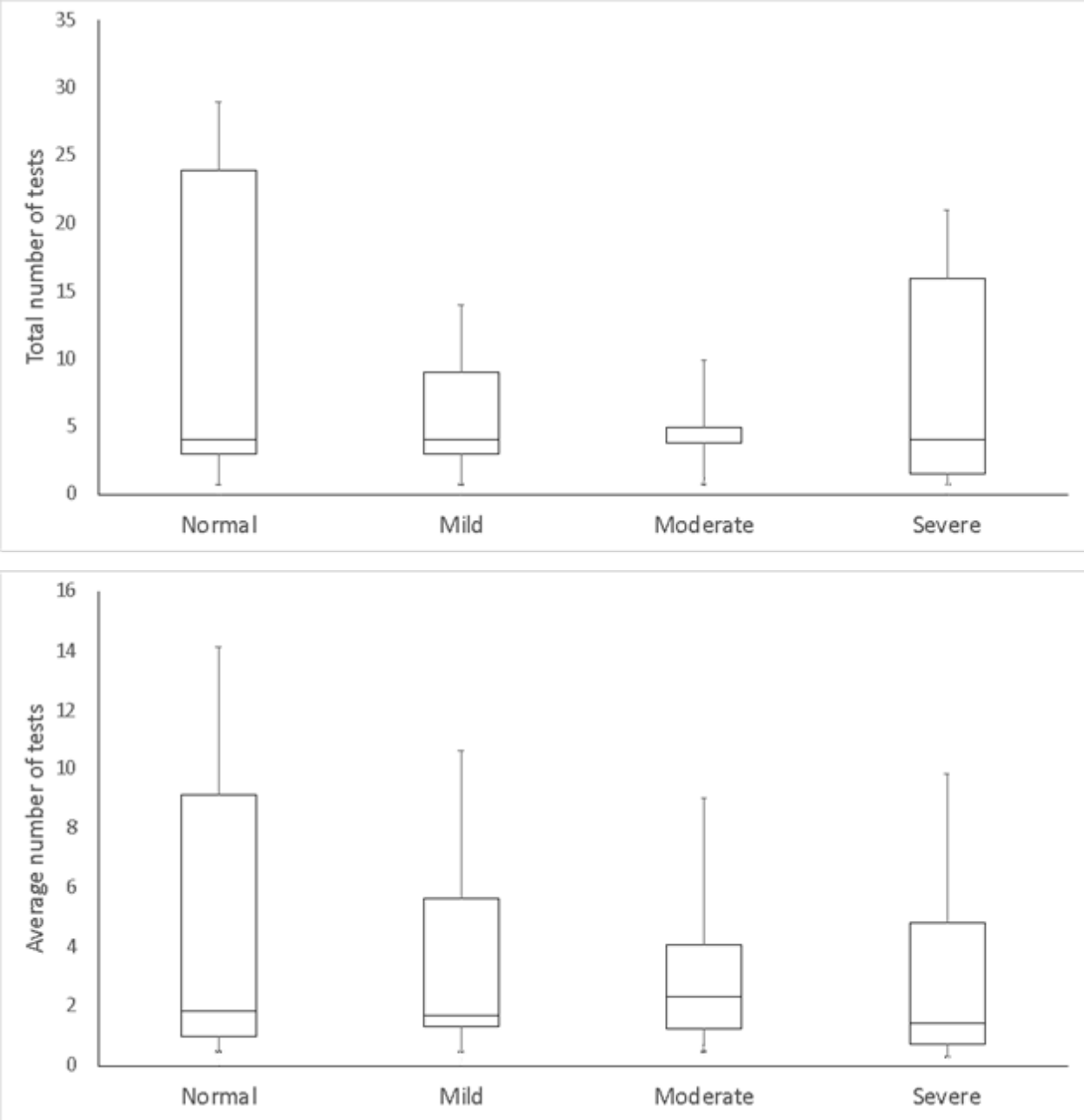

Figure 6: The total number and average number of sodium tests in the study population

3.5 Renal function on admission

370 of the 398 patients (92.96%) were admitted with normal estimated glomerular filtration rates (eGFR) of more than 89 mL/min/1.73m^2.

15 patients (4%) were admitted to SSMMH with mild renal dysfunction with an eGFR of between 60 and 89 mL/min/1.73m^2 (Levey et al., 2005). 9 patients (2%) were admitted with moderate renal dysfunction defined as an eGFR between 30 and 59 mL/min/1.73m^2 (Levey et al., 2005). 4 of the patients (1%) were admitted with severe renal dysfunction which was defined as an eGFR between 15 and 29 mL/min/1.73m^2 (Levey et al., 2005). The findings are demonstrated in figure 7.

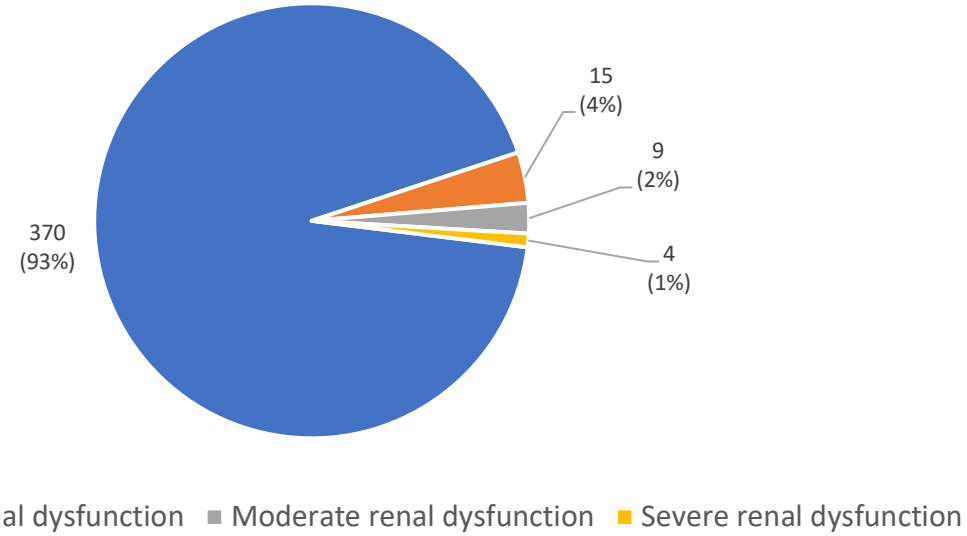

Figure 7: The distribution of normal renal function and renal dysfunction of the patients on admission

3.6 Frequency and distribution of medication and diagnoses

Table 3 provides the frequency distribution of patients on various medications and clinical diagnoses. The medications include all medications prescribed for the psychiatric

conditions and other medical conditions. The clinical diagnoses include all the psychiatric diagnoses and the diagnoses of all the other medical conditions.

Table 3 demonstrates that significantly more patients were on second generation antipsychotics (n=318, p<0.001), anticonvulsants / mood stabilisers (n=230, p=0.002) and anticholinergics (n=249, p<0.001) than by chance.

In contrast, significantly fewer patients were on antidepressants (n=39, p<0.001), sedatives / benzodiazepines (n=93, p<0.001) and other medications than occurred by chance (n=163, p<0.001).

Significantly more patients suffered from psychotic disorders (n=338, p<0.001) and other medical disorders (n=224, p=0.012), whereas significantly fewer patients had mood disorders (n=35, p<0.001) and other psychiatric disorders (n=70, p<0.001) (Table 3). The list and numbers of the most frequently used medications and diagnoses in the sample is represented in figures 7 and 8. Schizophrenia was the most common diagnosis in the study sample (n=318, 79.8%) and orphenadrine was the most common medication prescribed (n=239, 60.1%).

Table 3: Frequency and distribution of hyponatraemia according to medication class and diagnosis

Clinical variable	Absence/Presence	Frequency	Statistics
Antipsychotics - First generation	Yes	218 (55%)	$x^2 = 3.62$, df = 1, p = 0.056
	No	180 (45%)	
Antipsychotics - Second generation	Yes	318 (80%)	$x^2 = 142.32$, df = 1, p < 0.001
	No	80 (20%)	
Antidepressants	Yes	39 (10%)	$x^2 = 257.28$, df = 1, p < 0.001
	No	359 (90%)	
Anticonvulsants/Mood stabilizers	Yes	230 (58%)	$x^2 = 9.61$, df = 1, p = 0.002
	No	168 (42%)	
Anticholinergics	Yes	249 (63%)	$x^2 = 25.12$, df = 1, p < 0.001
	No	149 (37%)	
Antihypertensives	Yes	88 (22%)	$x^2 = 123.82$, df = 1, p < 0.001
	No	310 (78%)	
Sedatives/Benzodiazepines	Yes	93 (23%)	$x^2 = 112.92$, df = 1, p < 0.001
	No	305 (77%)	

Combined antipsychotics (First and second generation antipsychotic)	Yes	77 (19%)	$x^2 = 124.92$, df = 1, $p < 0.001$
	No	398 (81%)	
Other	Yes	163 (41%)	$x^2 = 13.02$, df = 1, $p < 0.001$
	No	235 (59%)	
Psychotic disorders	Yes	338 (85%)	$x^2 = 194.18$, df = 1, $p < 0.001$
	No	60 (15%)	
Mood disorders	Yes	25 (6%)	$x^2 = 304.28$, df = 1, $p < 0.001$
	No	373 (94%)	
Other – psychiatric diagnoses	Yes	70 (18%)	$x^2 = 167.24$, df = 1, $p < 0.001$
	No	328 (82%)	
Other – medical diagnoses	Yes	224 (56%)	$x^2 = 6.28$, df = 1, $p = 0.012$
	No	174 (44%)	

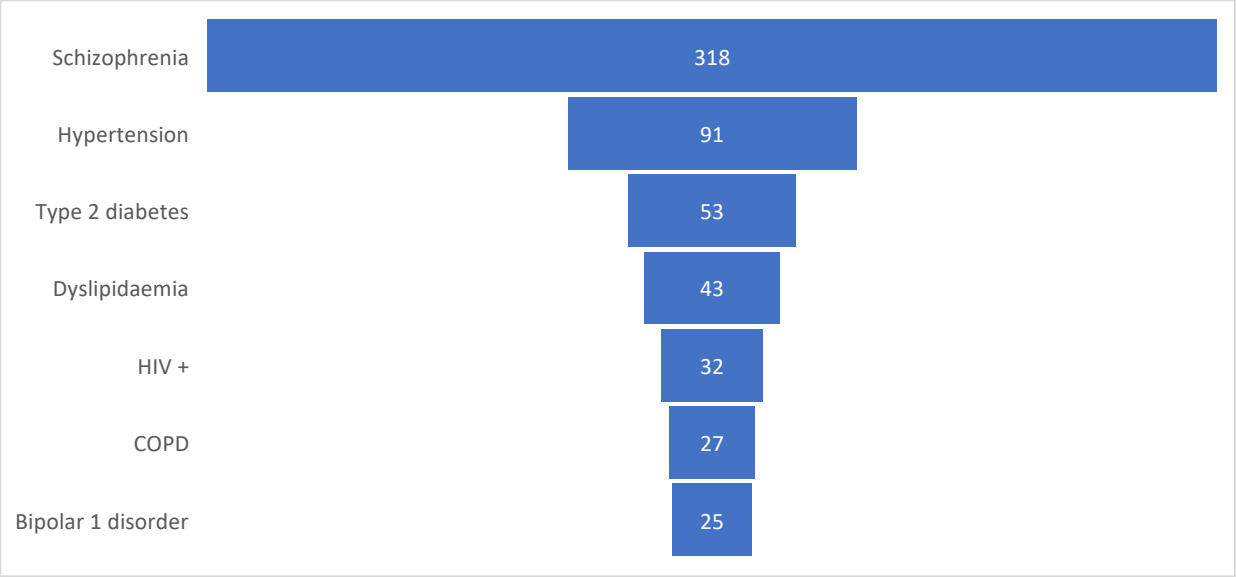

Figure 8: The list and count of the most common diagnoses in the study population

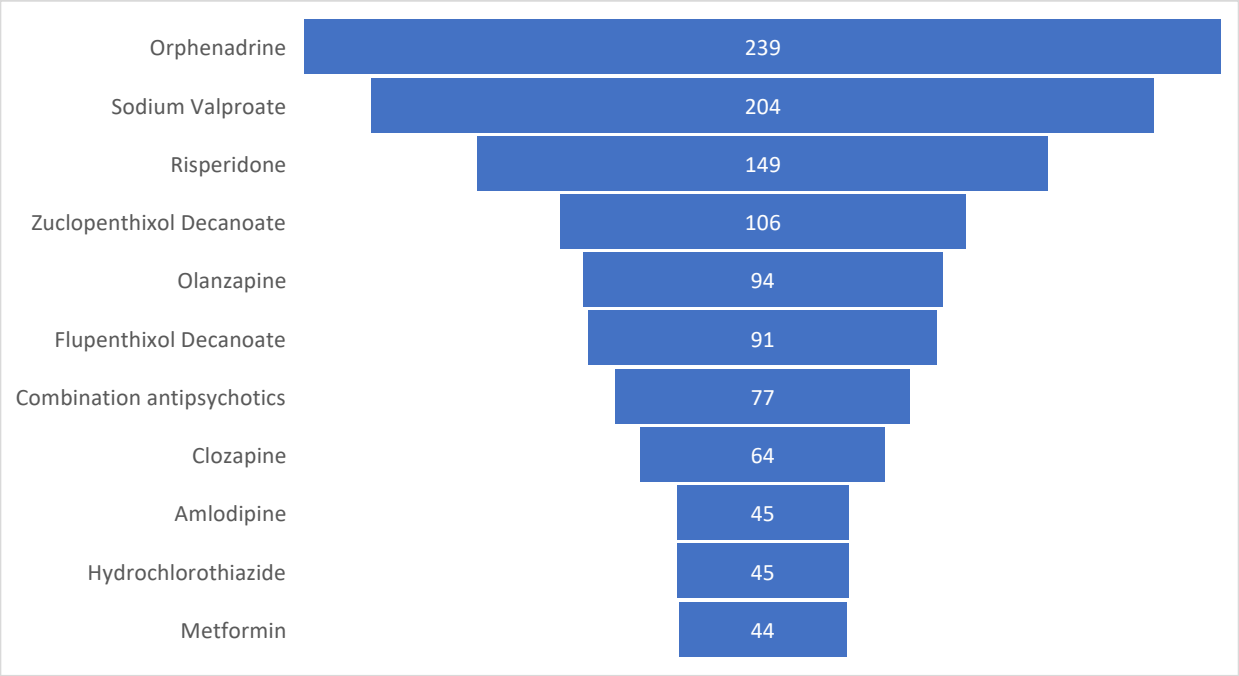

Figure 9: The list and count of the most common medications prescribed in the study sample

3.7 Hyponatraemia compared to the clinical variables

Comparisons between socio-demographic variables, clinical profiles and sodium levels (on admission and post-admission) are shown in Figures 10 to 23.

