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Demographic and clinical features of children receiving psychiatric medication at a specialist psychiatric clinic

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Demographic and Clinical Features of Children Receiving Psychiatric Medication at a Specialist Psychiatric Clinic

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand in partial fulfillment of the requirements for the degree of the Masters of Science in Medicine in Psychiatry.

Johannesburg 2014

Declaration:

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

Signed: _____ (Antoinette Miric)

Date: _____

Dedication:

This work is dedicated to the memory of my dear uncle,

Michael Nils Walsh Sparks.

Abstract:
Introduction:

In the past ten years, there has been an increased awareness about the diagnosis and treatment of psychiatric disorders in childhood. As a consequence, there has been a concomitant increase in the prescription of psychiatric medication for children. Off-label and concomitant medication are particular issues of concern in child psychiatry. In South Africa, there is limited data on paediatric prescribing trends. It is important to know the demographic trends and clinical reasons for medication use in order to assess, plan, improve and budget for children's mental health care services. The results of this study will give insight into the current prescribing patterns at Tara's Outpatient Child Clinic (TOCC).

Aim and Objectives:

To describe the demographic profile and diagnoses of children between the ages of six and fourteen years old at TOCC for whom psychotropic drugs are prescribed. The objectives are to examine the initial prescription of psychotropic medication in children attending TOCC and to evaluate the demographic data associated with medication use. Additionally, comparisons will be made between prescribing practices internationally and at TOCC>

Methods:

This study was a retrospective descriptive record review. The study population reviewed was children between and including the ages of six to fourteen, who attended TOCC between January 2010 and December 2011. Data analysed included age, gender, race, diagnoses and psychiatric medication prescribed.

Results:

More than twice as many male patients were prescribed psychiatric medication compared to females. Attention deficit/Hyperactivity Disorder (ADHD) was the most common diagnosis (81%), followed by anxiety disorders (24.9%) and disruptive disorders (12.2%). With regards to

demographic variables, psycho-stimulants were significantly more likely to be prescribed in the six to ten year old age group (85% of 6-10 year olds) and anti-depressants were more commonly prescribed in ten to fourteen year old children. (38% of 10-14 year olds). No significant associations were found when looking at gender. White patients were more likely to be diagnosed with anxiety disorders, (15.1%) compared to Black patients who were more likely to be diagnosed with a learning disorder (7.3%). Psycho-stimulants were the most commonly prescribed medication (78%), followed by anti-depressants (24%) and anti-psychotics (5.3%). Concomitant prescribing occurred in eight percent of the sample.

Conclusion:

This study indicates prescribing trends within a public tertiary child psychiatry outpatient clinic in South Africa. Psycho-stimulants were more frequently prescribed for the treatment of ADHD. Selective Serotonin Reuptake Inhibitors (SSRI's) are used predominantly for treatment of mood and anxiety disorders, whilst Tricyclic Antidepressants (TCA's) were only prescribed in the presence of an elimination disorder. Due to the limited registered uses of anti-psychotics, the majority of their use was off-label. Overall anti-psychotic prescriptions were prescribed less than in other studies and this demonstrates that the TOCC has adopted a cautious approach. The main aim of this research report has been fulfilled in that the clinical and demographic features of six to fourteen-year-old children attending TOCC have been described. It has been shown that prescription patterns of psycho-tropics at TOCC mostly follow international trends and guidelines.

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Abbreviations:

ADHD	Attention Deficit Hyperactivity Disorder
TOCC	Tara H Moross Outpatients Child Clinic
PFC	Pre-Frontal Cortex
CSTC	Cortico-Striatal-Thalmic-Cortical
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Anti-depressants
NH	Non-Hispanic
MDT	Multi-Disciplinary Team
RMH	Rahima Moosa Child & Adolescent Mental Health Clinic
5HT	5-Hydroxytryptamine (Serotonin) DSM-IV-TR
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.
DSM 5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.
PDD	Pervasive Developmental Disorders

CHAPTER ONE: INTRODUCTION:

1.1 Background:

In the last decade, there has been an increased awareness about the diagnosis and treatment of psychiatric disorders in childhood. As a consequence, there has been a concomitant increase in the prescription of psychiatric medication (psychotropics) for children. Unregulated off-label and concomitant medication is a particular issue of concern in child psychiatry, due to its increased prevalence and potential for harmful (and unknown) side-effects.[2, 3]

Research on the use of psychiatric medication in children is sparse and inadequate in South Africa, and needs to be enhanced. It is crucial to understand the current patterns of prescribing in order to assess, plan, and improve children's mental health care services. It is also useful to compare the data from Tara Hospital Outpatient Child Clinic (TOCC) (at the Tara H Moross Centre) in Hurlingham, Johannesburg, South Africa) psychotropic prescribing patterns to local and international sites.

This research report is based on data obtained from the TOCC found in Hurlingham, Johannesburg. The study will look at a group of recently referred patients receiving psychotropics, between the ages of 6 and 14 years old. These patients were seen in the period between January 2010 and December 2011. A review of the literature reveals that the majority of children receiving psychotropics fall in this age range.[1] The results of this study will give insight into the current prescribing patterns at the clinic and hopefully promote further research at TOCC.

1.2 Aim and Objectives:

To describe the current prescribing patterns of medical practitioners at TOCC for new patients between the ages of 6 and 14 years old.

The objectives of the study are:

- To examine the overall use of psychiatric medication in recently referred children presenting at the clinic.
- To evaluate the demographic and clinical diagnoses associated with the prescribed medication.
- To compare the use of psychiatric medication at TOCC to internationally accepted prescribing practices.

1.3 Hypothesis:

Significant differences will be found in the demographic profile and clinical features of children that have been prescribed psychotropics at TOCC.

1.4 Study motivation:

There is a general paucity of knowledge with regards to the prescription of psychiatric medication in children in South Africa. Specifically at TOCC, the psychopharmacological practices of the child psychiatrists and psychiatric registrars are unknown. This information is crucial in order to monitor current patterns and prevent potential harmful prescribing of psychotropics.

1.5 Structure of report:

In the following chapter, the report looks at existing international and local research on the use of psychotropics in children. Chapter Three follows with a

description of the methodology used in this research. In Chapter Four, the results of the study are revealed, and these are discussed in Chapter Five. The conclusion, references and the appendices follow.

1.6 Literature search strategy:

The literature search was conducted with PubMed using the following words: child, children, outpatient, community, office, office based, clinic, psychotropic, psychostimulant, antidepressant (selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCAs), antipsychotic, epidemiology, demographic, off-label, polypharmacy, concomitant. Additional appropriate websites and textbooks were used.

CHAPTER TWO: LITERATURE REVIEW:

Overview:

The three most commonly used and prescribed psychiatric medications in children are psychostimulants, antidepressants and atypical antipsychotics. Very few drugs are licensed in children when compared to adults due to a lack of randomized control trials, with treatment targeted towards symptoms rather than diagnoses.[4] Medications are thus frequently prescribed off-label. [1,2,3,5,6,7] Medications that are approved by the Food and Drug administration (FDA) for paediatric use, are reflected in the Table 2.2.[2] Concomitant use of medications in children is increasing, and this will be discussed later.[1, 2,5,6,7]

Table 2.1: FDA approved psychotropic drugs and indications for use in children and adolescents*:

Class, Subclass	Drug	Age limits, yr.	Indication
Stimulants	Amphetamines	3+	ADHD; Narcolepsy
	Methylphenidate	6+	ADHD; Narcolepsy
Antidepressants			
SSRI			
	Fluoxetine	8+	Depression
		7+	OCD
	Fluvoxamine	8+	OCD
TCA			
	Imipramine	6+	Enuresis
		12+	Depression
Antipsychotics			
Typical			
	Haloperidol	3+	Tourette's disorder; Psychosis; Severe Behavioural
	Fluphenazine	12+	Psychosis
Atypical			
	Risperidone	10+	Acute and mixed mania(BD1)
		5-16	Irritability in Autism
		13+	Schizophrenia
	Aripiprazole	10+	Acute and mixed mania (BD1)
		6+	Irritability in Autism
	Olanzapine	13+	Acute and mixed mania (BD1)
		13+	Schizophrenia
	Quetiapine	10+	Acute mania(BD1)
		13+	Schizophrenia
Miscellaneous			
	Lithium Carbonate	12+	Manic episodes
	Atomoxetine	6+	ADHD

BD1=Bipolar disorder 1

*Adapted with permission from (2).