Figure 10 has top and bottom panels. The top panel represents the sodium levels of the patients on admission to SSMMH. The top panel is graded into normal sodium and mild, moderate and severe hyponatraemia. The bottom panel displays the patients that had normal sodium levels and those with hyponatraemia. In both panels, the numbers are displayed within the graph.

Gender was a significant predictor of hyponatraemia on admission ($\chi^2 = 53.95$, df = 3, $p < 0.001$). Amongst males, 241 patients (78%) had normal sodium levels on admission to SSMMH. This is significantly more than the 29 females (48%) who had normal sodium levels on admission (Figure 10). In addition, significantly more females (n= 23; 38%) had severe hyponatraemia on admission compared to males (n=2; 0.7%) (Fisher's exact test $p < 0.001$, Odds ratio 92.9). During the admission, males were 3.1 times more likely than females to have normal sodium levels (Fisher's exact test $p < 0.001$).

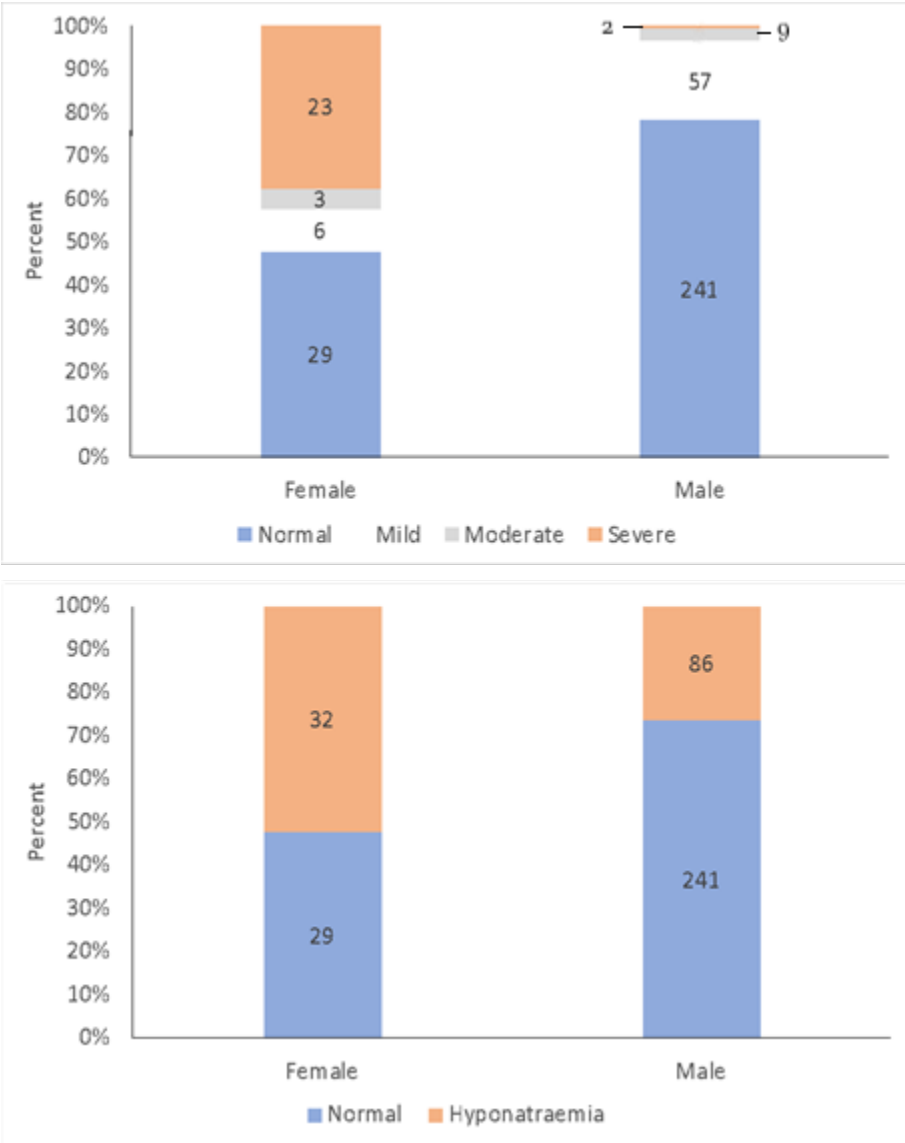

Figure 10: The percent of female and male patients with normal sodium levels and hyponatraemia on admission to SSMMH

Age was not a significant predictor of hyponatraemia on admission to SSMMH (F = 0.86, df = 3, 386, p = 0.461) and post-admission (Welch's t test = -0.60, df = 254.4, p = 0.551). In both periods, patients were similarly distributed by age for those with normal sodium levels and those with hyponatraemia (Figure 11).

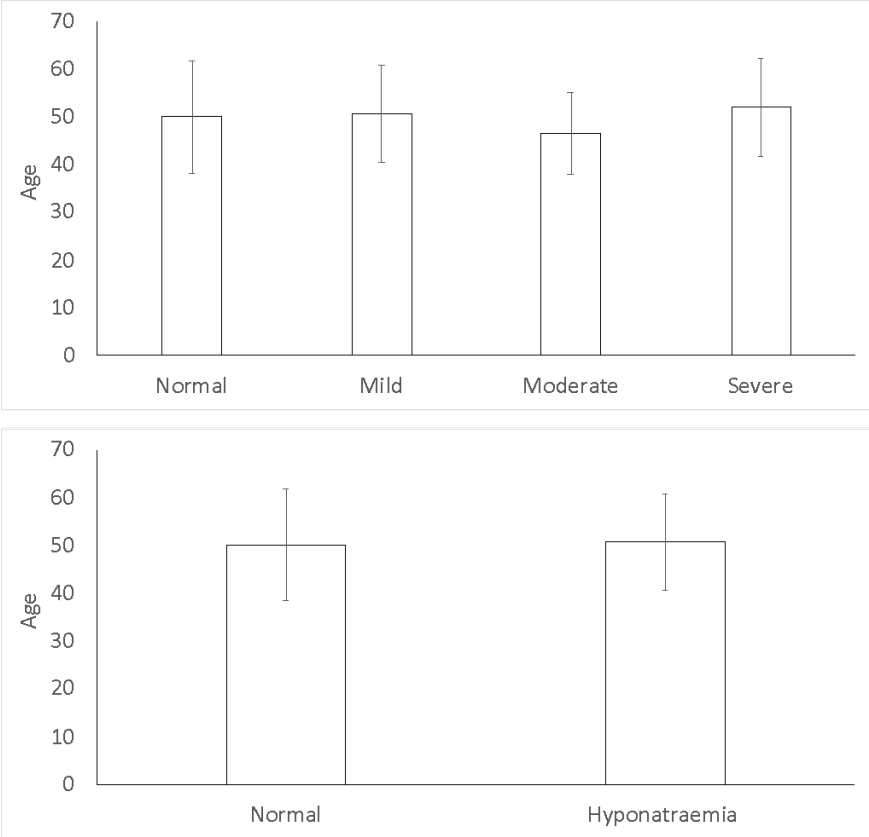

Figure 11: The mean ages of the patients with normal sodium levels and the patients with hyponatraemia on admission (top panel). The mean ages of the patients with normal sodium levels and hyponatraemia post-admission (bottom panel).

In Figure 12, the top panel represents the patients on first generation antipsychotics (on the left) with normal sodium levels and mild, moderate and severe hyponatraemia on admission to SSMMH compared to those not on first generation antipsychotics (on the right). The bottom panel represents the patients on first generation antipsychotics (on the left) with normal sodium levels and hyponatraemia during their hospital stay compared to the patients not on first generation antipsychotics (on the right).

The use of first-generation antipsychotic medication was a significant predictor of hyponatraemia on admission to SSMMH ($X^2 = 9.30$, df = 3, p = 0.026) (Figure 12). Patients not on first-generation antipsychotics were 3.7 times more likely (odds ratio) to show moderate hyponatremia than those on first generation antipsychotics (Fisher's exact test p = 0.072) (Figure 12).

Post-admission, there was no significant difference between the patients that were on first generation antipsychotics and those that were not on first generation antipsychotics (Fisher's exact test p = 0.747). A similar proportion of patients in both groups had normal sodium levels and hyponatraemia (Figure 12).

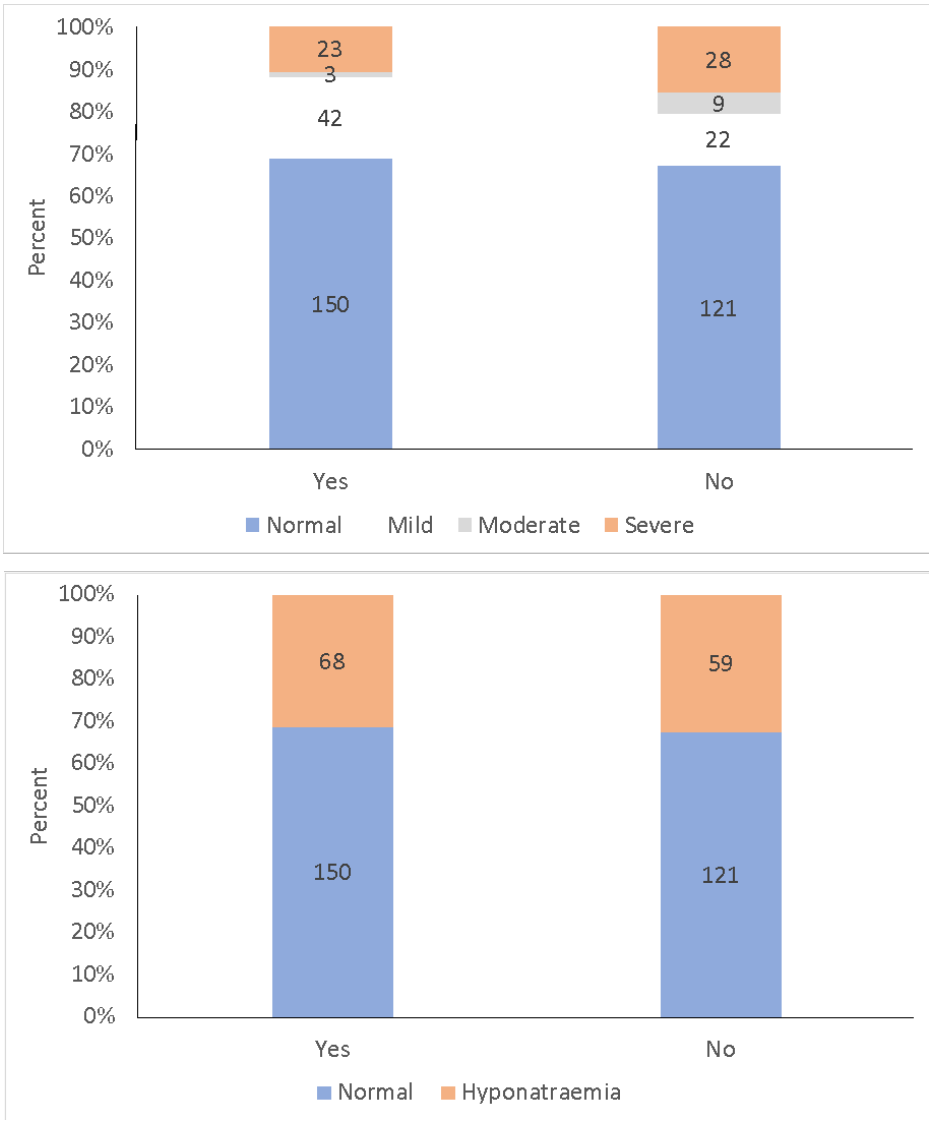

Figure 12: The percentage and numbers of patients on first-generation antipsychotics with normal sodium levels and those with hyponatremia compared to the patients not on first-generation antipsychotics.

In Figure 13, the top panel represents the patients on second-generation antipsychotics (on the left) on admission with normal sodium and those with various grades of hyponatraemia compared to the patients not on second-generation antipsychotics (on the right). The bottom panel represents the patients on second-generation antipsychotics (on the left) with normal sodium and hyponatraemia during their hospital stay compared to those not on second-generation antipsychotics (on the right).

The use of second-generation antipsychotics was not a significant predictor of hyponatraemia on admission ($\chi^2 = 6.03$, df = 3, p = 0.110). A similar proportion of patients on and not on second-generation antipsychotics had normal sodium levels (Figure 13). Post-admission, there was no significant difference between the patients that were on second-generation antipsychotics and those that were not on second-generation antipsychotics (Fisher's exact test p = 0.110). A similar proportion of patients in both groups had normal sodium levels and hyponatraemia (Figure 13).

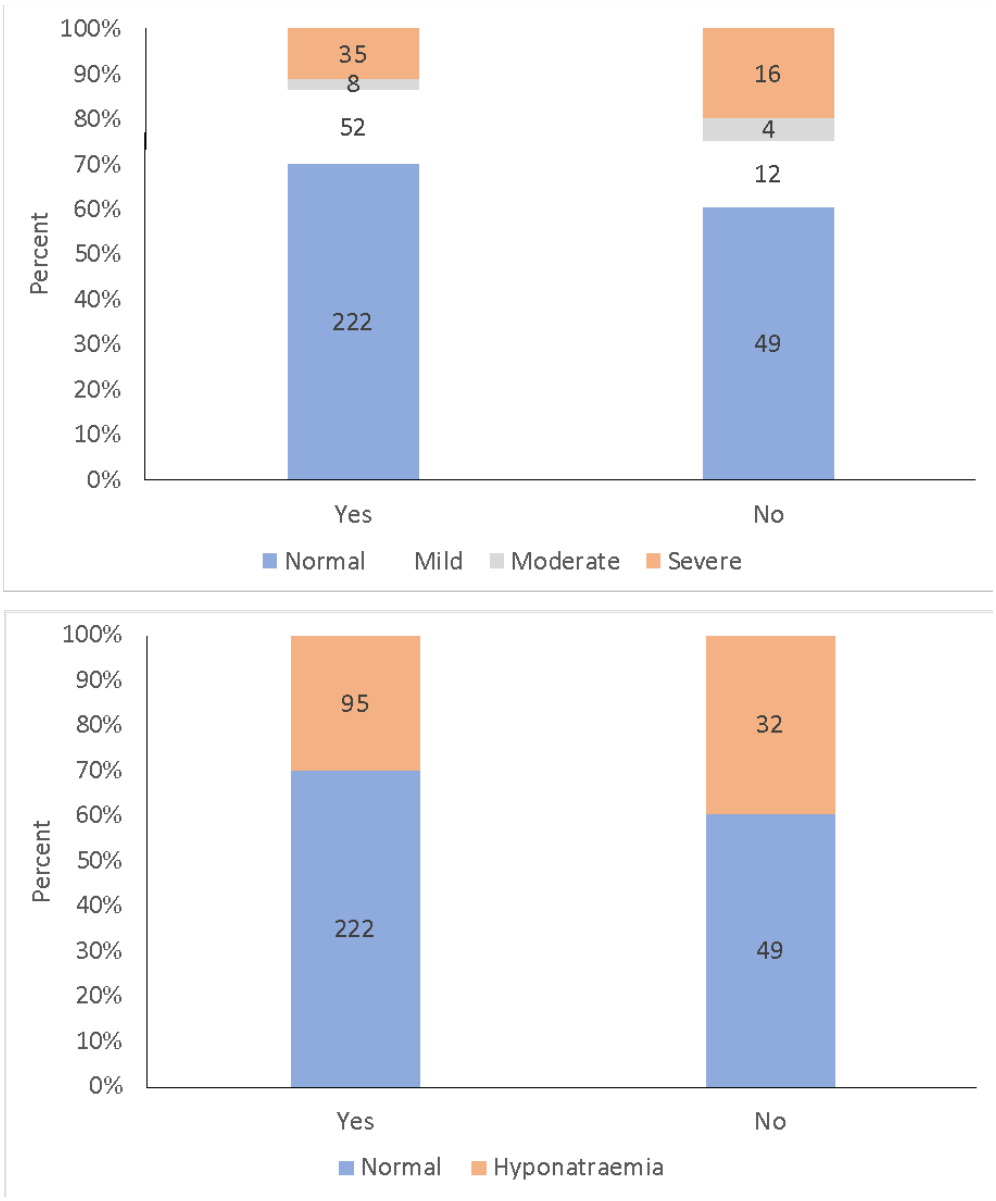

Figure 13: The percentage and numbers of patients on second-generation antipsychotics with normal sodium levels and hyponatraemia compared to the patients not on second-generation antipsychotics

In Figure 14, the top panel represents the patients on antidepressants on admission to SSMMH with normal sodium levels and those with various grades of hyponatremia compared to those that were not on antidepressants (on the right). The bottom panel represents the patients on antidepressants with normal sodium levels and hyponatremia during their hospital stay compared to those not on antidepressants (on the right).

The use of antidepressant medication was not a significant predictor of hyponatraemia on admission ($\chi^2 = 2.90$, df = 3, p = 0.408). A similar proportion of patients that were on antidepressants and those that were not on antidepressants had normal sodium levels (Figure 14). Post-admission, there was no significant difference between patients on and not on antidepressants (Fisher's exact test p = 0.719). A similar proportion of patients in both groups had normal sodium and hyponatraemia (Figure 14).

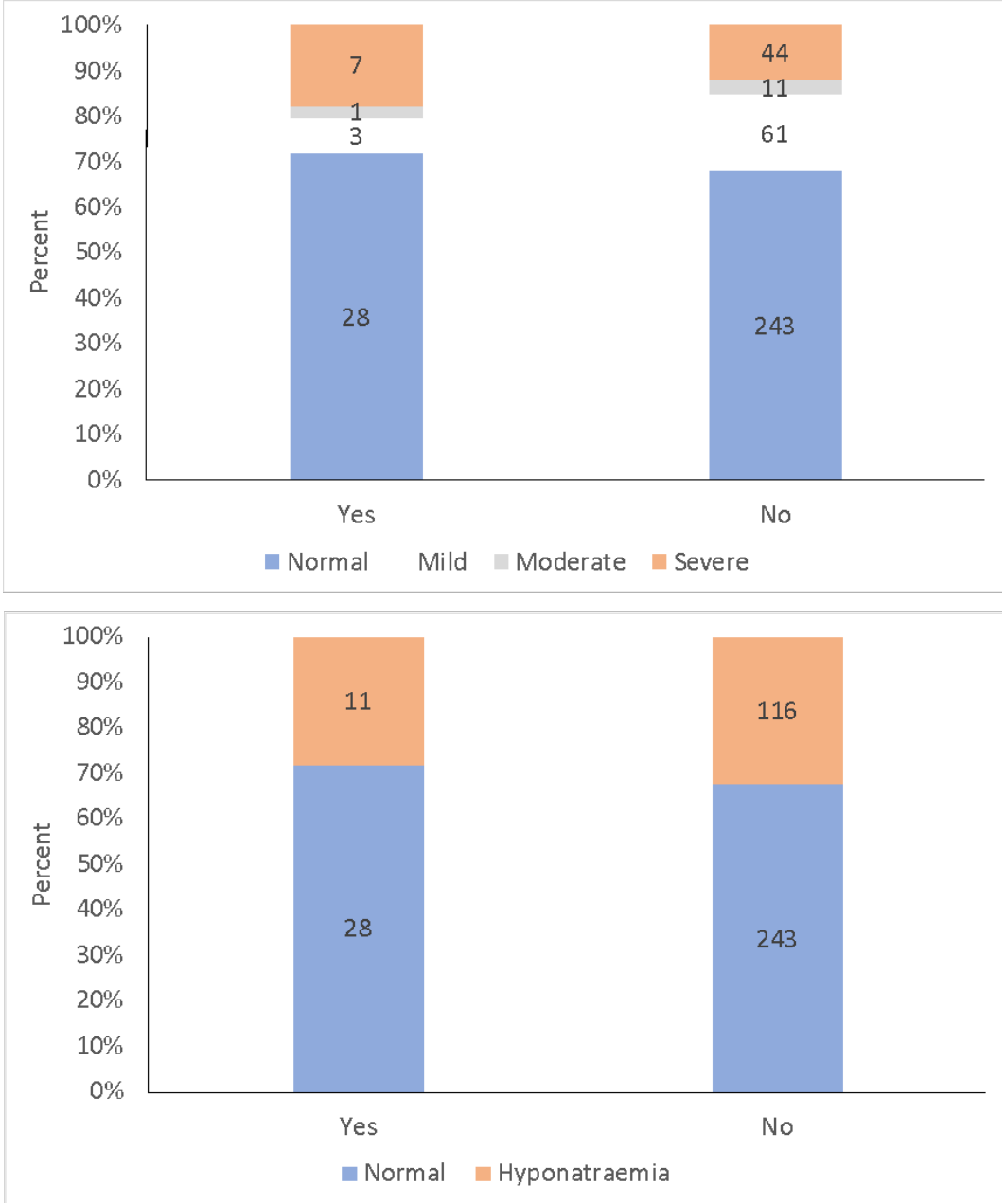

Figure 14: The percentage and numbers of patients on antidepressant medication with normal sodium levels and those with hyponatraemia compared to the patients not on antidepressants.

In Figure 15, the top panel represents the patients on anticonvulsants/mood stabilizers on admission with normal sodium levels and those with hyponatraemia graded into mild, moderate and severe hyponatraemia compared to those not on anticonvulsants/mood stabilizers (on the right). The bottom panel represents the patients on anticonvulsants with normal sodium levels and hyponatraemia during their hospital stay, compared to

those who were not on anticonvulsant/mood stabilizers (on the right). The number of patients is shown within the bars.

The use of anticonvulsant/mood stabilizer medication was not a significant predictor of hyponatraemia at admission ($\chi^2 = 1.51$, df = 3, p = 0.679). A similar proportion of patients on and not on anticonvulsant/mood stabilizers had normal sodium levels (Figure 15). Post-admission, there was also no significant difference between patients that were on anticonvulsant/mood stabilizer medication and those who were not (Fisher's exact test p = 0.745). A similar proportion of patients in both groups had normal sodium levels and hyponatraemia (Figure 15).

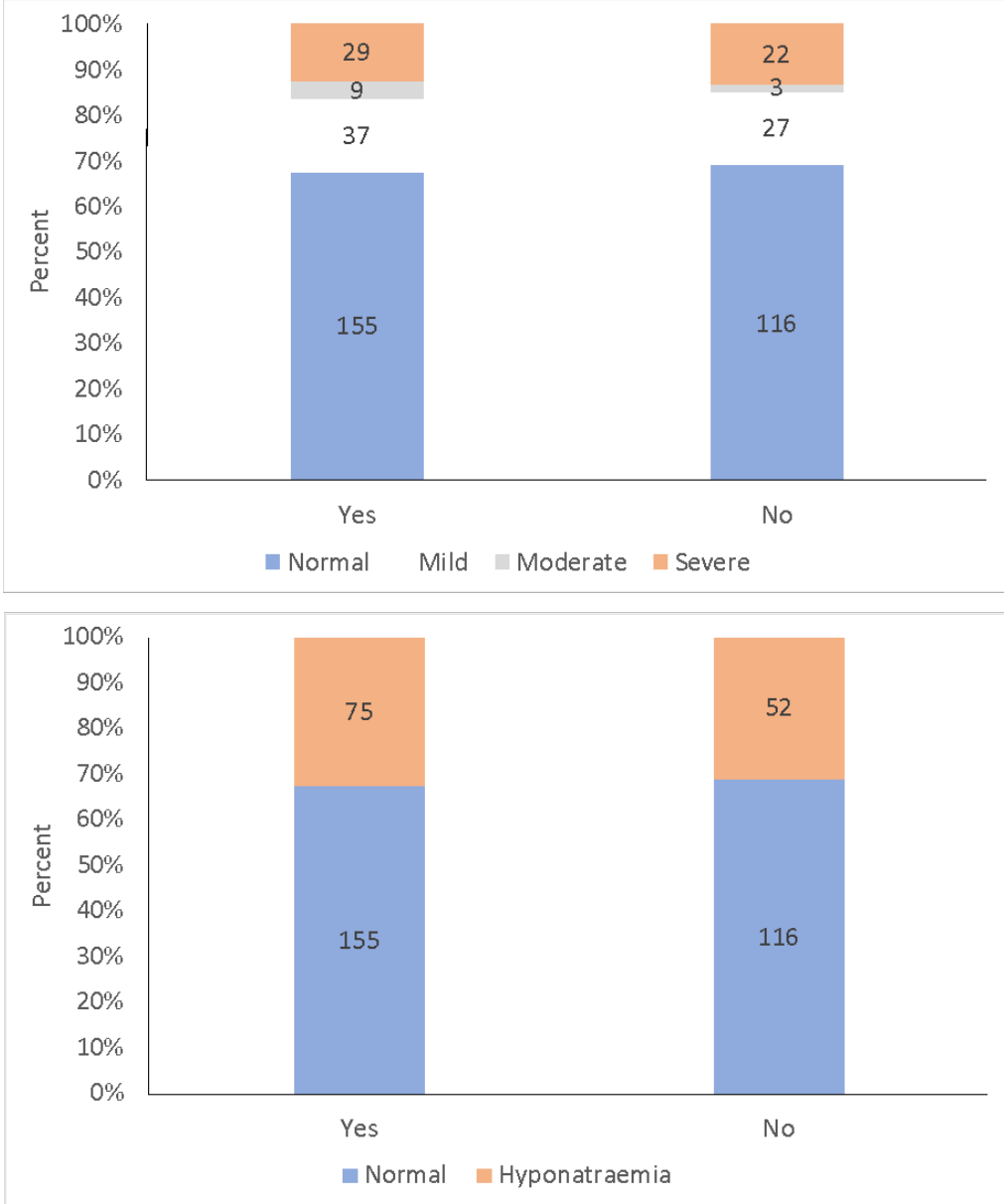

Figure 15: The percentage and numbers of patients on anticonvulsants/mood stabilisers with normal sodium levels and those with hyponatraemia compared to patients not on anticonvulsants/mood stabilisers

In Figure 16, the top panel represents the patients on anticholinergic medication with normal sodium levels and those with hyponatremia graded as mild, moderate and severe hyponatraemia on admission, compared to those not on anticholinergic medication (on the right). The bottom panel represents the patients on anticholinergic medication with

normal sodium readings and those with hyponatraemia during their hospital stay compared to those not on anticholinergic medication (on the right).