2.1 Psychostimulants:

2.1.1 Indications for use of psychostimulants:

Psychostimulants are indicated for the treatment of Attention Deficit Hyperactivity disorder (ADHD), a behavioural and neurocognitive disorder that affects 5% of children worldwide. [4,8,9] According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR), symptoms include inattention, hyperactivity and impulsivity.[10] In order for these symptoms to be diagnostically relevant, they should develop before the age of 7 years and must be developmentally inappropriate and impair the child's social and academic functioning.[10]

ADHD has a multi-factorial aetiology, including environmental, genetic and neurobiological factors.[5] Neurobiological factors include catecholaminergic dysregulation in cortical areas, specifically the pre-frontal cortex (PFC) and the cortico-striatal-thalamic-cortical circuits (CSTC).[11] These cortical regions are responsible for modulating attention, motor activity and impulsivity. Psychostimulants increase the concentration of catecholamines in these regions, improving cortical functioning.[11]

Psychostimulants should be part of a comprehensive treatment plan for ADHD which includes psychological, behavioural and social interventions.[4] Registered medications for use in children with ADHD in South Africa are psychostimulants which include various versions of Methylphenidate.[12] Methylphenidate (a psychostimulant), binds and inhibits the function of the norepinephrine transporter receptor and dopamine transporter receptor on neurons in the PFC and CSTC.[11] This results in decreased catecholamine reuptake, increasing the concentration of these neurotransmitters in the synapse. The resultant enhanced cortical processing leads to an improvement in

the ADHD symptoms.[11] Atomoxetine is another medication registered in South Africa for the treatment of ADHD.[12] It works in a similar way, but selectively acts on the norepinephrine re-uptake inhibitor and is classified as a selective norepinephrine reuptake inhibitor.[11,12]

The South African Society of Psychiatrists (SASOP) recently published guidelines for the treatment of ADHD.[13] They advise a full psychiatric evaluation and appropriate assessment prior to commencing treatment and provide guidelines for acute non-pharmacological and pharmacological treatment.[13] Should pharmacological treatment be indicated, they advise to start with a low dose of methylphenidate (5-10mg Immediate Release) in the morning.[13] The dose should then be titrated upwards if needed and split during the day. Similarly, the National Institute of Health and Clinical Excellence (NICE) guidelines recommend Methylphenidate as a first line medication, but add that atomoxetine is an accepted first line alternate.[8] Third line medications for treatment of ADHD according to the Maudsley Prescribing Guidelines and the NICE guidelines, include clonidine and TCAs.[4, 8]

Psychostimulants are the most common psychotropics prescribed in the paediatric population.[14] A recent study from McCabe et al, looked at a large multi-cohort of high school seniors (modal age 18) in the United States of America (USA), and found that the lifetime prevalence of medical use of prescription stimulant was 9.5%.[14] Clark et al[15] looked at prescribing practices in British children, and found that 46%(n=845) received psychostimulants for hyperkinetic disorders (International Classification of Disease 10th edition equivalent of ADHD).[16] Similarly, a New York outpatient study[5] showed that 35% of 956 children prescribed psychotropics, received psychostimulants. In a local study, Raman et al[17] looked at the Child and Adolescent Mental Health

Service at Rahima Moosa Mother and Child Hospital (RMH) in Coronationville, Johannesburg. The study investigated clinical and demographic features of children attending this clinic and revealed that 38% of the children that were prescribed medication, received psychostimulants.[17]

Psychostimulant prescriptions are on the rise, with an increased prevalence of prescriptions in the USA, UK and the Netherlands.[1] Hodgkins et al[18] found in a Netherlands based study, that the prevalence of psychostimulants prescriptions rose from 110 per 10,000 in 2000 to 210 per 10,000 in 2007. Studies in the United Kingdom established similar findings, with a doubling of the rate of Methylphenidate prescriptions between 2003 and 2008.[19] Reasons postulated for this trend include an increased awareness of ADHD by parents and educators and improved knowledge about the appropriate use of psychostimulants.[19] There is a dearth of studies about the prevalence of prescriptions of psychostimulants in South Africa.

Concerns with psychostimulant use, not covered in this report, include the growing abuse of prescription stimulants for non-medical reasons. McCabe's research showed that in USA high school seniors there is a 9.5% lifetime prevalence of prescription stimulants for non-medical use.[14] They also found that children who abuse prescription stimulants have a higher risk for substance abuse.[14]

2.1.2 Demographic characteristics associated with psychostimulant prescription:

Gender:

More males than females have ADHD, and accordingly more males receive psychostimulants.[11] Studies in Canada has shown male to female ratios of

psychostimulant prescriptions of 4:1.[20] Furthermore, a retrospective study in the Netherlands showed that males made up 82% (n=4030) of a group of 4,909 children initiated on ADHD treatment.[18] Multiple international studies support these findings.[1, 15,19] Likewise, in a large South African study based on paediatric medical aid data, Truter[21] found a 3:1 male predominance of psychostimulant prescriptions.

Age:

Psychostimulants are most frequently prescribed in the seven to fourteen year old age groups. Hodgkins et al[18] revealed that 73% of the children starting ADHD treatment in the Netherlands in 2007 were between the ages of six and twelve. A recent study in the UK showed that the six to twelve year old group received the majority of psychostimulants.[15] Locally, Truter[21] found that seven to twelve year olds made up 63.14 % of patients receiving psychostimulants (n=1028).

Race:

Data is inconsistent and scant with respect to investigating racial variances in psychostimulant prescribing. Some earlier American studies indicate increased psychostimulant prescription in non-African American children compared to their African American counterparts.[5] More recent studies have shown a narrowing of differences in prescribing patterns between different racial groups.[22] Zito et al reviewed data that looked at racial differences and concluded that racial bias or confounding factors such as medical insurance type may affect results.[22] There are no data on racial differences in South African prescribing patterns

Psychostimulants are the most commonly prescribed psychotropics in children. Male children between the ages of seven and twelve are most likely to be prescribed this

class of medication.

2.2 Antidepressants:

Significant differences in the prescribing patterns of antidepressants have been observed with reference to patient clinical and demographic features. Antidepressants have antidepressant, anxiolytic and impulse-reducing properties.[11] Furthermore antidepressants are also used in the treatment of enuresis.[23] Selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCAs) are the most widely prescribed antidepressants in the paediatric population.

2.2.1 Indications for use of Antidepressants:

Antidepressants are used for the treatment of childhood mood, anxiety, disruptive and enuretic disorders.[23-26] Mood and anxiety disorders have complex aetiologies. They occur because of a multi-faceted interaction between environmental and neurobiological factors**.**[11] It is postulated that the underlying biological factors for the development of mood and anxiety disorders, are the deficiencies and/or dysregulation of the serotonin, noradrenaline and dopamine in various neural circuits.[11] In children presenting features of depression are age-dependent, and include irritability, somatic complaints, sleep changes and sensitivity to rejection.[25]

Antidepressant use in Mood and Anxiety Disorders:

The only antidepressants registered for use in South Africa are Clomipramine (a TCA for treatment of obsessive compulsive disorder) in over 5 year olds, and Imipramine (a TCA for treatment of nocturnal enuresis) in 5 to 8 year olds.[12] According to the South African Medicines Formulary (SAMF) 11th edition, Fluoxetine (SSRI) can be used off-label in over 7 year olds for major depressive disorder and obsessive compulsive

disorder. [12] Likewise sertraline (SSRI) can be used off-label in 6 to 12 year olds for the treatment of obsessive compulsive disorder.[12] The NICE guidelines, recommend fluoxetine as a first line medication of choice in depression in combination with psychological treatment.[25] Citalopram (SSRI) and escitalopram(SSRI) are also recommended by NICE for treatment of depressive disorders. Additionally NICE advise against the use of TCAs for depression, due to their higher propensity to cause side effects.[25]

Antidepressants are used for a range of anxiety disorders including (as per DSM-IVTR), generalised anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder and social or specific phobias.[10,24] Anxiety disorders in children tend to respond well to Cognitive Behavioural Therapy (CBT), but if the anxiety disorder is severe or if CBT has failed/or is not indicated, then medication is prescribed.[4,24] Furthermore, first line pharmacological treatment of anxiety disorders are SSRI's.[4,24]

Tricyclic antidepressants block serotonin and norepinephrine reuptake transporters, thus increasing the concentration of these neurotransmitters resulting in the alleviation of mood and anxiety symptoms.[11]However a meta-analysis, carried out by Hazell et al [27] found that TCAs were no more effective than a placebo in treating depressed children and adolescents. This information combined with undesirable side effects such as drowsiness, dizziness and constipation, should make one cautious when prescribing this class of medication in children for mood and anxiety disorders. [11]

Selective serotonin reuptake inhibitors have relatively few side effects and therefore their use has increased since their introduction in the 1980's.[28]SSRI's became the preferred treatment for depression in children from the early 2000s.[28] Currently SSRI's

are the first line antidepressants for the treatment of mood and anxiety disorders in children. SSRI's have a complicated mechanism of action and inhibit the reuptake of 5-hydroxytryptamine (5HT, serotonin), resulting in an increase of 5HT at the neural synapses.[11]

The use of SSRI's increased dramatically since the late 1990's; that is until the widely publicised Black Box warning in 2004 by the FDA resulted in a worldwide decrease in SSRI prescriptions.[28, 29,30] The concern was that on initiating SSRI's, there was an initial increase in suicidal ideation.[29] More recent studies, have clarified and refuted these claims, and have found that the benefits of SSRI use outweigh any potential side effects.