The use of anticholinergic medication was a significant predictor of hyponatraemia on admission (χ^2=20.54, df=3, p<0.001)(Figure 16). A significantly greater proportion of patients not on anticholinergics (n=32; 21%) had severe hyponatremia than those on anticholinergics (n=19; 8%) (Fisher's exact test p < 0.001, Odds ratio 3.2)(reference category). Post-admission, there was no significant difference between the patients that were on anticholinergics and those who were not on anticholinergics (Fisher's exact test p = 0.080). A similar proportion of patients in both groups had normal sodium and hyponatraemia (Figure 16).

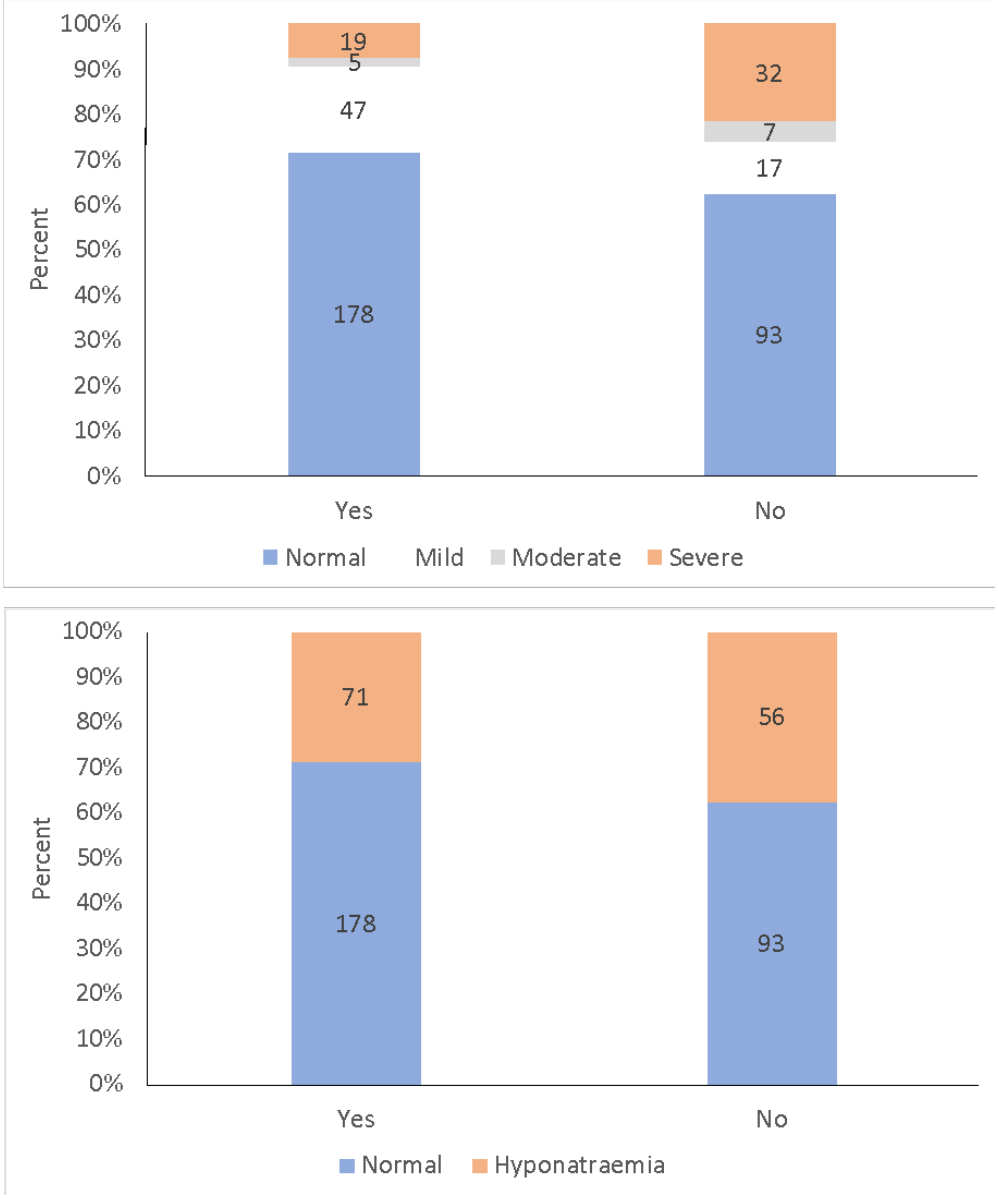

Figure 16: The percentage and numbers of patients on anticholinergic medication with normal sodium levels and those with hyponatraemia compared to the patients not on anticholinergic medications

In Figure 17, the top panel represents the patients on antihypertensive medication with normal sodium levels and those with mild, moderate, and severe hyponatraemia on admission. The bottom panel represents the patients on antihypertensive medication

found to have normal sodium levels and hyponatraemia during their hospital stay compared to those not on antihypertensive medication (on the right).

The use of antihypertensive medication was a significant predictor of hyponatraemia on admission ($\chi^2 = 25.02$, df = 3, $p < 0.001$). Interestingly, patients on antihypertensives were 2.6 times less likely (odds ratio) to have normal sodium levels than patients that were not on antihypertensives on admission to SSMMH (Fisher's exact test $p < 0.001$). Similarly, post-admission, patients not on antihypertensive medication were 2.6 times more likely (odds ratio) to have normal sodium levels than patients on antihypertensive medication (Fisher's exact test $p < 0.001$; Figure 17).

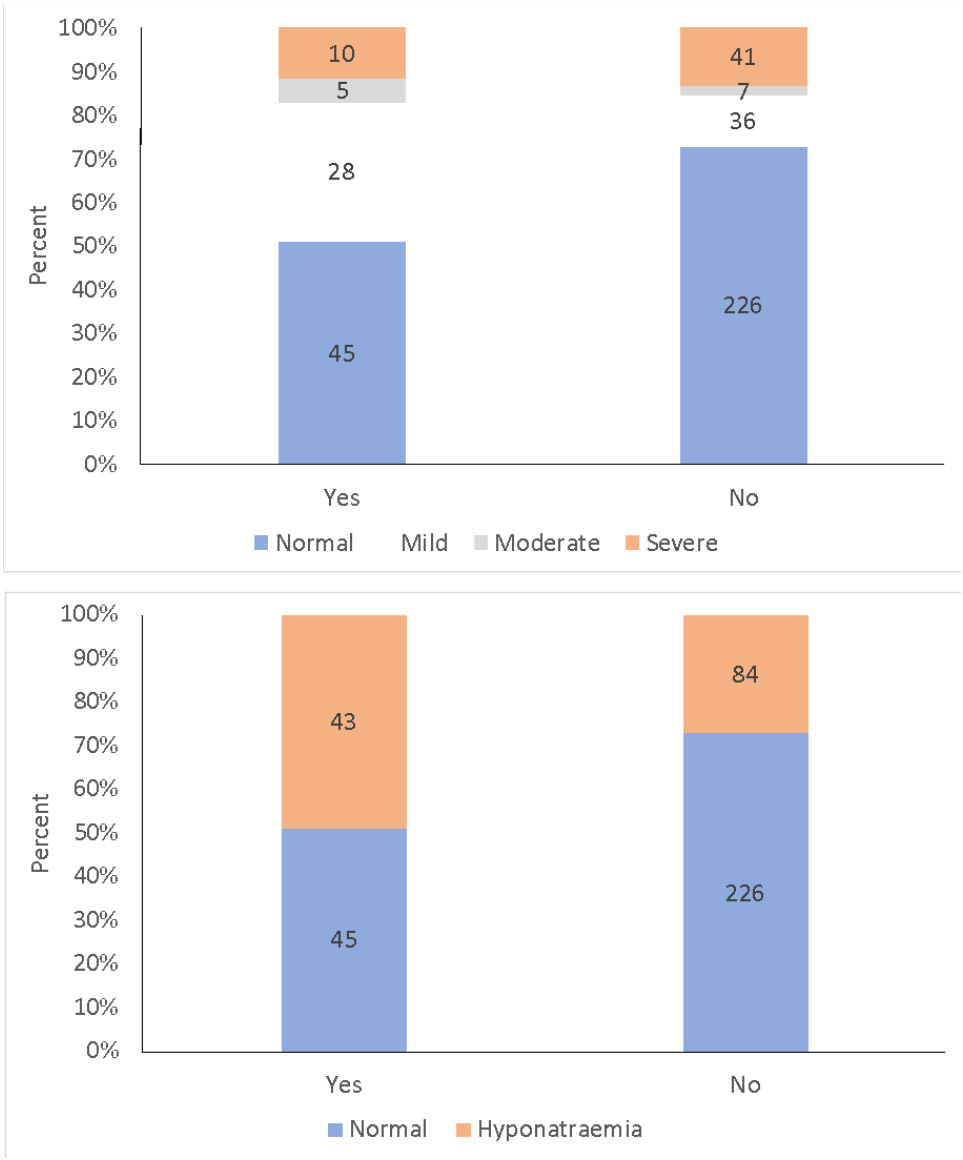

Figure 17: The percentage and numbers of patients on antihypertensive medication with normal sodium levels and those with hyponatraemia compared to the patients not on antihypertensive medications

In Figure 18, the top panel represents the patients on sedatives/benzodiazepines with normal sodium levels and hyponatraemia graded into mild, moderate and severe, on admission, compared to the patients not on sedatives/benzodiazepines (on the right). The bottom panel represents the patients on sedatives/benzodiazepines found to have normal sodium levels and hyponatraemia during their admission, compared to the patients that were not on sedatives/benzodiazepines (on the right).

The use of sedative/benzodiazepine medication was not a significant predictor of the occurrence of hyponatraemia on admission (χ^2 = 1.97, df = 3, p = 0.580). A similar proportion of patients that were on sedatives/benzodiazepine medication and those that were not had normal sodium levels (Figure 18). Post-admission, there was no significant difference between patients who were on sedatives/benzodiazepine medication and those who were not on sedative/benzodiazepine medication (Fisher's exact test p = 0.100)(Figure 18).

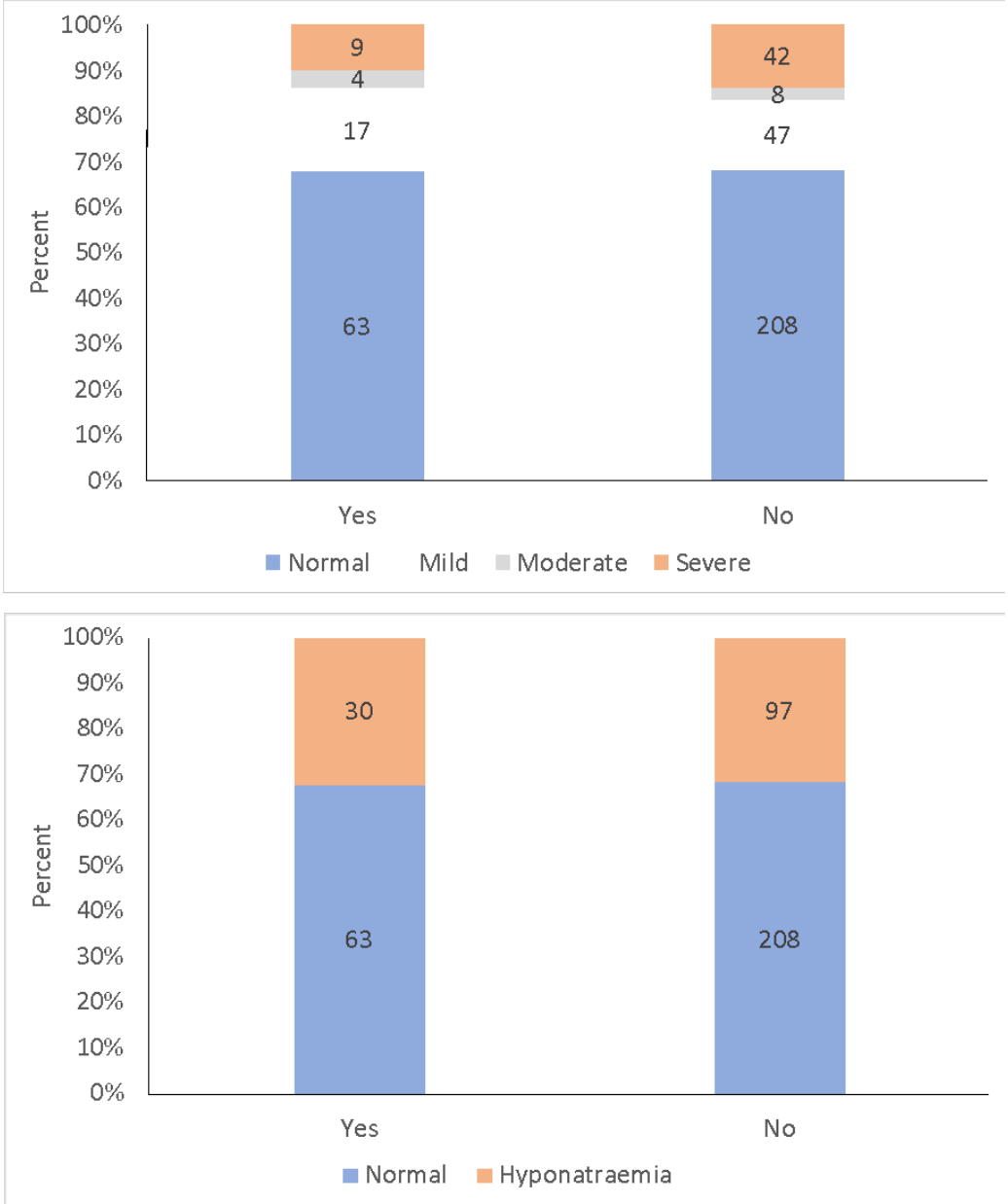

Figure 18: The percentage and numbers of patients on sedatives/benzodiazepines with normal sodium levels and those with hyponatraemia compared to the patients not on sedatives/benzodiazepines

In Figure 19, the top panel represents the patients in the “other medication” group who had normal sodium levels and those who had hyponatraemia graded into mild, moderate and severe on admission. The bottom panel represents the patients on other medication

with normal sodium levels and hyponatraemia during their admission compared to those not on other medication (on the right).