Various countries have different prescription patterns. Studies in the UK, USA and Canada, showed that SSRI's are more likely to be prescribed than TCAs.[15,20,28] In contrast, Germany and France show higher prescription rates of tricyclic antidepressants and homeopathic products compared to other types of antidepressants.[1] A South African study[34] looking at medical aid data in 2006 (n=1013), showed that 43 % of antidepressants prescribed for under-18's were SSRI's and 42.7 % were TCAs. Unfortunately, indications for prescriptions were not available in this study.

Antidepressant use in other disorders:

Low-dose TCAs (specifically imipramine) are recommended by NICE to treat enuresis, a common childhood condition, and are a recognised 3rd line treatment for ADHD.[4,8,24,26] With respect to enuresis, NICE guidelines caution that TCAs are not first line pharmacological treatment and should only be used if the patient has not responded to all other treatments and has been assessed appropriately by an expert health care

professional.[26] Tricyclic antidepressants are also used in the treatment of ADHD, however only after failure to respond to two or more stimulants and Atomoxetine.[8]

2.2.2 Demographic characteristics associated with antidepressant prescription:

As stated above, antidepressants are mainly used in the treatment of depressive, anxiety and enuretic disorders. There are differences in the demographics in terms of the presentation of these disorders, which reflects in antidepressant prescription trends.[3, 33]

Gender:

Antidepressant prescription differs between the sexes.[3,20] In the majority of studies, females under the age of 18 receive more prescriptions for antidepressants (specifically SSRIS) than their male counterparts.[1,29] This is because of the increased prevalence of mood and anxiety disorders in females.[25] Females over the age of 13 are twice as likely to develop a unipolar depression compared to males.[28,36] In prepubescent children however, there is an equivocal number of males and females that develop depression.[25] Locally, Burger et al confirmed the findings of the majority of international studies that showed that more females under the age of 18 year received prescriptions for antidepressants than males.[34] Anxiety disorders are also more commonly found in females.[36,37] In contrast to this female predominance, males are 1.5 to 2 times more likely to develop an enuretic disorder.[23,3]

Age:

Antidepressant prescriptions increase with age.[25,38,39] The age differences in antidepressant prescription relate to the mean age of onset of psychiatric disorders.

Kessler et al in the National Survey in 2005, looked at the median age of onset of psychiatric disorders in the United States of America (USA).[40] They found that the median age of onset for anxiety disorders was 11 years and mood disorders was 25 year.[40] Locally the South African Stress and Health (SASH) study reported that the median age of anxiety and mood disorders was 32 years and 37 years respectively.[36] Enuresis decreases with increasing age and accordingly TCA prescriptions for this disorder are found to be higher in prepubescent children.[24, 34, 38]

Murray et al looked at antidepressant prescription in British children and showed that antidepressant use increased with age.[38] Additionally he showed that the prescription of antidepressants in over 15 year olds was at a ratio of female to male of 3:1, and were mainly SSRI's. Moreover, he showed that in the under-twelve year's group, males received more antidepressants (specifically TCAs) than females with a 5:3 ratio of male to female.[38]

Locally, Burger et al[34] confirmed the majority of international findings, showing that more females receive prescriptions for antidepressants than males. Additionally, they showed that under nine year olds were more likely to receive tricyclic antidepressants, and older age groups were more likely to be prescribed SSRI's. [34] These findings correlate with Murrays finding from the UK.[38]

Race:

Racial disparities were most significant the prescription patterns in the antidepressant group of psychotropics. .[41] A large USA study by Stevens et al[42] looking at Medical Aid data, showed convincingly that Black youths were statistically less likely to have antidepressants prescribed for them than Non-

Hispanic (NH) White youths. Other studies on children and adults made similar findings, when comparing NH Whites to Blacks and Hispanics.[22,43] Cultural differences between the doctor and the patient and variances in the perception of mental health amongst various race groups may also account for the disparities.[44]

In summary, antidepressants treat paediatric mood, anxiety and elimination disorders. Selective serotonin reuptake inhibitors are the preferred medication. Antidepressants are more commonly prescribed in females and adolescents and in NH White children.

2.3 Antipsychotics:

2.3.1 Indications for use of antipsychotics:

Typical and atypical antipsychotics treat psychotic and non-psychotic conditions in children. Psychotic disorders include schizophrenia, organic psychosis and substance induced psychotic disorder.[45] They are also used to treat psychosis associated with mood disorders.[45] Non-psychotic disorders include bipolar Disorder 1 without psychotic features, Tourette's syndrome, and behavioural symptoms associated with autism spectrum disorder, conduct disorder, mental retardation and ADHD.[46-49]

Dopamine is one of the main neuro-transmitters targeted by antipsychotics.[11] Typical antipsychotics were used primarily to treat psychotic disorders, before the widespread use of atypical antipsychotics. As a result of the mechanism of action of the typical antipsychotics (i.e. potent dopamine_2 (D_2) receptor antagonism with cholinergic and histaminergic antagonism) side effects from typical agents are common. These include extrapyramidal side effects, elevations in prolactin and cognitive flattening.[11] Atypical antipsychotics have less extra-pyramidal side effects than typical agents and are more frequently used in children.

Atypical antipsychotics, used in paediatric patients, are serotonin-dopamine antagonists. They include olanzapine; quetiapine, aripiprazole and risperidone.[11] These atypical antipsychotics exert their action through their antagonistic effects on dopamine_1 receptor (D_1), dopamine_2 receptor (D_2) and 5HT receptors. They exert multiple effects and are used to treat psychosis, mood instability and problematic behaviour. Major concerns with atypical antipsychotics are adverse effects of hyperprolactinemia, weight gain, and metabolic syndrome.[11] Data are scarce regarding the long-term safety and adverse effects of these agents on the developing brain.

Doey et al looked at atypical antipsychotic prescriptions in children and reasons for their prescription.[47]They found that a considerable percentage of physicians prescribe the medications for symptoms and for diagnoses that have not been previously studied for efficacy and safety. The most common indication for the prescription was 'poor frustration tolerance' (75%) followed by 'impulsivity' (65%). [47]

Atypical Antipsychotics are first line pharmacological treatment for irritability, aggression and self-injurious behaviour in children with autism spectrum disorder and conduct disorder.[4, 48,49] The NICE guidelines caution that antipsychotics should only be used once other psychosocial interventions aimed at reducing disruptive behaviour have not worked or are not possible.[48,49] In South Africa, risperidone is registered for the treatment of conduct and behavioural disorders in children (5-12 years old) with sub-average intelligence or mental retardation.[12] Holford et al[50] looked at mild to moderately intellectually disabled paediatric outpatients with behavioural disorders.[50] This local multicentre study showed that 34 children with behavioural disorders largely responded well to a slowly titrated, low dose of oral risperidone (mean dose 1.47mg daily). They found with this low dose that there were transient side effects (weight

gain, raised prolactin levels and sleepiness) that peaked at three months and did not evolve further during the yearlong trial.[50]

In the last fifteen years there has been an increase in paediatric antipsychotic prescribing.[16,22,51] An FDA advisory committee looking at the use of atypical antipsychotics in children showed that from 2004, there was a 22% increase in prescriptions of these medications.[51] This has been attributed to the increase in off-label prescriptions.[51] Of controversy in the literature currently is the increasing off-label use of antipsychotics as behavioural modifiers in foster care children.[52,53]

Burcu et al[53] recently published a large study looking at atypical antipsychotic use in children on Medicaid Insurance in the USA. Children in foster care had the greatest duration of atypical antipsychotic exposure. Additionally one in three children in foster care with a diagnosis of ADHD alone were treated with atypical antipsychotics presumably for troublesome behaviour.[53] The benefits of treating disruptive behaviour in children in foster care with atypical antipsychotics needs to be carefully weighed up against the risk of harmful side effects (e.g. metabolic syndrome and weight gain) of the medication.[51,54]

Atypical antipsychotics are also used in the treatment of child and adolescent onset bipolar disorder and schizophrenia.[55, 56] FDA approved agents for treatment of acute mania or mixed episodes include risperidone, olanzapine, quetiapine and aripiprazole.[57-60] Recent research has shown that atypical antipsychotics may be more efficacious than traditional mood stabilizers (anticonvulsants and lithium) in treating bipolar disorder.[55, 61] The main concern with using these agents in children as mentioned previously is the high incidence of significant side effects, and the FDA

labelling cautions with regard to the increased potential for weight gain and hyperlipidemia in children and adolescents compared to adults.[54, 57,60]

There is limited research in South Africa on atypical antipsychotic use, but looking at Raman's aforementioned study in Johannesburg at RMH, she found that almost 15% of the children on medication (n=227) received anti- psychotics.[17] Over 80% of these antipsychotic prescriptions were for off-label use.[17]

2.3.2 Demographic characteristics associated with antipsychotic prescription:

Gender:

There is a preponderance of males in all age groups receiving prescriptions of antipsychotics compared to their female counterparts.[1,62] Males present more frequently with tic disorders, disruptive disorders and pervasive developmental disorders. Studies in Canada, UK, USA, Denmark and Netherlands all support the finding of a male preponderance for the prescription of antipsychotics.[63-66]

Age:

Consistently across all studies, adolescents receive more prescriptions for antipsychotics. Olfson et al[66] in his latest research looking at large amounts of Medicaid data showed that adolescents (14-20 year olds) received over twice as many antipsychotic prescriptions compared to children (< 13 years old). Likewise studies in Denmark and the Netherlands support these findings.[1,65] Antipsychotic use increases in adolescence and early adulthood due to the onset of psychotic disorders during this developmental phase.[67] Substance abuse psychosis and disruptive conduct disorder increase during this time.[67] Psychotic disorders under the age of 13 are very rare. [67]

Race:

Racial differences in the prescribing of antipsychotics are inconsistent. This appears to be due to the sample populations from which the data is derived. Olfson et al[66] showed that when confounding factors such as medical insurance and number of health care visits were taken into account, they showed that there were few differences in prescriptions according to race. Sleath et al found no differences in a smaller outpatient New York study, whereas other larger studies showed an African–American predominance of antipsychotic prescription.[44]

In summary, the use of atypical antipsychotics in children is increasing and remains controversial. Atypical antipsychotics are used for licensed indications, and are commonly used off-label to treat aggression, hyperactivity and irritability. Older male children and adolescents and those in foster care are more likely to receive a prescription for these psychiatric medications compared to females.