The use of other medication was not a significant predictor of hyponatraemia on admission ($\chi^2 = 2.11$, df = 3, p = 0.549). A similar proportion of patients who were on other medication and those who were not on other medication had normal sodium levels (Figure 19). Post-admission, there was no significant difference between the patients who were on other medication and those who were not in the "other medication" group (Fisher's exact test p = 0.345)(Figure 19).

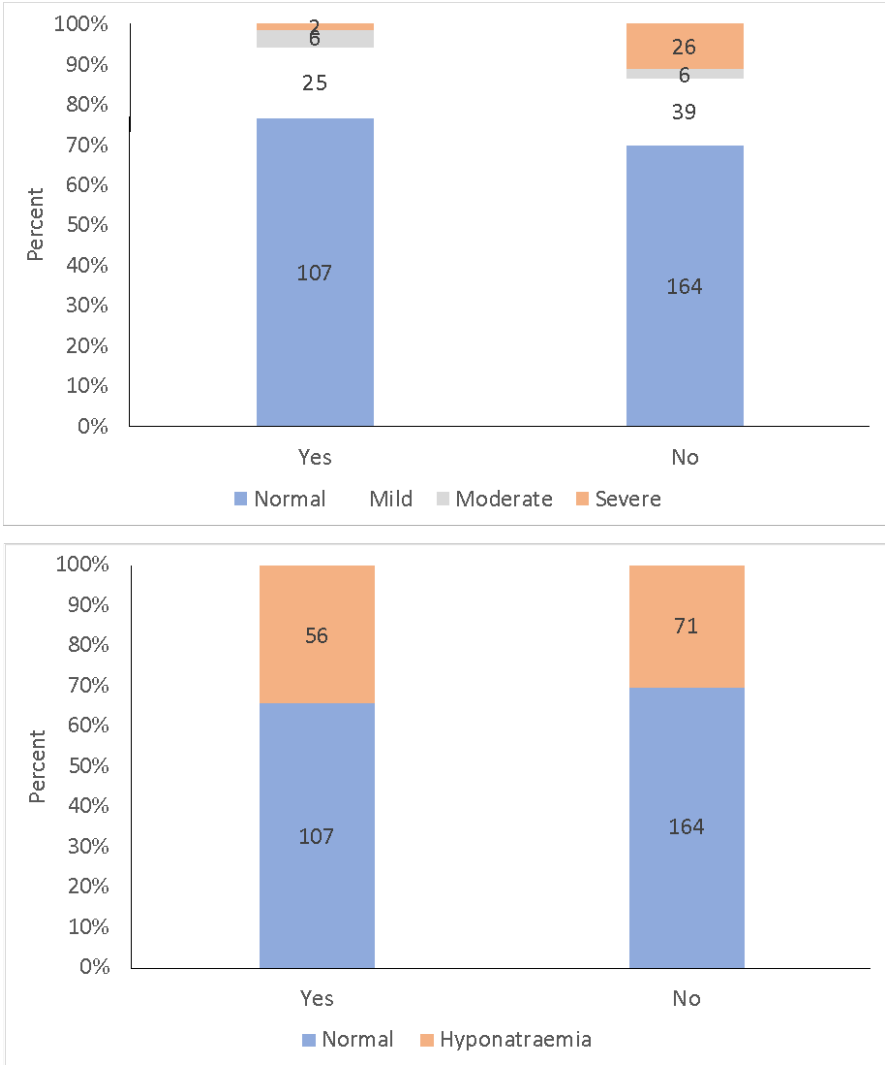

Figure 19: The percentage and numbers of patients on other medication with normal sodium levels and those with hyponatraemia compared to the patients not on other medication

In Figure 20, the top panel represents the patients with psychotic disorders with normal sodium levels and those with hyponatraemia, graded into mild, moderate and severe on admission compared to those without a psychotic disorder (on the right). The bottom panel represents the patients with psychotic disorders with normal sodium levels and hyponatraemia during their hospital stay, compared to patients without the diagnosis of a psychotic disorder (on the right).

Having a psychotic disorder was a significant predictor of hyponatraemia on admission (χ^2 = 13.62, df = 3, p = 0.004)(Figure 20). A significantly greater proportion of patients without psychotic disorders (n= 16; 26%) had severe hyponatremia than those with psychotic disorders (n=35; 10%) (Fisher's exact test p < 0.001, Odds ratio 3.0) (reference category). Post-admission, there was no significant difference between patients with or without psychotic disorders (Fisher's exact test p = 0.103). A similar proportion of patients in both groups had normal and low sodium levels (Figure 20).

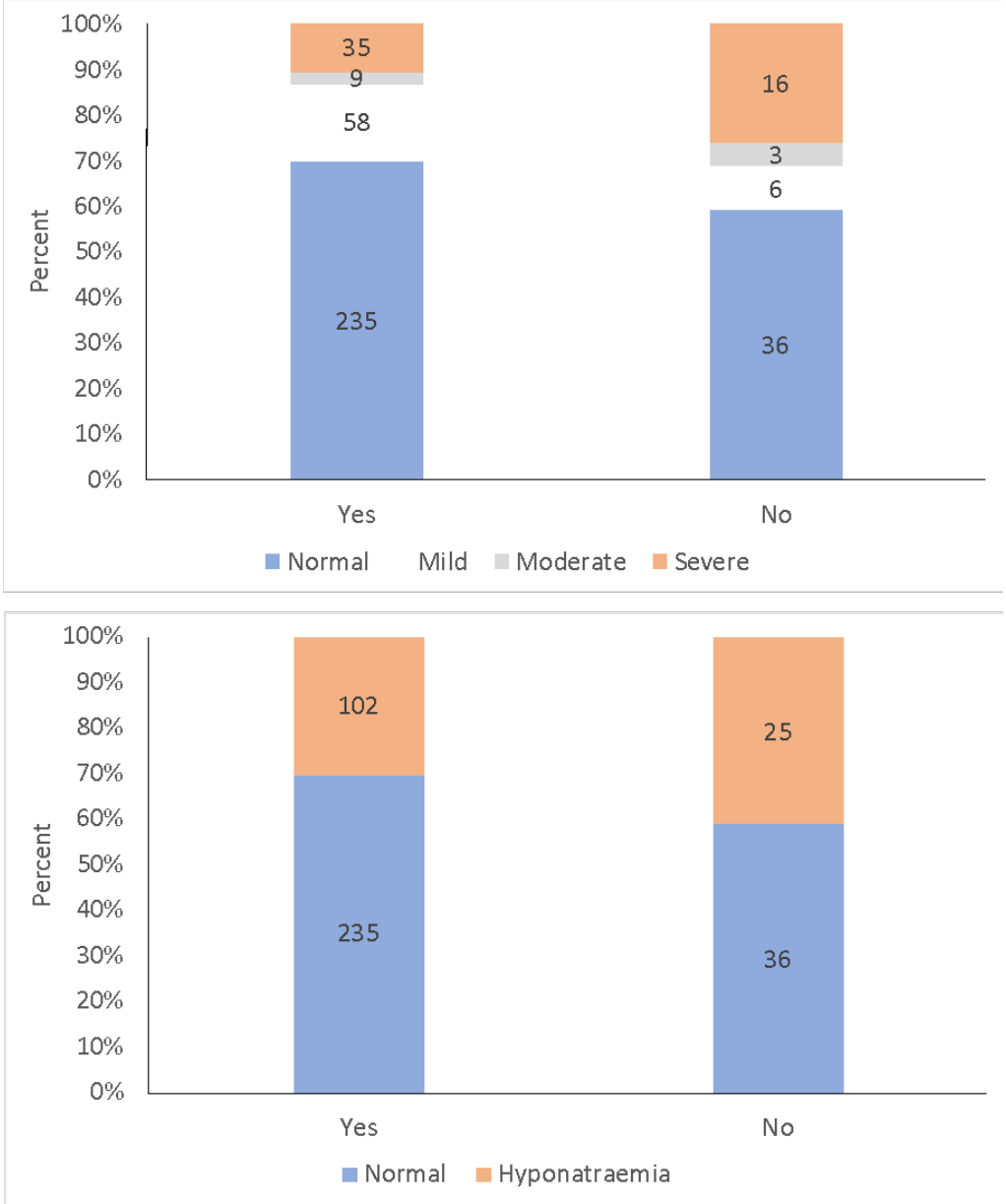

Figure 20: The percentage and numbers of patients with a psychotic disorder with normal sodium levels and those with hyponatraemia compared to the patients without a psychotic disorder

In Figure 21, the top panel represents the patients with a mood disorder found to have normal sodium levels and those found to have hyponatraemia, graded into mild, moderate and severe on admission. They are compared to the patients without a mood disorder (on the right). The bottom panel represents the patients with a mood disorder who were found to have normal sodium levels and those with hyponatraemia during their hospital stay, they are compared to the patients without the diagnosis of a mood disorder (on the right).

Having a mood disorder was not a significant predictor of hyponatraemia on admission ($\chi^2 = 1.44$, df = 3, p = 0.696). A similar proportion of patients with or without the diagnosis of a mood disorder had normal sodium levels (Figure 21). Post-admission, there was no significant difference between patients with or without a mood disorder (Fisher's exact test p = 0.825)(Figure 21).

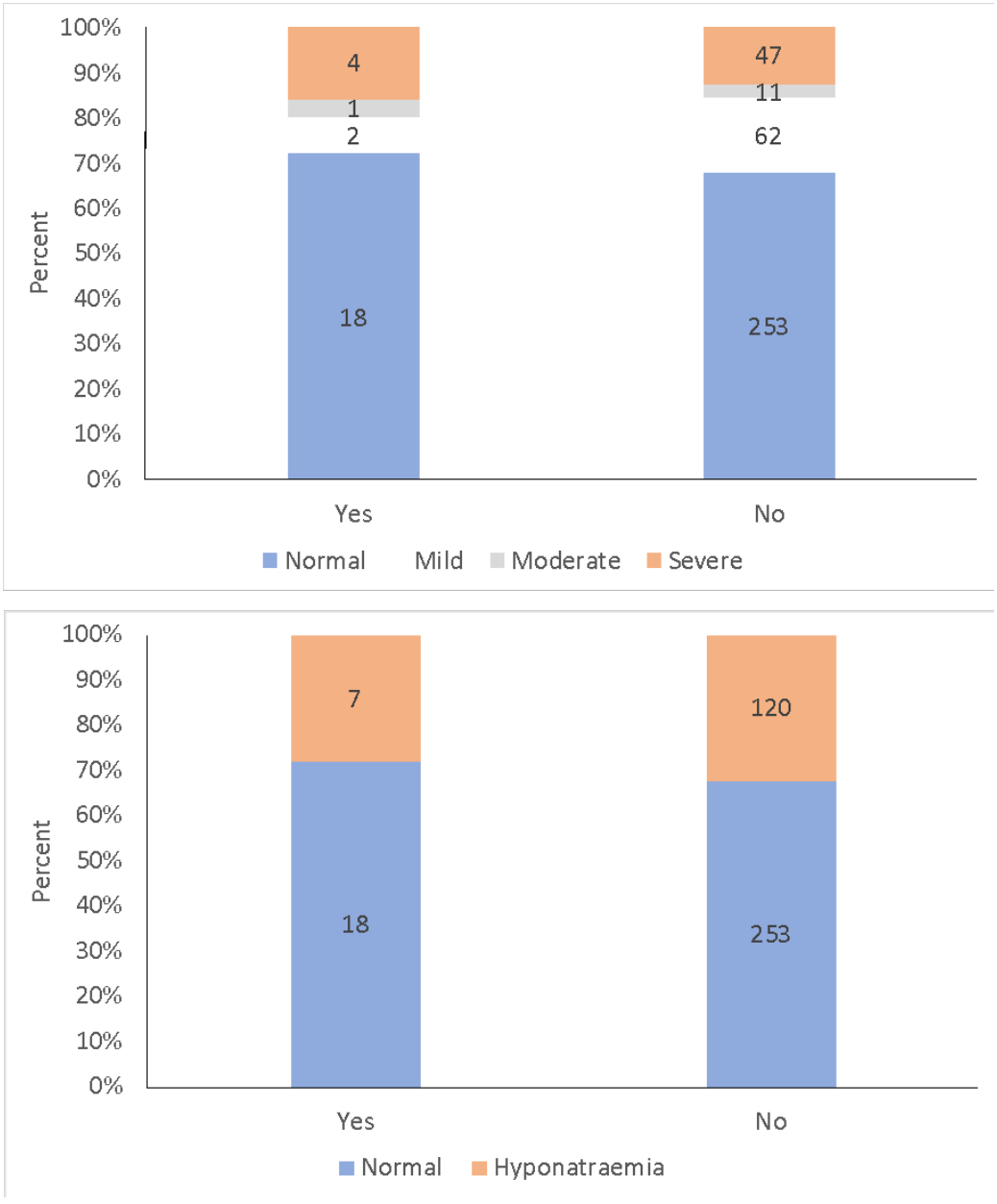

Figure 21: The number and percentage of patients with mood disorders and with normal sodium levels and hyponatraemia compared to the patients without a mood disorder

In Figure 22, the top panel represents the patients with other psychiatric disorders found to have normal sodium levels and hyponatraemia graded as mild, moderate and severe on admission. They are compared to patients without a diagnosis in the other psychiatric disorders category (on the right). The bottom panel represents the patients with other psychiatric disorders found to have normal sodium levels and hyponatraemia during their hospital stay, compared to the patients without the diagnosis of other psychiatric disorders (on the right).