2.4 Indications for use of other psychotropics:

Pharmaco-epidemiological information on other psychotropics including mood stabilizers (anticonvulsants and lithium) and alpha-antagonists (clonidine) have been explored in the literature, and as a group they make up a relative minority of the total prescriptions in children and adolescents.

The NICE guidelines indicate that mood stabilisers (anticonvulsants and lithium) are used in the treatment and prophylaxis of Bipolar disorder in children.[55] They are used in the long-term prophylaxis and the acute treatment of manic, mixed or depressive

episodes. NICE guidelines indicate that the pharmacological treatment of Bipolar disorder in children and adolescents is similar to adults.[55]

Lithium, valproate and carbamazepine have been shown to treat acute manic phases in children. There are fewer trials investigating acute bipolar depressive episodes, but there is some evidence of a response to lithium and lamotrigine (either as monotherapy or augmentation). It is advised that psychological treatment aimed at treating a depressive episode should also be considered when treating a bipolar depressive episode in under 18 year olds.[55]

Alpha agonists (e.g. clonidine hydrochloride) are used in the treatment of ADHD and tics. They are also used off-label for treatment of autism spectrum disorder, anxiety, disruptive and sleep disorders.[9, 68]

2.5 Concomitant prescribing of psychotropics:

Concomitant prescribing has been defined as "The use of two or more medications for either the same or different psychiatric symptoms or disorders (either for the same or different emotional/behavioural target symptoms)". [69]

Concerns with prescriptions of concomitant medication, is the lack of rigorous research to promote the use of these agents together as well as reports of adverse drug events.[69] Concomitant medication is either used to treat two comorbid conditions with different medications, or is used to augment existing treatment to which there may have been an inadequate response.[69] Factors increasing concomitant psychotropic use include male sex, older children and/or multiple psychiatric or comorbid neurologic diagnoses.[69, 70]

Safer et al[69] reviewed and discussed concomitant medication practices internationally

and advised that adding additional medication to augment treatment could be useful in some situations. They caution that this practice needs careful monitoring.[69] Comer et al[70] looked at data from the National Ambulatory Medical Care Surveys, and showed that the most common combination in child psychiatry in the USA between 1996 and 2007 was an antidepressant with an ADHD medication. Interestingly approximately 35 % of children receiving this combination had a comorbid mood, anxiety or disruptive disorder in addition to a primary ADHD diagnosis. Recently Betts et al[71] looked at prescribing data for over 100,000 children between 6 and 17 years of age receiving a stimulant for a primary ADHD diagnosis). The most common combination of medication was a stimulant and an SSRI (17.6%), followed by atypical antipsychotics (12.6%) and lastly clonidine (8.3%). Concomitant psychotropic use was 12.6% in patients with an ADHD diagnosis only and 41.7% for a comorbid ADHD diagnosis, (i.e. ADHD and an additional diagnosis). [71]

Rate of concomitant prescribing varies internationally. Zonfrillo et al [72] review on poly-psychotropic prescribing in the USA in 2005 revealed that approximately 20% of children on psychotropics received two or more medications.[72] Since the prevalence rate of antipsychotic prescriptions (commonly used as augmentation agents) is increasing it is suspected that the current figures are higher. Comer's recent USA study[70] showed a concerning rate of 32% concomitant prescriptions. Prevalence studies in Iceland and Turkey have shown around an 18% rate of polypharmacy.[73,74] There are no South African studies looking at paediatric concomitant psychotropic prescribing.

2.6 Off-label prescribing of psychotropics:

Off-label prescribing involves the prescribing of medications for indications or

population subgroups that regulatory agencies have not officially approved**.**

Off-label prescribing is common in children and does not imply contra-indicated prescribing.[75] These prescriptions are based on the extrapolation of efficacy and side effect profiles in adults. In child psychiatry off-label use includes use of a medication in an unregistered age group for a registered condition or unregistered use of a medication for a condition or symptoms, as indicated in Table 2.2. Areas of concern with off-label use are the safety, efficacy and the use of these medications in the absence of strong evidence.[2]

Off-label use is common in children for the following reasons. Firstly most drug trials are developed for adults, with efficacy in children needing to be extrapolated.[2,3] Because of this there is a relative lack of psychotropics registered for children which limits clinician's options. It is suggested that off-label prescribing occurs based on either clinician's opinion/experience with the medication, evidence from research findings or because of patient preferences.[2,3]

Table 2.2: Common off-label uses of psychiatric medication in children:

Class, Subclass	Drug	Indication	Target symptoms
Antidepressants			
SSRI	Citalopram	Depressive and Anxiety disorders	Depression; Anxiety
	Duloxetine	"	Depression; Anxiety
	Escitalopram	"	Depression; Anxiety
Antipsychotic	Risperidone	Autism	Irritability, Aggression, Hyperactivity
		Developmental disabilities	Aggression
		Disruptive behavioural disorders (including ADHD)	Conduct problems, Irritability, Hyperactivity, Aggression
		Tourette syndrome	Tics
	Olanzapine	PDD	Aggression
		Bipolar 1 disorder	Manic or mixed episodes
		Schizophrenia	Positive and negative symptoms

Adapted with permission from [2, 70].

Off-label prescribing is noted with use in antidepressants and atypical antipsychotics. Lee et al[3] looked at data in the National Ambulatory Medical Care Survey (NAMCS) for on and off- label antidepressant prescribing in 6-18 year olds.[3] He found nine out of ten antidepressant prescriptions were for off-label indications. The most commonly prescribed off-label antidepressants included sertraline, bupropion, escitalopram, venlafaxine and paroxetine hydrochloride. These were prescribed for the treatment of

depression. [3]

Over the last fifteen years, there has been an increase in paediatric antipsychotic prescribing.[5,22] An FDA advisory committee looking at the use of atypical antipsychotics in children showed that from 2004 there was a 22% increase in prescriptions of these medications.[51] This has been attributed to the increase in off-label prescriptions.[51] Off-label antipsychotic use was discussed above in section 2.3.1.

Our study aims to describe the demographic and clinical variables associated with psychotropic prescription at TOCC, and contribute to the body of knowledge both locally and internationally.

CHAPTER THREE: METHODS:

3.1 Study design:

The study is a retrospective file review. Data was collected from all new patients attending the TOCC from 1st January 2010 to the end of December 2011. Further analysis of the records followed to determine the sample. The data from the sample was then captured onto data collection sheets.

3.2 Study setting:

The Child Outpatient Clinic is at the Tara H Moross Psychiatric Hospital (Tara), Hurlingham, Johannesburg, South Africa. Tara is a state hospital providing specialised psychiatric services and also forms part of the University of the Witwatersrand Academic Circuit. , ?. Tara H Morros Hospital accepts referrals from various centres within Gauteng. Outpatient files stored at the TOCC were reviewed. Multi-disciplinary team (MDT) members working in this unit record their findings in these files. The MDT consists of two child consultant psychiatrists, two psychiatric registrars, two psychiatric nursing sisters, two senior psychologists, one community service psychologist, two intern psychologists, an occupational therapist, and a social worker.

3.3 Sample:

The sample in this study consists of children meeting the inclusion criteria below.

3.3.1 Inclusion criteria:

1) New patients that presented to TOCC, during the study period. (January 2010 to the end of December 2011).

2) Children between 6 and 14 years old. (6 ≤ and ≥14).

3) Patients that have seen a medical doctor at the clinic, and for whom a management plan has been formulated, and medication prescribed.

4) Children with an Axis I Diagnosis as defined by the DSM-IV-TR criteria. (See Appendix 1).

5) Children with a diagnosis on other axes, in addition to an Axis I diagnosis.

3.3.2 Exclusion criteria:

1) Children with a V code diagnosis only on Axis I.

2) Children with an Axis II diagnosis, in the absence of an Axis I diagnosis.

3) Children already on psychiatric medication. These children were excluded since the study investigated prescribing practices for new patients at clinic; it reflects the prescribing practices at TOCC (and not at other centres).

The sample was determined after the inclusion and exclusion criteria were applied to the raw data collected from the outpatient files and clinical records.