Having other psychiatric disorders was not a significant predictor of hyponatraemia on admission ($\chi^2 = 1.49$, df = 3, p = 0.684). A similar proportion of patients with or without the diagnosis of other psychiatric disorders had normal sodium levels (Figure 22). Post-admission, there was no significant difference between patients with or without other psychiatric disorders (Fisher's exact test p = 0.380). A similar proportion of patients in both groups had normal and low sodium levels (Figure 22).

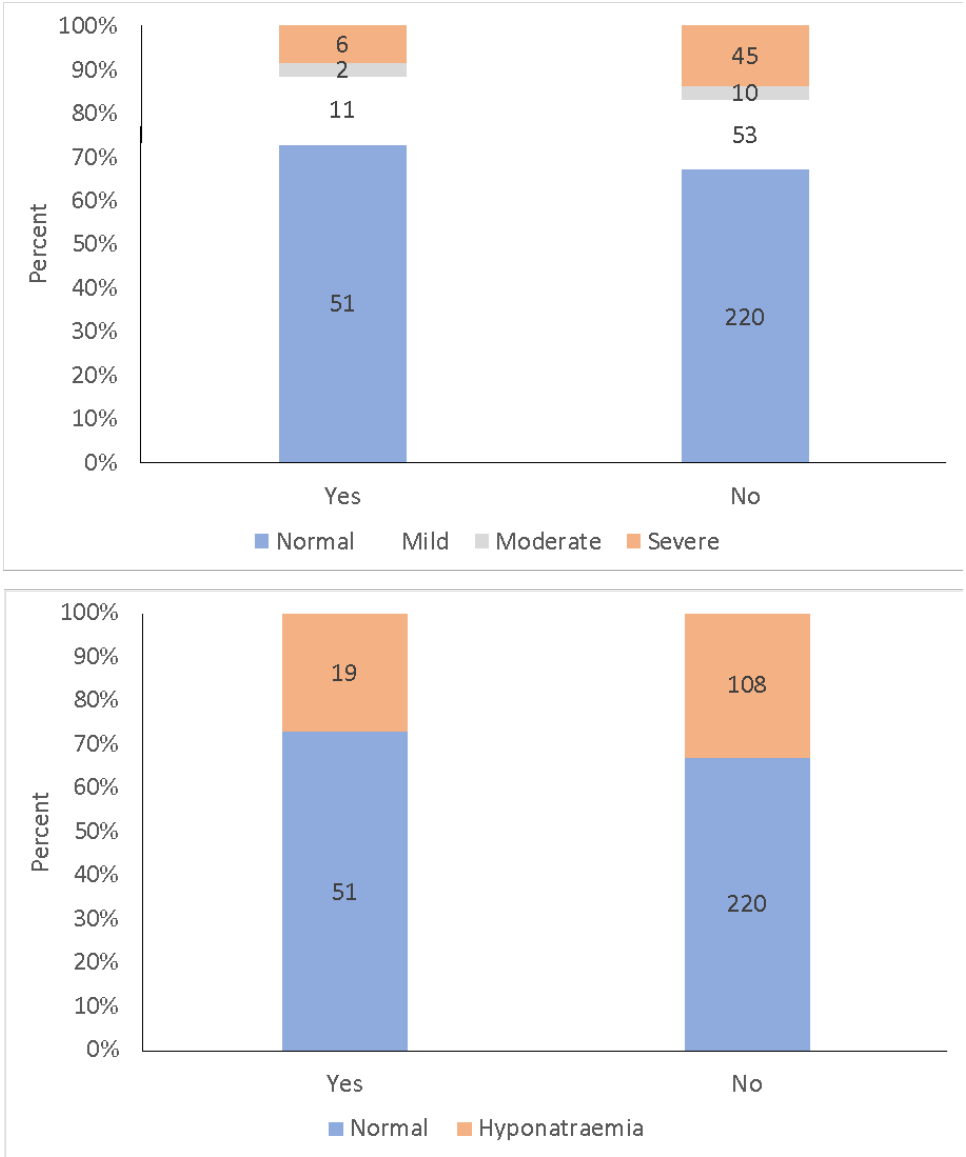

Figure 22: The percentage of patients with other psychiatric disorders and with normal sodium levels and those with hyponatraemia compared to the patients without other psychiatric disorders

In Figure 23, the top panel represents the patients with other medical conditions found to have normal sodium levels and hyponatraemia graded into mild, moderate and severe on admission compared to those without other medical conditions. The bottom panel represents the patients with other medical disorders found to have normal sodium levels and hyponatraemia during their hospital stay compared to those without the diagnosis of other medical disorders (on the right).

Having other medical disorders was a significant predictor of hyponatraemia on admission (χ^2 = 9.36, df = 3, p = 0.003)(Figure 23). A significantly greater proportion of patients without other medical disorders (4%) had mild hyponatremia compared to those with other medical disorders (1.7%) (Fisher's exact test p = 0.012, Odds ratio 2.1) (reference category). However, post-admission, patients with other medical disorders were 1.9 times (Odds ratio) more likely to show hyponatremia than those without other medical disorders (61% vs 32%; Fisher's exact test p = 0.004; Figure 23).

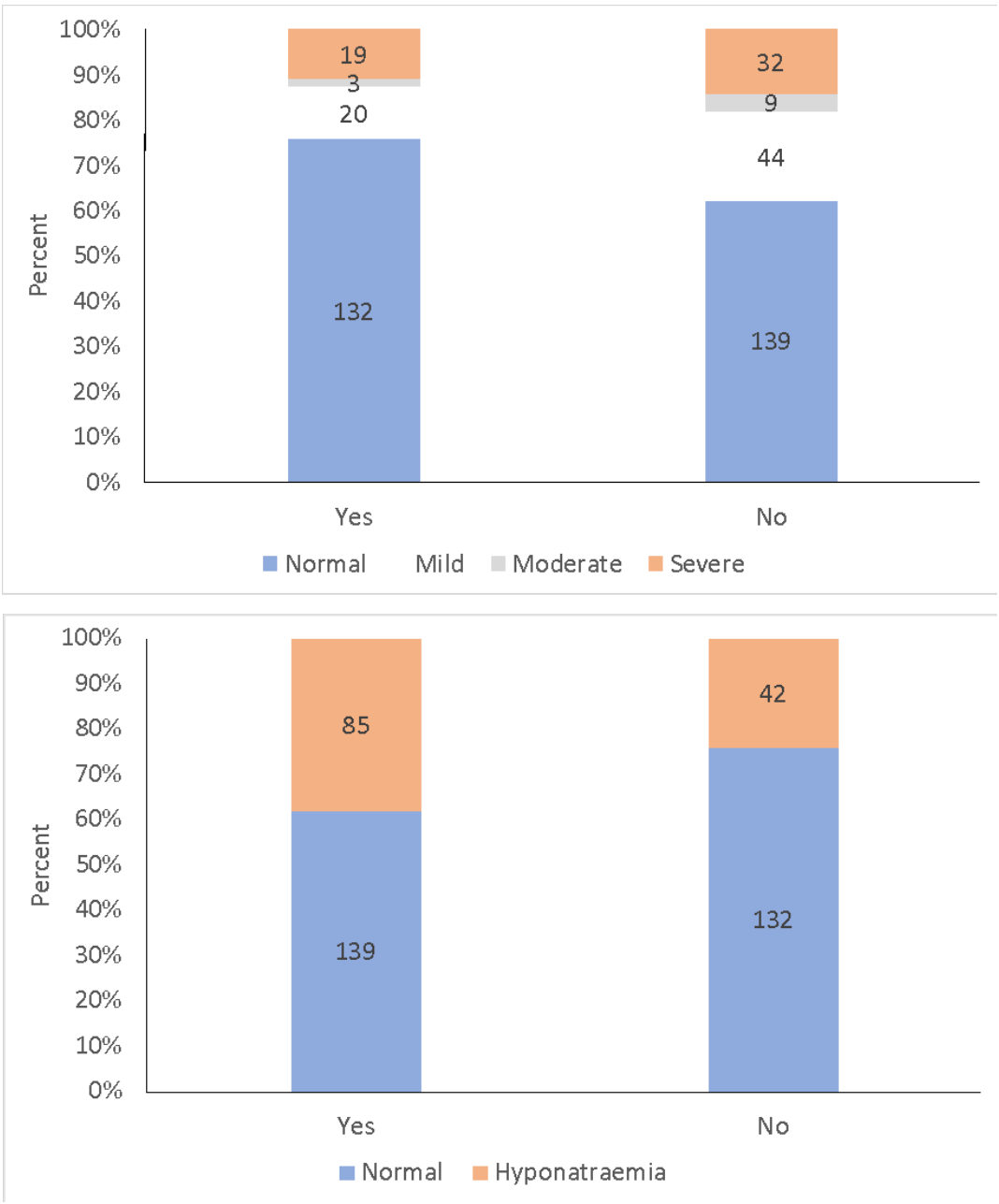

Figure 23: The number and percentage of patients with other medical disorders with normal sodium levels and those with hyponatraemia compared to the patients without other medical disorders

Chapter 4: Discussion

4.1 The occurrence of hyponatraemia – Cases, severity and trends

This study sought to establish the number of cases, severity and trends of hyponatraemia in patients with SMI admitted at SSMMH, among other objectives. In this study, that had a sample size of 398 participants, it was found that 32% (n=127) of the study participants had hyponatraemia on admission. This finding was significantly higher than expected as the prevalence of hyponatraemia in admitted patients with SMI ranges from 0.01% to 6.49% in the literature (Shafti et al., 2019, Lange-Asschenfeldt et al., 2013, Manu et al., 2012, Gleadhill et al., 1982). The number of cases of hyponatraemia found in this study were significantly higher than the 4.9% prevalence established by Lange-Asschenfeldt et al (2013); a study done under similar conditions but with a longer surveillance period. The findings in this study also surpass the prevalence rates established by Manu et al (2012), which reported a 6.49% prevalence of hyponatraemia in patients with SMI on admission to hospital. The findings by Manu et al (2012) remain one of the highest recorded prevalence rates of hyponatraemia in patients with SMI on admission to hospital. In an older study, Ohsawa et al, (1992) found a prevalence rate of 10.5% amongst inpatients with SMI, however this sample also included inpatients with neurological conditions such as severe epilepsy.

The significant occurrence of hyponatraemia in this study was more in keeping with the prevalence of hyponatraemia in patients that are admitted in surgical, medical and intensive care units. Hyponatraemia is well-recognised as the most commonly encountered electrolyte abnormality in general medical wards, with a prevalence of between 20% and 35% amongst admitted patients (Rondon and Badireddy, 2022). However, the literature confirms that the same rates of occurrence are not expected in hospital units that treat patients with SMI (Shafti et al., 2019, Lange-Asschenfeldt et al., 2013, Manu et al., 2012). This particular finding highlights that the patients in the sample were just as vulnerable, if not more, to the development of hyponatraemia when compared to patients in general medical wards. The increased occurrence of hyponatraemia that has been established in this study may be due to factors such as the

combination of psychiatric illness, the long-term treatment with psychotropic medications and psychogenic polydipsia. In addition, the presence of other non-psychiatric medical conditions in the sample likely increased the risk for the development of hyponatraemia in the study participants.

The significant prevalence of hyponatraemia on admission in this sample indicates that the patients developed hyponatraemia prior to hospital admission. This highlights the need for purposeful, routine monitoring of patients with SMI for the development of hyponatraemia on an outpatient basis. With the knowledge that patients with SMI, of older age and comorbid medical conditions are at a higher risk for the development of hyponatraemia, testing and monitoring of sodium levels should be more established as part of the maintenance plan in patients with SMI. Routine monitoring would lead to early detection of the hyponatraemia and early intervention, avoiding further morbidity in patients with SMI.