3.4 Data variables:

Data was obtained from patients' files at the clinic as well as from the Consultant Child Psychiatrist's (Dr Vermaak) clinic records. Data variables were captured onto the data collection sheet (Appendix 2). Included in this data collection sheet were demographic, clinical and medication variables. (Table 3.1)

Table 3.1: Outline of variables collected: *

Variable	
Demographic	
	Age
	Gender
	Race
Clinical	
	Axis I category/ies
Medication	
	Name of medication
	Class of medication

*Refer to Appendix 3 for more details

Children may have more than one Axis I diagnosis, and each unique diagnosis was grouped into diagnostic categories. There are thirteen diagnostic categories and four medication categories. (Table 3.2) The diagnostic categories are not strictly DSM-IV-TR categories. Details of the unique diagnoses making up these categories can be found in Appendix 3, 4 and 5.

Table 3.2: Details of diagnostic and psychotropic categories:

Category	
Diagnostic	Disruptive disorder
	Anxiety disorder
	Mood disorder
	Elimination disorder
	Tic
	Disorder
	Substance Use disorder
	Attachment disorder
	Psychotic disorder
	Somatoform disorder
	Learning disorder
Psychotropic	Psychostimulant
	Antidepressant
	Antipsychotic
	Other

3.5 Data Analysis:

Descriptive analyses of all variables occurred, and data were grouped according to categories in order to make statistical calculations more meaningful:

- Age: The age of the patient at the time of the appointment was calculated using Microsoft Excel®. The date of birth was subtracted from the date the patient was seen. For statistical purposes the patients were grouped into two age groups. Patients who were exactly six years or greater but less than ten years old were grouped in the (6-10 year old) age group. Patients who were exactly 10 years or older, but less or equal to 14 years were grouped in the (10-14 year old) age group.

- Race: Patients were classified as Black African (Black), Coloured, Indian or White as per the Census 2011(South Africa) classification.[76] Indian and Coloured patients were grouped together in a group called 'Other' since the number of these patients was negligible.

- Diagnostic category: If two diagnoses on Axis I were from the same diagnostic group, they were counted as one (i.e. were not double counted; if a patient suffered from generalised anxiety disorder and separation anxiety disorder, this was only counted as one anxiety disorder). Diagnoses were collected individually according to DSM-IV-TR nosology, and then diagnoses were grouped together into diagnostic categories. These categories were needed in order for statistical calculations to be more meaningful.(Appendix 3 and 4)

- Psychotropic category: Although Atomoxetine is not a stimulant; it was recorded as a stimulant medication along with methylphenidate, since they are both used to

treat ADHD. The number of children on atomoxetine was minimal.

- The frequencies of the categorical demographic data, clinical data and treatment data were noted.

- The mean and standard deviation was calculated for the age variable.

- Data from the demographic, diagnostic and psychotropic categories were investigated quantitatively using the chi-squared test. A P-value of $P< 0.05$ was considered significant.

- The majority of the statistical analyses were performed using the software Graph pad Instat® for Macintosh (2009) and the remainder using Microsoft Excel® for Mac 2011.

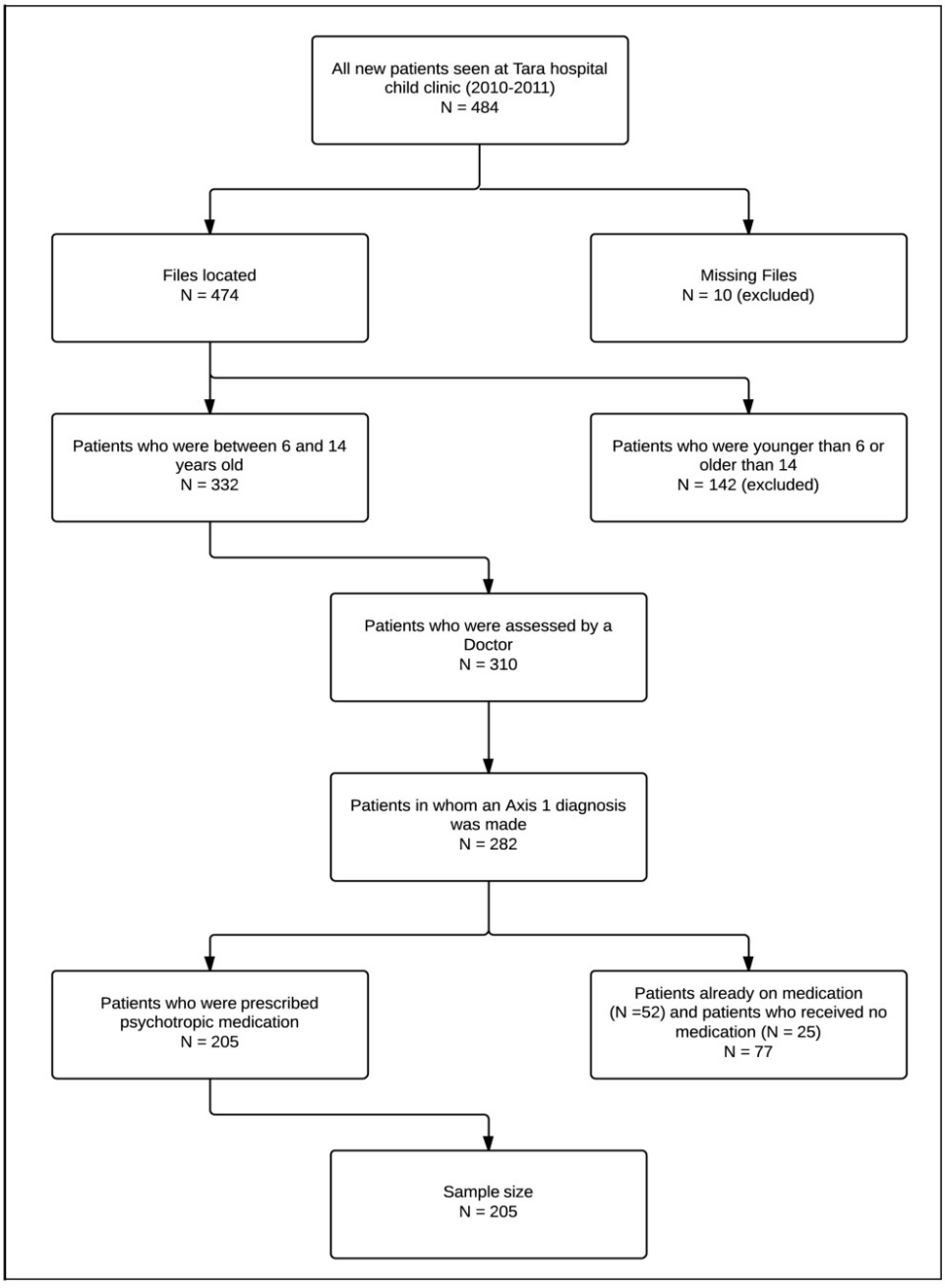
3.6 Ethical considerations:

Permission was sought from the Chief Executive Officer at Tara H Moross Hospital prior to data collection. Every patient/guardian presenting at Tara Hospital routinely sign a consent form for the use of their clinical data. Data was collected on site, from an office at TOCC. The primary researcher alone had access to the patient names and a collating number was allocated to each file number.. This research protocol was submitted and approved by the Department of Neuroscience postgraduate research committee. Ethics clearance was granted from the Human Research Ethics Committee at the University of the Witwatersrand: No. M111106. (See Appendix 6)

CHAPTER FOUR: RESULTS:

4.1 Sample population:

A total of 484 new patients attended the clinic in the study period (Figure 4.1). After the inclusion and exclusion criteria were applied to the data, 205 patient files remained.



4.1 Flow diagram of patient group

4.2 Demographic variables:

Male patients accounted for the bulk of the sample (Table 4.1). Children between the ages of six and ten years old were more likely to present to the clinic compared to ten to fourteen year old patients. The Black patients formed the biggest group seen at the clinic, followed by White patients and then other (Indian and Coloured) patients.

Table 4.1: Demographic characteristics of the sample (n=205)

Variable		%(N)
Gender	Male	70.2(144)
	Female	29.8(61)
Age	mean(±SD)	9.4(SD 2.2)
	6-10 years	62.4(128)
	10-14 years	37.6(77)
Race	Black	56.6(116)
	White	40(82)
	Other*	3.4(7)

*Other = Indian + Coloured

4.2.1 Demographic characteristics of patients receiving psychiatric medication:

A total of 222 psychotropics were prescribed for the 205 patients. Psychostimulants were prescribed in over three-quarters of the population. (Table 4.2) Approximately one quarter of patients was on antidepressants. Psychostimulants were more commonly prescribed to males, Black patients and patients between the ages of six and ten. Conversely, antidepressants were most commonly prescribed in White patients, and males between the ages of ten and fourteen years old. Antipsychotics were infrequently prescribed.

Table 4.2: Psychotropic prescriptions and associated demographic characteristics:

		Psychostimulant N (% of sample)	Antidepressant N (% of sample)	Antipsychotic N (% of sample)
Total		161 (78.5)	51 (24.9)	10 (4.9)
Gender				
	Male	117 (57.1)	31 (15.1)	6 (2.9)
	Female	44 (21.5)	20 (9.8)	4 (2.0)
Age				
	6-10 years	110 (53.7)	22 (10.7)	5 (2.4)
	10-14 years	51 (24.9)	29 (14.1)	6 (2.9)
Race				
	Black	94 (45.9)	22 (10.7)	6 (2.9)
	White	61 (29.8)	30 (14.6)	5 (2.4)
	Other	6 (2.9)	1 (0.5)	0 (0)

4.2.2 Statistical correlations between psychotropic prescription and demographic variables:

The following section analyses the relationships between the psychotropic prescribed and demographic variables. Due to small numbers antipsychotics, antiepileptics and TCAs were grouped together into 'other medication'.

Gender:

The chi squared test was performed to examine the correlation between gender and the different psychotropic prescription (Figure 4.2). The relationship between these variables was non-significant.

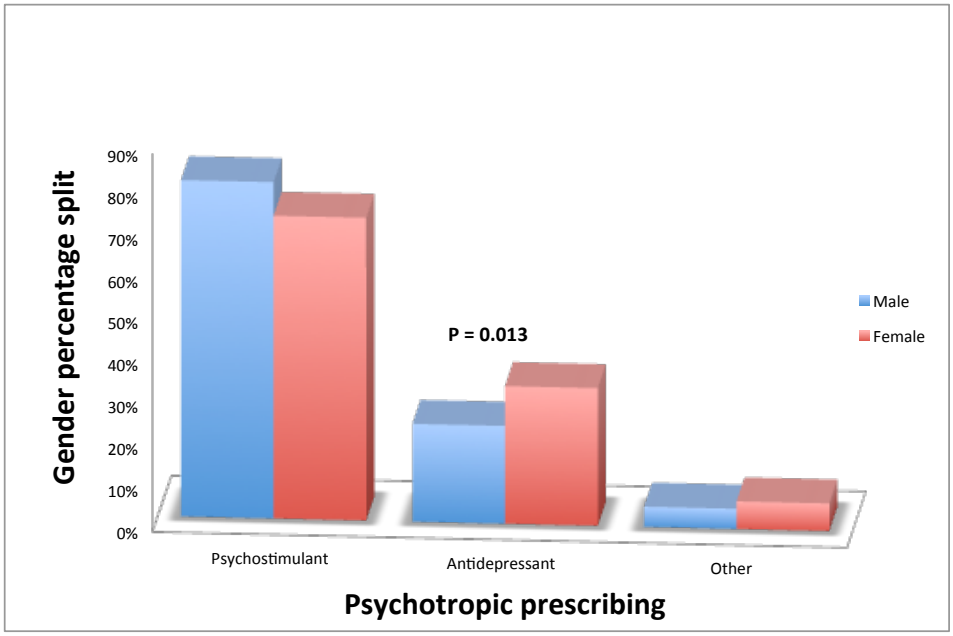


Figure 4.2 Gender characteristics associated with psychotropic prescribing

Age Group:

The chi square test showed significant association between the age group of the patient and the psychotropic prescribed. (X^2 (2, N = 222) = 12.15 P = 0.003) (Figure 4.3) Specifically psychostimulants were more likely than antidepressants and other medications to be prescribed in the six to ten year old age group, and antidepressants were more commonly prescribed in the ten to fourteen year old age group.

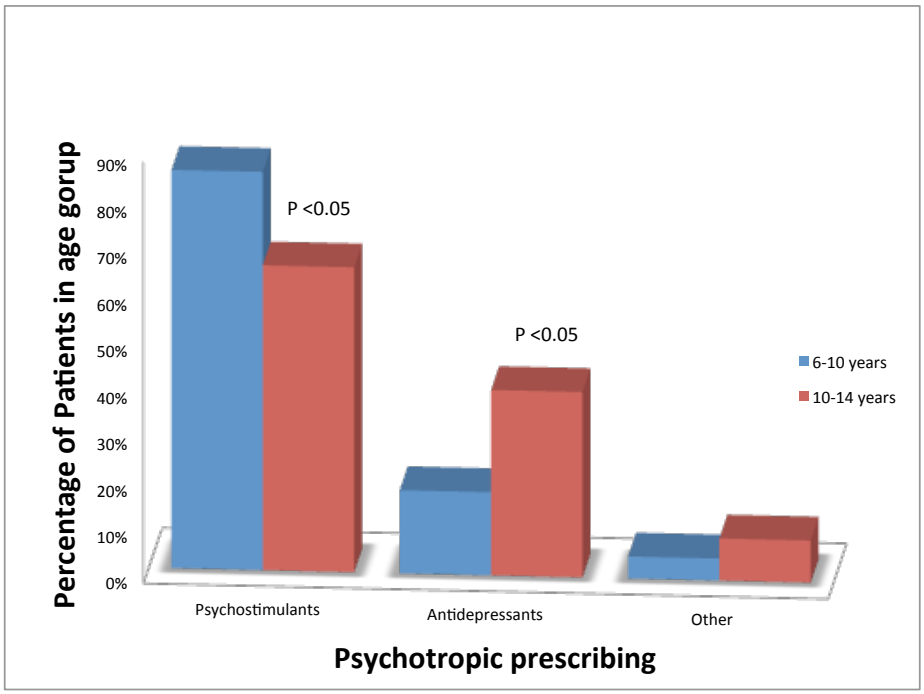


Figure 4.3:

Age group characteristics associated with psychotropic prescribing

Race:

The chi square test showed significant association between the race of the patient and the psychotropic prescribed. (X^2 (2, N = 222) = 6.4 P = 0.04). A significant association was found between race and antidepressant prescriptions. White patients were statistically more likely to receive a prescription of an antidepressant. (P value = 0.013).

Only Black and White patients are portrayed on this frequency diagram since the numbers in the "Other" group were small and would not be accurately displayed, however they were included in the statistical analysis. ("Other" data was combined with the Black patients) (Figure 4.4).

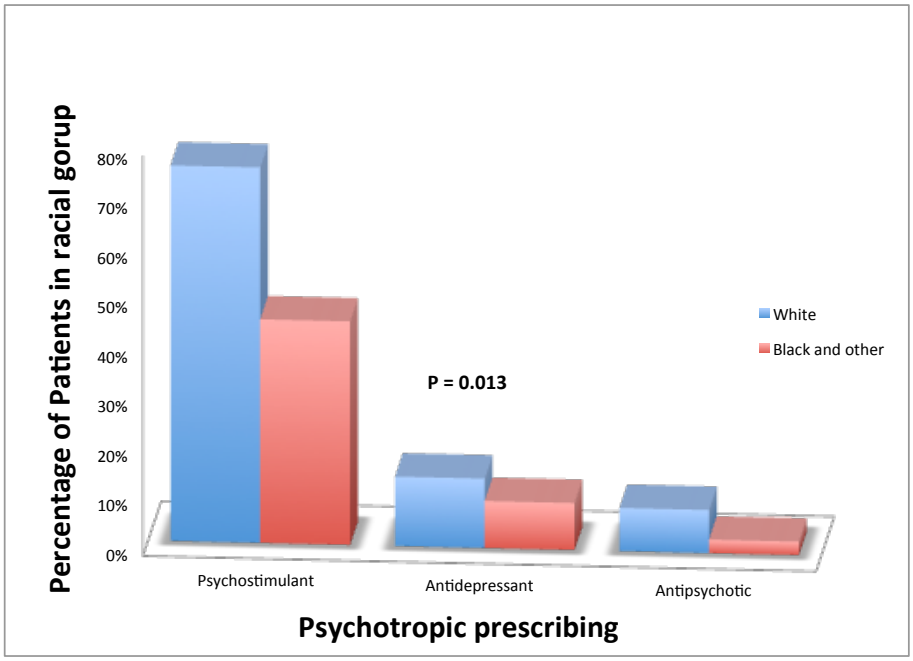


Figure 4.4: Racial characteristics associated with psychotropic prescribing

4.3 Clinical variables:

4.3.1 Diagnostic profile of the sample:

All patients in this study on psychiatric medication had an Axis I diagnosis. The frequency of these diagnoses in the sample is shown below in Table 4.3. There were a total of 309 individual diagnoses made. The percentage in Table 4.3 is the percentage of each diagnostic category in the sample. (N= 205)

Table 4.3: Frequency distribution of diagnostic categories in the sample:(n=205)

Diagnostic category	% (N)
Attention deficit hyperactivity disorder	81 (166)
Anxiety disorder	24.9 (51)
Disruptive disorder	12.2 (25)
Mood disorder	9.3 (19)
Learning disorder	8.8 (18)
Elimination disorder	5.4 (11)
Attachment disorder	3.4 (7)
Psychotic disorder	0.5 (1)
Pervasive developmental disorder	0.5 (1)
Somatoform disorder	0.5 (1)
Selective Mutism	0.5 (1)
Substance Use disorder	0 (0)
Tic disorder	0 (0)

Attention deficit hyperactivity disorders make up the vast majority of Axis I diagnoses, followed by one quarter of the sample that has anxiety disorders (Table 4.3). Learning,

disruptive and mood disorders occur at a similar rate to each other, around 8-10% of the sample. The remaining diagnostic categories were found in less than 11% of the population.