This study also sought to demonstrate the severity of the cases of hyponatraemia in the study sample. It was found that the majority of the patients reported to have hyponatraemia upon admission had mild hyponatraemia (n=64; 16%). This result is in keeping with the findings from Lange-Asschenfeldt et al (2013) that established that 78% of the cases of hyponatraemia were mild in hospitalized patients with SMI. Although the clinical impact of hyponatraemia increases with its severity, mild hyponatraemia is associated with cognitive impairment and mild neurological abnormalities such as gait disturbances (Adrogue et al., 2022). Both the cognitive impairment and gait disturbances worsen the outcomes of patients with SMI and may be misattributed to the SMI rather than the hyponatraemia (Sivaraman and Manivel, 2016). Mild hyponatraemia is also often asymptomatic, increasing the chances of the hyponatraemia going undetected until complications of the hyponatraemia arise. Mild cases of hyponatraemia may be diagnosed more efficiently with more stringent testing of sodium levels in patients with SMI.

Fewer patients in the sample had moderate (n=12; 3%) or severe hyponatraemia (n=51; 13%), this is in keeping with the literature, as patients with more severe forms of hyponatraemia are more likely to be physically unwell and suffer complications such as

seizures and respiratory depression (Lange-Asschenfeldt et al., 2013, Verbalis, 2010). Such patients are likely to be managed in a general medical ward. The patients in the sample that had moderate and severe hyponatraemia were likely to have had chronic hyponatraemia which results in less severe illness due to the compensation by the aquaporin proteins in the neurons. However, despite the chronicity, moderate and severe hyponatraemia are known to worsen the long-term outcomes of the patients.

In addition to the significant prevalence of the hyponatraemia in the sample, the patterns of occurrence of the hyponatraemia were equally noteworthy. This study demonstrated that 16% (n=64) of the patients continued to have hyponatraemia throughout the study period despite the patients being in a hospital setting i.e., despite clinical intervention. This demonstrates that the patients continued to have hyponatraemia while in the ward despite clinical intervention. This study also found that a further 27% (n=109) of patients were admitted with normal sodium levels but subsequently developed hyponatraemia during their hospital stay. This observation demonstrates the complexity of hyponatraemia in SMI because the patients developed hyponatraemia despite being in a hospital setting where there is continuous monitoring and management. This suggests that the aetiology, in this sample, is likely linked to the SMI, comorbid conditions and the treatment that the patients received while in the ward. The most common cause of hospital-acquired hyponatraemia in patients remains the administration of intravenous hypotonic fluids (Moritz and Ayus, 2007). The use of intravenous hypotonic fluid is not routine in the treatment of psychiatric inpatients. However, intravenous fluids are often indicated in the treatment of comorbid medical conditions and in the administration of intravenous psychotropic treatment (Nasrallah, 2014). In this study sample, the significant use of intravenous fluids was unlikely and there was no evidence of use of intravenous psychotropic medications.

Psychogenic polydipsia is another significant cause of hyponatraemia due to hypotonic fluid intake that may occur in a hospital setting. Mercier- Guidez and Loas (2000) studied water intoxication in over 300 inpatients with SMI and demonstrated that inpatients with SMI were still able to have severe polydipsia that resulted in hyponatraemia (Mercier-Guidez and Loas, 2000). It has been demonstrated that between 5 and 20% of patients

can have psychogenic polydipsia despite being closely monitored in a ward (DeLeon et al., 1993, Mercier-Guidez and Loas, 2000). To further confirm whether the cases of hyponatraemia in this study were caused by psychogenic polydipsia, water-intake monitoring of the patients would have to be implemented in the ward. In addition, the measurement of the patient's urine osmolality would further confirm the psychogenic polydipsia as the cause of the hyponatraemia.

4.2 The demographic profiles of the patients with hyponatraemia

This study found that the most significant demographic variable associated with hyponatraemia was being female. A larger proportion of patients who had hyponatraemia were female (n=32; 52%) and the females had more cases of severe hyponatraemia on admission to SSMMH (n=23). This has been observed in other studies, Mohan et al (2013) found that there was a higher prevalence of hyponatraemia in females (almost double) compared to males. Wang et al. (1993) proposed that this occurrence was attributed to the smaller body sizes of females as well as the effect of oestrogen on the secretion of ADH. This is confirmed by the propensity of female patients to experience water retention in the luteal phase of their menstrual cycle, indicating increased ADH sensitivity (Nishimura et al., 2019). The effect of ADH on the kidney is modified by oestrogen, resulting in variations in diuresis and subsequent sodium control. Oestrogen is understood to have diuretic properties, thus reducing ADH secretion by decreasing the osmoreceptor sensitivity and increasing the threshold required by the renal tubules to retain fluid (Nishimura et al., 2019).

In this study, age was not found to be a significant predictor of hyponatraemia in the sample, despite multiple studies concluding that age was a significant risk factor for the development of hyponatraemia (Mohan et al., 2013, Hawkins, 2003). The patients were similarly affected by the hyponatraemia despite the wide range in age. As previously discussed, the literature postulates that age-related dysfunction of the hypothalamic-pituitary-renal axis causes hyponatraemia in the elderly (Cowen et al., 2013). The finding in this study was also unexpected because as the patients age, they are prone to having

comorbidities such as pulmonary disease, malignancies and disorders of the central nervous system which are known to cause SIADH (Spasovski et al., 2014). The similarity in the occurrence of hyponatraemia in the various ages in this study suggests other possible causes for the hyponatraemia besides age-related pituitary dysfunction. This finding suggests that a possible cause of the hyponatraemia could be due to a variable that affects all the age groups equally such as the psychotropic medications. Medications such as risperidone, orphenadrine and sodium valproate were widely used in this study sample and can be postulated as possible causes (figure 8).

4.3 The clinical profiles of the patients with hyponatraemia

The study found that hypertension was the most common non-psychiatric medical diagnosis, with 23% (n=91) of the study participants having hypertension. However, the total number of cases of hypertension in this study was slightly lower than the prevalence of hypertension in the general South African population. According to data from the World Health Organization, 26.1% of females and 27.4% of males in South Africa have hypertension (World Health Organization, 2015). This incidental finding, of a slightly lower prevalence of hypertension in this sample, is unexpected as weight gain and metabolic syndrome are significant side effects of psychotropic medications. This finding may also indicate that continued blood pressure monitoring and diet control may aid in the reduction of the incidence of hypertension in psychiatric in-patients.

In this study, medical conditions such as hypertension, COPD and type 2 diabetes mellitus were significant predictors of the occurrence of hyponatraemia once the patients were admitted. It was found that 10.5% (n=42) of the patients who were in the “other medical conditions” group had hyponatraemia on admission. This number doubled to 21% (n=85) during their hospital stay. In stark contrast, the patients who had no other medical conditions had less than half the cases of hyponatraemia during their hospital stay (n=42; 10.5%) as compared to on admission (n=85; 21.3%). This finding corroborates with the research completed in 2016, where the incidence of hyponatraemia was associated with the risk factors of hypertension, type 2 diabetes mellitus and COPD (Kayar, 2016). It is

also well researched that SIADH occurs in cases of pulmonary and central nervous system pathology (Spasovski et al., 2014).

Hyponatraemia is closely associated with hypertension as it commonly occurs in patients who are treated with thiazide and potassium-sparing diuretics. This is caused by the mechanism of the diuretics causing increased sodium chloride excretion, which increases water excretion and controls the blood pressure (Hwang and Kim, 2010). Patients in the sample who were on antihypertensive medication were found to have a propensity for hyponatraemia. The patients in the sample who were on antihypertensives (n=88; 22%) were 2.6 times more likely to be diagnosed with hyponatraemia when compared to the patients who were not on antihypertensives (n=43; 10,8%). Hypertension, itself, predisposes the patient to conditions such as renal dysfunction and cardiac dysfunction which both could lead to the development of hyponatraemia (Hwang and Kim, 2010). The findings of this study are also corroborated by the findings of Manu et al., 2012, who found that hypertension was a significant risk factor for the development of hyponatraemia in psychiatric inpatients.

The majority of the sample had normal glomerular filtration rates on admission. Of the patients admitted with renal dysfunction, the majority were admitted with mild renal dysfunction (n=15; 3,78%). This finding is lower than the prevalence rates of previous studies that established that renal dysfunction occurred in 14.6% of patients with SMI (Iwagami et al., 2018). A cross-sectional study conducted in 2020 surveyed general inpatients in an Ethiopian hospital confirmed that the prevalence of renal dysfunction (eGFR of less than 60 mL/min/1.73m^2) was approximately 19.0% (Fiseha et al., 2021). This indicates that the prevalence of renal dysfunction in this sample was less than the prevalence of renal dysfunction in general patients, as well as in patients with SMI. Fiseha et al (2021) attributed the high rates of renal dysfunction to increasing age, HIV, type 2 diabetes, and a family history of chronic kidney disease. This could be explained by the lower rates of hypertension in the sample, as the rates of hypertension and HIV were found to be lower than that of the general population. The relatively lower rates of renal dysfunction (using glomerular filtration) confirm that the cases of hyponatraemia detected

in the sample were unlikely due to volume loss or salt wasting. Significant volume loss would be confirmed by the increase in serum urea and creatinine levels which would reduce the eGFR. From the prevalence of renal dysfunction in the sample, it can be deduced that renal and pre-renal causes of hyponatraemia in the sample were not the most significant cause of hyponatraemia.

According to the results, having a psychotic disorder was not a significant predictor of whether the patient was admitted with hyponatraemia or developed hyponatraemia during their admission. It was found that a significant proportion of the patients diagnosed with a psychotic disorder had developed hyponatraemia (n=102; 25,6%). However, this did not differ significantly when compared to the patients without a psychotic illness. This is an unexpected finding as psychotic illnesses, such schizophrenia, are closely linked to psychogenic polydipsia (Sailer et al., 2017). It can be postulated that the continuous nursing and monitoring in the ward prevented more severe cases of psychogenic polydipsia in the study population. However, this would need to be confirmed with close water intake monitoring of each patient. A major difference between the patients with psychotic illness in the sample and those without psychotic illness is that patients with the diagnosis of psychotic illness are treated with antipsychotics. This could suggest that medications other than antipsychotics could be a cause of the hyponatraemia. However, the use of second generation antipsychotics has increased and are often used in the management of patients with mood, personality and neurodevelopmental disorders (Verdoux et al., 2010). This is also corroborated by the finding that risperidone was the third most common medication used in the sample (n=149).

Mood disorders were not associated with the development of hyponatraemia in this study. This finding was unexpected as patients with mood disorders such as bipolar disorder are likely to be treated with mood stabilisers which possess some of the strongest evidence for the cause of medication-induced hyponatraemia (Intravooth et al., 2018). However, patients with mood disorders are also often treated with antipsychotics and vice versa, likely rendering the two groups indifferentiable in terms of occurrence of hyponatraemia (Rhee et al., 2020).

On assessing the patients' clinical profiles further, it was found that there was a similar occurrence of hyponatraemia between the patients treated with first generation antipsychotics and those who were not. This finding was the same for the occurrence of hyponatraemia in patients treated with second-generation antipsychotics. Although there has been prior research that has demonstrated antipsychotic-induced hyponatraemia (Yang and Cheng, 2017), the results of this study suggest that the role of first-generation antipsychotics in the development of hyponatraemia is unclear. This is in keeping with the contradicting prior research on the role of dopamine antagonism on the osmoreceptors. There was evidence that concluded that the antipsychotics either increased osmoreceptor sensitivity, therefore, reducing ADH secretion, and there was evidence of the inverse of this relationship (Yamaguchi et al., 1990, Wells and Forsling, 1992). This is apparent in the results of this study where a significant proportion of the patients on first-generation antipsychotics were found to have hyponatraemia (n=68; 17,1%), but the number was comparable to the patients who were not on first-generation antipsychotics. This number did not differ significantly on admission and during their hospital stay. A possible cause of these results includes the patients being on multiple agents to treat psychosis such as being on a combination of a first-generation antipsychotics in the form of LAI and a second oral second-generation antipsychotic.

A significant proportion of the patients on a combination of a first and second-generation antipsychotic were found to have hyponatraemia at some point during their hospital stay. Of the 77 patients on both a first- and second-generation antipsychotic, 67 patients (87%) had hyponatraemia. The pattern of first and second-generation antipsychotic use in the sample was the use of first-generation LAI antipsychotics such as flupenthixol decanoate or zuclopenthixol decanoate in combination with an oral second-generation antipsychotic such risperidone or olanzapine. To date, there is no research on the occurrence of hyponatraemia following the administration of both an LAI and oral antipsychotic. It can be theorised that the greater dopamine receptor occupancy conveyed by both the LAI and oral agent predisposes the patient to more side effects such as the altered sensitivity of the hypothalamic osmoreceptors.

Antidepressants were not found to be a significant predictor of hyponatraemia in the sample. The class of psychotropic medication with the strongest evidence for their propensity to cause hyponatraemia remains the SSRIs (De Picker et al., 2014). In this study, the use of SSRIs was underrepresented making it difficult to make an association between hyponatraemia and the use of SSRIs. This was because the study population was composed of participants with SMI and the majority of the patients were diagnosed with schizophrenia (n= 318; 79,9%). There were no patients in the sample with the principal diagnosis of major depressive disorder or anxiety disorders which would be an indication for possible SSRI monotherapy. A study with the aim of exploring the relationship between SSRIs and hyponatraemia in the South African context is required. However, this will most likely not be undertaken in hospitalized patients with SMI.