4.3.2 Diagnostic profile compared to demographic variables:

Over 80% of the sample was diagnosed with ADHD; the majority were Black males between the ages of six and ten years old (Table 4.4). The next big category was anxiety disorders, which consisted mostly of White males between the ages of ten and fourteen years old. Mood disorders, learning disorders and elimination disorders made up the remainder of the top six common diagnoses.

Table 4.4: Frequency distribution of demographic variables in comparison to diagnostic categories:(n=205)

	ADHD (%)	Anxiety disorder (%)	Disruptive disorder (%)	Learning disorder (%)	Mood disorder (%)	Elimination disorder %)	Other disorders (%)
Total	81	24.9	12.2	8.8	9.3	5.4	5.4
Age first seen:*							
6 - 10 years	55.6*	14.6	3.4*	5.4	1.5*	3.9	2.4
10- 14years	25.4*	10.2	8.8*	3.4	7.8*	1.5	2.9
Gender:							
Female	22.4	10.2	1.5	2.4	2.4	0.5	1.5
Male	58.5	14.6	10.7	6.3	6.8	4.9	3.9
Race:							
White	31.2	15.1*	4.9	1.5	3.4	2	3.9
Black/ Other	49.8	9.8*	7.3	7.3	5.9	3.4	1.5

* P <0.05

Other = Attachment disorder, psychotic disorder, pervasive developmental disorder, somatoform disorder, selective mutism, substance use and tic disorder.

4.3.3 Statistical correlations between diagnostic variables and demographic variables:

To avoid problems with statistical calculations with the data in Table 4.4 the categories; elimination disorder, attachment disorder, psychotic disorder, pervasive developmental disorder, somatoform disorder and selective mutism were combined into one diagnostic category, “Other disorders”.

Gender:

The chi square test of independence showed no association between the gender of the patient and the diagnostic category.

Age Group:

The chi square test of independence showed a significant association between the age group of the patient and the diagnostic category. (X^2 (6, N = 309) = 30.72 P < 0.00) (Table 4.4) Further analysis revealed that six to ten year olds are more likely than ten to fourteen year olds to be diagnosed with ADHD (Fishers exact test P = 0.00). Conversely, ten to fourteen year olds are statistically more likely to be diagnosed with a mood disorder and/or a disruptive disorder**.**

Race:

The chi square test of independence showed no association between the race of the patient and the diagnostic category.

4.4 Diagnostic category and psychotropics prescribed:

Table 4.5: Diagnostic profiles of the sample and the psychotropic/s prescribed:

	Stimulant	SSRI	Antipsychotic(AP)	TCA	Stimulant,SSRI	Stimulant,AP	Stimulant,TCA	SSRI,TCA	Stimulant,SSRI,AP	Total
ADHD	92									92
Anxiety disorder		12								12
Mood disorder		6	1							7
Disruptive disorder		1	3							4
Selective mutism		1								1
Psychotic disorder			1							1
ADHD, anxiety disorder	14	4			5	1			2	26
ADHD,learning disorder	15									15
ADHD,disruptive disorder	10		1			1				12
ADHD,elimination disorder	4				1		2			7
Anxiety disorder,mood disorder		7								7
ADHD,disruptive disorder,attachment disorder	4									4
ADHD,attachment disorder	3									3
Mood disorder,disruptive disorder		3								3
ADHD,mood disorder					2					2
Anxiety disorder,elimination disorder				1				1		2
ADHD,anxiety disorder,learning disorder	1									1
ADHD,anxiety disorder,disruptive disorder					1					1
ADHD,pervasive developmental disorder	1									1
Anxiety disorder,disruptive disorder		1								1
Anxiety disorder,somatoform disorder		1								1
ADHD,disruptive disorder,elimination disorder	1									1
ADHD,elimination disorder,learning disorder	1									1
	146	36	6	1	9	2	2	1	2	205

SSRI – Selective serotonin reuptake inhibitor, TCA – Tricyclic antidepressant, AP - Antipsychotic

4.4.1 Psychostimulants and ADHD

There were 166 patients diagnosed with ADHD and 97% (n= 161) of these patients received a prescription for a psychostimulant. Concomitant prescribing was found in 15 patients who were diagnosed with ADHD. (9.03%, n = 15/166) The most common psychotropic combination found in 11 of these patients, was an

antidepressant and a psychostimulant. (See Appendix 7).

4.4.2 Antidepressants and Anxiety/Mood disorders:

Anxiety disorders:

There were 51 patients diagnosed with an anxiety disorder. Anxiety disorders are commonly diagnosed with other disorders. (76.5% comorbid diagnoses, n=39/51) (Table 4.5) The most common comorbid diagnosis with anxiety disorders is ADHD (anxiety and ADHD diagnosis = 51% n = 26/51), followed by anxiety disorder with a mood disorder (anxiety and mood diagnosis, 13.7%, n=7/51). Monotherapy made up of either antidepressants or psychostimulants occurred in 40 patients diagnosed with anxiety disorders. Twenty-five of these patients were on antidepressants only. (49% (n = 25/51)) Of the 26 patients who had anxiety disorders and ADHD, fifteen were on psychostimulants only (29.4% n =15/51). Only 34 of the 51 children with anxiety disorders were started on an SSRI (67%). Concomitant prescribing in patients with anxiety disorders only occurred in 10 patients. (19.6 % n = 10 / 51) The most common combination of medication was an antidepressant and a psychostimulant (See Table 4.5).

Mood disorders:

Mood disorders were equally likely to be diagnosed in isolation (36.8 % n = 7/19) or with a comorbid anxiety disorder (36.8 % n = 7/19). Antidepressants (all SSRI's) were prescribed in 94.7 % of patients with mood disorders. (n = 18 /19). Only two patients with a mood disorder received concomitant medication. (For more detail see Appendix 8). Significantly more patients with a mood disorder received a prescription for an SSRI compared to patients with an anxiety disorder ($p = 0.015$).

4.4.3 Antipsychotics and associated diagnoses:

Antipsychotics were prescribed in ten patients for a variety of disorders, disruptive disorder ± ADHD (n = 5), mood disorder (n = 1), psychotic disorder (n = 1) and an anxiety disorder with comorbid ADHD. (n = 3) They were typically prescribed in isolation with only four patients on antipsychotics receiving concomitant prescriptions, two with a psychostimulant and two with a psychostimulant and antidepressant. (SSRI) (For more detail see Appendix 9).

4.5 Concomitant prescribing:

Concomitant prescribing occurred in 16 patients (Table 4.6). The majority of these patients received a combination of a stimulant and a SSRI for comorbid ADHD and anxiety disorder. For more information regarding individual patients and comorbid diagnoses and medication please see Table 4.5 and the flow charts in the Appendices.

Table 4.6: Concomitant prescribing frequencies:

	%(N)
Total:	100(205)
Single psychotropic Stimulant:	71.2 (146)
Antidepressant:	18 (37)
Antipsychotic:	2.9 (6)
Two psychotropics:	
Stimulant + Antidepressant:	5.4 (11)
Stimulant + Antipsychotic:	0.9 (2)
Antidepressant + Anti-depressant:*	0.5 (1)
Three psychotropics: Stimulant	
+ Antidepressant + Antipsychotic:	0.9 (2)

Concomitant prescribing occurred in 16 patients. The majority of these patients received a combination of a stimulant and a SSRI for comorbid ADHD and anxiety disorder. For more information regarding individual patients and comorbid diagnoses and medication please see Table 4.5 and the flow charts in the Appendices.

4.6 Off-label prescribing:

Table 4.7: Off-label prescribing:

		Off-label use (N)	FDA approved use (N)	Total (N)
Antidepressants:				51
SSRI	Fluoxetine	5	1	6
	Citalopram	41	0	41
TCA	Imipramine	0	3	3
	Citalopram + Imipramine	1	1	1
Psychostimulants:				161
	Methylphenidate IR/LA/XR	0	158	158
	Atomoxetine	0	3	3
Antipsychotics:				10
	Risperidone	10	0	10

The majority of antidepressants prescribed were off-label. All Imipramine prescriptions (n=4) were for a FDA-approved condition, enuresis. (*See Table 1.1)* Only one case of fluoxetine prescribing for major depressive disorder was FDA-approved. The remaining 47 fluoxetine prescriptions and all citalopram prescriptions were off-label. Conditions treated included major depressive disorder, generalised anxiety disorder, adjustment disorder and dysthymic disorder. Risperidone was the only antipsychotic prescribed in the sample. All prescriptions were off-label, and diagnoses included: disruptive behaviour disorder (n=5) psychotic disorder secondary to general medical condition (n=1), mood disorder (n=1), and ADHD with comorbid generalised anxiety disorder (n=3).

CHAPTER 5: DISCUSSION:

5.1 Summary and interpretation of main results:

Prescriptions of only three classes of psychotropics were seen in this study. These were psychostimulants, antidepressants and antipsychotics. Psychostimulants were most frequently prescribed, followed by antidepressants and antipsychotics. Concomitant prescribing was sporadic. There were some significant demographic and clinical differences found in prescription of these medications.