Anticholinergics were widely used in this sample (n=239; 60,1%) and in this study, anticholinergics were not found to be a significant predictor for the development of hyponatraemia. It was found that a greater number of patients (n=56; 14,07%) who were not on anticholinergics were found to have hyponatraemia on admission to SSMMH compared to the patients prescribed anticholinergic medication. The research on the association between anticholinergics and the development of hyponatraemia is limited to case reports and requires further investigation (Rizzi and Tan, 2017, Singh and Linas, 1995). Anticholinergic medications are prescribed to reduce the extra pyramidal side effects caused by antipsychotic medications (Kaplan and Sadock, 2015). The anticholinergics in this study could also be a confounding factor as anticholinergics are often prescribed in conjunction with antipsychotics. It can also be considered that the finding in this study, regarding the hyponatraemia and the psychotic disorders, may have been impacted by the use of anticholinergic medications. To manage the confounding factors, a cohort study would be required into the association between hyponatraemia and anticholinergic medication, directly comparing patients on anticholinergic medications with those who are not.

Other medications such as sedatives and benzodiazepines were not significant predictors for the development of hyponatraemia in this study. Antiretroviral medication, aspirin, and

statins such as simvastatin were not significantly linked to the development of hyponatraemia in the patients. This finding is in keeping with the latest research as there are no current studies proving the association of antiretroviral drugs and the development of hyponatraemia. Statins such as simvastatin have been demonstrated to cause hypernatraemia and not hyponatraemia (Skov et al., 2021). However, further studies are required to exclude the associations between these medications and the development of hyponatraemia.

4.4 Factors associated with hyponatraemia in this study

The study population had multiple risk factors for the development of hyponatraemia, including the psychiatric diagnosis, comorbid medical conditions and the use of chronic medications. More specifically, the female gender and the use of antihypertensives were associated with the development of hyponatraemia. However, hyponatraemia is a complex disorder and it is impossible to attribute just one factor as being the cause of hyponatraemia in this study. Besides the clinical factors that may be linked to the hyponatraemia in this study sample, larger, more contextual factors can also be considered. South Africa is a developing country in the middle of an epidemiological transition (Kabudula et al., 2021), with population mortality rates heading towards the pre-HIV era due to the advent of antiretroviral therapy. This has led to longer life expectancies and an older population with more age-related comorbidities. This has led to resource constraints that further worsen the socio-health vulnerabilities in populations such as patients with SMI. Such an example would be the LE tragedy. Thus, the researcher hypothesizes that the significant finding of the hyponatraemia in this study may be a consequence of a combination of various factors.

4.5. The trends in sodium monitoring

Sodium testing, amongst the patients in the sample, varied from one test in their entire hospital admission to four tests per year testing throughout their hospital stay. It was found that the patients who were admitted with moderate hyponatraemia were tested the most frequently, with an average of 4.87 tests throughout their admission. A confounding factor in the number of tests performed on each patient was the indication for the testing. As the

sodium level was often part of a urea and electrolyte panel, the sodium test results were often part of renal function and potassium monitoring. Patients known with renal dysfunction or other electrolyte abnormalities would have an increased number of tests. The monitoring trends are roughly in keeping with the guidelines that recommend electrolyte monitoring at baseline, one month and then 3 months after initiation of SSRIs (Mannesse et al., 2010, Taylor et al., 2018). Monitoring guidelines, with regards to the other classes of psychotropic medication, do not recommend routine testing. It is recommended that electrolytes , in general, are tested at baseline, prior to initiation of the mediation (Taylor et al., 2018, Keepers et al., 2020). It is then recommended that further testing is done when clinically indicated (Keepers et al., 2020). This can result in mild or asymptomatic cases of hyponatraemia going undetected which may lead to the delay in the treatment of the hyponatraemia. The testing in this study sample was adequate, according to current guidelines. Each patient was tested at least once on admission to SSMMH. Subsequent sodium testing was then dependent on the initial result.

Chapter 5: Conclusion

Hyponatraemia is a significant but underrecognized electrolyte abnormality that occurs in patients with SMI. Patients with SMI are vulnerable to the development of hyponatraemia due to multiple factors including their psychiatric conditions, medical comorbidities and their chronic medications. This study found that being female, having comorbid medical conditions and the treatment with antihypertensive treatment greatly increased the likelihood of the patient developing hyponatraemia. With this information, more caution is required in the monitoring of female patients with SMI and those with comorbid medical diagnoses for conditions such as hyponatraemia.

5.1 Recommendations

With the finding of the vulnerability to the development of hyponatraemia in patients with SMI, the following recommendations can be considered.

5.1.1 Frequent testing and earlier intervention

Current treatment guidelines recommend that sodium testing is done only when clinically indicated. However, regular monitoring for hyponatraemia should be implemented in all admitted psychiatric patients as chronic, untreated hyponatraemia worsens the outcomes of the already vulnerable patients. Early detection and correction of the hyponatraemia would aid in reducing the hospital stay and the morbidity. Undiagnosed hyponatraemia in the patients would lead to worsening of the patient's cognitive functioning and eventual death. Furthermore, elderly patients with hyponatraemia are prone to falls and subsequent fractures. From the findings in this study, it can be recommended that the monitoring of hyponatraemia be more stringent. It can be suggested that prior the initiation of any class of psychotropic medications, the patient's sodium level be tested and regularly monitored. Patients with comorbid medical conditions, on polypharmacy, or known to have longstanding SMI, should have their sodium levels tested within three months of treatment change or initiation.

Monitoring of the patients' serum sodium levels should be monitored more frequently in patients with comorbid conditions and combination antipsychotics. Patients without further risk factors may be monitored yearly.

To reduce the cost implication of the increased testing, clinicians may be advised to test only the sodium rather than requesting the entire electrolyte panel. The use of venous blood gas analysers may also be more cost efficient in screening patients frequently for the development of hyponatraemia. The use of blood gas analysers may also be more efficient in the screening of outpatients for the development of hyponatraemia.

5.1.2 Improved screening for psychogenic polydipsia

In the ward setting, patients' water intake should be screened regularly for psychogenic polydipsia. This may be done briefly during patient interviews by enquiring about the patients' fluid intake. Patients may also be monitored for behaviour that indicates increased fluid intake such frequent urination. Indications of increased water intake should warrant closer water intake monitoring which involves documenting the daily fluid input and output of the patient. The daily urine production of greater than 2000mL should be further investigated. Patients may also be screened for increased water intake at all outpatient appointments.

5.1.3 Continued research and integration of care

Continuous research into the latest treatment modalities, for hyponatraemia, is encouraged. The use of salt tablets may be a safer treatment modality in treating patients with hyponatraemia whilst avoiding the adverse effects such as pontine myelinolysis (Lattore et al., 2022). Continued research into the development of newer guidelines is also required. Guidelines that consider the patients that are more at risk for the development of hyponatraemia should be implemented. In addition, further research regarding the risk of hyponatraemia and the combination of oral antipsychotics and LAI is required. Similar studies, in the same South African context, need to be conducted to further confirm the high occurrence of hyponatraemia in patients with SMI.

The findings of this study also suggest the need for more integrated care in the management of patients with SMI. Disciplines such as internal medicine and psychiatry may need to adopt a more collaborative approach in the long-term management of patients with SMI. In addition, the acknowledgement of the vulnerability of patients with

SMI is required across the medical fraternity with greater measures implemented for the protection of some the population’s most vulnerable.

Chapter 6: Limitations

The study method was a retrospective record review which included recording of all demographic data, clinical variables and sodium levels of each patient. The sodium readings were often part of a UE panel. The indication for the UE panels varied beyond the need for sodium testing. This finding likely impacted the testing trends, as UE testing is often indicated for the monitoring of renal filtration and the monitoring of other electrolytes such as potassium.

Other electrolyte abnormalities were not specifically documented in this study but were recorded as “other medical diagnoses”. Hypernatraemia, hypokalaemia and hyperkalaemia all could have impacted the testing trends as well as the results of the sodium levels.

Although smoking has been clearly determined as a causative factor in the development of hyponatraemia (Allon et al., 1990) , via the induction of SIADH, data regarding smoking was not taken in this study. This was due to the method of documentation in the patients’ files, where the patients’ smoking status was not studied as a variable. However, COPD was documented and recorded within the “other medical diagnosis” group. This limited the ability to make clear associations between smoking, COPD and the development of hyponatraemia.

The study sample may be considered a convenience sample as the patients were all admitted into the same facility (SSMMH) under similar circumstances. This led to the sample consisting, mainly, of patients with chronic SMI who are likely institutionalized. This may impact the generalisability of the findings in patients with SMI who may not be institutionalised.

Due to the methodology, the records review did not allow for the exploration of temporal relationships between the occurrence of the hyponatraemia and the various clinical variables. Therefore, it was not described whether the hyponatraemia occurred after a particular medication or diagnosis change in the individual patients. Causality of the

hyponatraemia could not be clearly explored. The study highlighted the clinical occurrence of hyponatraemia in patients with SMI, however, clinical correlates due to the hyponatraemia were also beyond the scope of this study.

To limit the scatter and variability of results, the clinical variables were grouped into larger categories such as “antipsychotics” or “other medical conditions”, however this limited the ability to distinguish the exact cause of hyponatraemia within the larger categories. Further study will be required to compare the exact occurrence of hyponatraemia with the individual clinical variables.

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Appendix

APPENDIX A

DATA COLLECTION SHEET

Patient details				
Patient Number	Male/ Female	Age	Admission date	Discharge date
1	Female	41	15-Jan-19	-

Sodium levels		Renal Function			Diagnosis		Antipsychotics		Antidepressants		Mood Stabilisers		Other treatment		
Sodium on adm. (mmol.L)	Date	Urea (mmol/L)	Creatinine (mmol/L)	eGFR (mL/min/1.73m2)	Psychiatric	Medical	Agent	Dose	Agent	Dose	Agent	Dose	Class of drug	Agent	Dose
130	21-Jan-19	5.1	65	60	Schizophrenia	Hypothyroidism	Clozapine	100mg bd	-	-	x	x	Thyroid drug	Eltroxin	50mcg

Sodium levels		
Patient number	Sodium (mmol/L)	Date Measured
1	134	30-Mar-19
1	136	3-Jun-19

APPENDIX B

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Natsai Nhiwatiwa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200355

NAME: (Principal Investigator)	Dr Natsai Nhiwatiwa
DEPARTMENT:	Psychiatry Solomon Stix Morewa Memorial Hospital (Selby Hospital)
PROJECT TITLE:	The occurence of hypervolaemic states syndromes in long-term psychiatric patients placed at Solomon Stix Morewa Memorial Hospital, Johannesburg
DATE CONSIDERED:	27/03/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Mvuyiso Talatala and Prof Yosuf Veriava
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/06/2020

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. I **agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C

Clinix
SOLOMON STIX MOREWA
MEMORIAL HOSPITAL
You Are Family

25 November 2019

Dear Dr N. Nhlwatiwa,

Request for Permission for Study Surveying the Chronic Psychiatric Patients at SSMMH

Thank you for considering our hospital for your study and based on your formal request to conduct your study at Solomon Stix Morewa Memorial Hospital.

Kindly note that permission is granted to conduct the study at Solomon Stix Morewa Memorial Hospital subject to you obtaining ethical clearance from the Wits Human Research Ethics Committee. Before commencing with your study, you must provide us with the proof of ethics clearance and a copy of your final protocol.

We look forward in hosting you at SSMMH and I would like to take this opportunity to wish you all the best in your study and your future endeavours.

Regards,

Phillisiwe Gumede
Hospital Manager
Solomon Stix Morewa Memorial Hospital
M: +27 76 271 5824
E: pgumede@clinix.co.za

Clinix
HEALTH GROUP
Solomon "STIX" Morewa Hospital
SELBY PARK
PO Box 62171, Marshalltown 2107
PR 0137286
Tel: 011 491 4101 Fax: 011 493 4145

Clinix
HEALTH GROUP

APPENDIX D

STUDY INFORMATION DOCUMENT

The occurrence of hyponatraemia in long term psychiatric patients currently placed at Solomon Stix Morewa Memorial Hospital, Johannesburg

Dear sir/madam

I, Natsai Nhiwatiwa, am a medical doctor who is specializing in the field of psychiatry. I am doing research on hyponatraemia (low sodium levels) in patients with mental illness admitted in Solomon Stix Morewa Memorial Hospital. Research is the process used in seeking new knowledge. In this study we want to learn more about patients that were found to have low sodium levels while admitted.

I am inviting you to take part in this research. This research aims to involve all the patients being treated for mental illness and are admitted at Solomon Stix Morewa Memorial Hospital.

As a study participant, you will not need to do anything except allow me to go through your past blood results and to go through your hospital file. I will be going through your file to look at details such as your age, gender, diagnosis and treatment.
Your past blood results and hospital file will only be accessed by myself and/or my supervisors and will be treated with the strictest of confidence. I will not be using or documenting any of your personal information such as your name, address or contact details.

The information I collect will be used, solely, to tally numbers of the patients with hyponatraemia and their basic clinical profile. The numbers/details will be recorded on a excel study datasheet. All data collected in the course of the study will be securely retained for two (2) years, if a scientific publication arises from the study and six (6) years, if there is no publication. Thereafter it will be destroyed accordingly.

There is no risk or additional benefit to you if you choose to participate. I invite you to sign consent (written permission) on the next page if you are willing to participate in the study. You will suffer no penalty or loss if you opt not to participate.

Contact details of researcher/s:

Researcher: Dr Natsai Nhiwatiwa
011 491 4100

Supervisor: Dr Mvuyiso Talatala
011 491 4100

Co-supervisor: Prof. Yosuf Veriava
011 491 4100

Contact details of HREC administrator and chair

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.
If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study information Sheet

Nov 2019