5.2 Demographic profile of sample:

There were more than twice as many male patients prescribed psychotropics compared to females. This is in keeping with the male predominance of prescriptions found in previous research.[1] The age range of the sample should be interpreted cautiously, since the sample only looked at six to fourteen year olds. The racial distribution of patients at TOCC does not reflect the demographic profile of the South African population where Black African patients constitute a significant majority.[76] White patients are overrepresented in the sample and this may be because of the fact that TOCC is located in an area that was previously reserved for White persons. The demographic profile of the clinic was significantly different to that of the RMH, which is approximately 16 km from TOCC yet in a suburb previously zoned for Coloured persons.[17] Raman et al[17] found equal frequency of presentation across all race groups, whereas at TOCC Black African and White patients predominated and there were small numbers of Coloured and Indian patients.

5.3 Demographic profile and association with psychotropic prescribing and diagnostic category:

5.3.1 Age:

ADHD was most likely to be diagnosed, and psychostimulants were significantly more likely to be prescribed in the six to ten year old age group. ADHD usually starts in childhood and according to DSM-IV-TR, symptoms have to be present before the age of 7 in order to make a diagnosis.[10]

It is difficult to compare this study to previous research, due to the age grouping in this study. Some research shows that patients between the ages seven and twelve receive the highest number of psychostimulant prescriptions, whereas other research shows that psychostimulants are prescribed more in ten to fourteen year old group.[9,15] In Truters' Eastern Cape analysis, she found the largest number of prescriptions in the seven to twelve age group. The mean age of her sample receiving medication was 10.4 years, compared to 9.4 years in this study. [21] The basis for lower mean age is most likely to be due to the age cut-off of 14 years old (the age range in the study were patients between 6 and 14 years).

Mood disorders were more commonly found in the 10 to 14 year old group, and correspondingly antidepressants were more likely to be prescribed in this age group. This is in line with previous studies, and reflects the positive correlation between the increase in the rates of the diagnosis of mood disorders with increasing age.[25]

Mood disorders commonly start in adolescence, due to a combination of genetic, environmental and hormonal factors. [40,77] Stress is a known predisposing factor for the onset of which includes abuse, neglect and early loss of a parent.[77] The interaction

between environmental stressors and genetic disposition of the adolescence may result in the development of a mood disorder.[11,77] Studies looking at pubertal status have shown that the onset of puberty is associated with depression.[78] Oestrogen has been linked to depression, and is thought to account for the differences in rates of depression in male and female adolescents. Marked hormonal shifts during puberty may also account for extreme emotionality shown during this time.[78]

5.3.2 Gender:

Surprisingly, no gender differences were found when looking at prescriptions. This is in contrast to international studies that showed an increased incidence of male psychostimulant and antipsychotic prescription.[18,20] Furthermore, Wijlaars et al and Zito et al have reported that antidepressants are more likely to be prescribed in females.[23,29] The gender differences may not have been found in this study due to the limits on the age range and the small sample size that may have limited the validity of the results. Depression is more commonly found in adolescents compared to younger children, and the cut-off of 14 years old in this study may have impacted the finding of no gender differences in psychotropic prescriptions.

5.3.3 Race:

Consistent with international research, there was racial disparity in prescribing practices.[42,43] Antidepressants were more likely to be prescribed in White patients. A significant amount of literature looks at racial differences in the diagnosis of psychiatric disorders and antidepressant prescribing. Whaley et al[79] suggests that there are two hypothesis as reasons for the discrepancies. The first is “clinician bias”, where although the manifestation of symptoms is similar in different race groups, the clinician’s interpretation is different. Furthermore, second hypothesis is “cultural relativity,” where

race groups express psychological distress in different modes and clinicians are unaware or appear to be insensitive to this cultural difference.[79] Unfortunately, there are no South African studies investigating the disparities in diagnoses across these groups and there is an opportunity for further research in this area.

5.4 Clinical profile associated with psychotropic prescribing:

5.4.1 Psychostimulants:

Psychostimulant prescriptions accounted for 80 % of the sample, and conformed with SASOP guidelines.[13] This frequency is high in comparison to other studies looking at frequencies of psychostimulant prescriptions.[9,17] However, it is necessary to remember that the age groups represented in the study have the highest frequencies of ADHD, and are most likely skewing results. Looking specifically at ADHD, comorbid diagnoses and psychostimulants, certain trends are observed. Prescriptions of psychostimulants occurred in the vast majority of patients with ADHD and only 0.03% of patients with a diagnosis of ADHD did not have a prescription for a psychostimulant. In keeping with literature, ADHD is most likely to be diagnosed in isolation; followed by comorbid diagnoses of ADHD and either an anxiety disorder, ADHD and a learning disorder and ADHD and a disruptive disorder.[48]

5.4.2 Antidepressants:

Selective serotonin reuptake inhibitors (SSRI) made up over 90% of the antidepressants prescribed. These prescriptions were mainly for anxiety and/or mood disorders. Treatment of elimination disorders with tricyclic antidepressants made up a minority of antidepressant prescriptions. This is in contrast to Burger et al's[34] South African study in 2009 that showed almost equal prescribing of SSRIs and TCAs. One of the main differences in Burger et al's[34] research was that they looked at all prescriptions by medical doctors, including general

practitioners, paediatricians and psychiatrists, whereas this study was limited to child psychiatrists and psychiatric registrars. Perhaps, child psychiatrists/psychiatric registrars, by virtue of their additional training are more comfortable in prescribing SSRI's for children.

This study revealed that, although SSRIS are the first line pharmacological treatment for depression and many anxiety disorders, patients with mood disorders received SSRIs significantly more than those patients with anxiety disorders. Approximately half of patients diagnosed with an anxiety disorder (with or without a comorbid diagnosis) were started on an SSRI. In contrast, over 95% of the 16 patients diagnosed with a mood disorder started on an SSRI initially.

It is recommended to treat mild to moderate childhood anxiety or depression initially with psychosocial measures e.g. Low intensity treatment (books, CDs), CBT or skills- based treatment.[25,80] Additionally when anxiety disorders are comorbid with ADHD, ACAPAP guidelines recommend treating ADHD first.[80] Fifteen of our study patients with comorbid ADHD and anxiety disorders were prescribed only psychostimulants following these guidelines. Only six patients with comorbid diagnoses (ADHD and mood/anxiety disorders) received psychostimulants and antidepressants. It would have been useful to note the severity of the anxiety disorder when collecting the data, so that it could have been determined why the patients were started on two agents at the first visit.

With regards to mood disorders, the large majority of patients received SSRI's on the first visit. Once again it would have been useful to determine the severity of the illness, to determine if immediate prescribing was indicated. ACAPAP and NICE guidelines both recommend where possible that psychosocial interventions and or 'wait full watching' are used when first diagnosing children and adolescents with mood disorders.[25,81] There is a

shortage of child and adolescent mental health services in South Africa, and this perhaps results in patients receiving pharmacological treatment instead of more intensive psychosocial interventions.[82] Reasons for not following these guidelines need to be investigated further.

5.4.3 Antipsychotics:

Prescriptions of antipsychotics were mainly for off-label indications. A diagnosis of disruptive disorder was most likely associated with antipsychotic prescription. This is in keeping with international trends.[46] (See Table 2.1 and 2.2). Only eleven patients in the sample (5%) started on antipsychotics on their first encounter with the doctor – all atypical antipsychotics. This is considerably less than other aforementioned research e.g. Raman found a 15% rate of antipsychotic prescription at the child psychiatric clinic in RMH.[17]

This relatively small number is a positive finding, especially considering the side effects of these medications and the relative paucity of data in this area. However, it is difficult to compare this result directly with other studies since the majority of other studies showed higher percentages of antipsychotic prescription, and looked at overall prescribing during multiple visits, whereas this study looked at initial prescription at the time of the first presentation to TOCC.

It would be useful to follow this group of children, to determine how many eventually received antipsychotics for behavioural disturbances. As shown by Lund et al's research[81] there are few psychosocial interventions available to treat these children, so it is possible that they would be treated with antipsychotics which are used as pharmacological behavioural modifiers.

5.5 Concomitant prescribing:

Concomitant prescribing was reasonably rare in our sample with approximately 92 % of the sample receiving only one psychotropic (Table 4.6). This is much lower than previously mentioned research.[70,72,73,74] However it must be remembered that this research is only looking at the patient's first encounter with TOCC. As expected the most common combination of psychiatric medication was an antidepressant and a psychostimulant (for a diagnosis of anxiety/mood disorder and ADHD).

5.6 Limitations:

Retrospective studies are known to have limitations such as reliability, validity, with the accessibility of data being a main concern. This study focuses purely on notes written by doctors in the files, and the accuracy of these notes and diagnoses cannot be verified. Only one doctor systematically reviewed every file and collected data, to decrease collection bias. There were ten missing files, which may have otherwise contributed to the data collected and findings.

It should be noted that these results were based on only two years of data, so it is difficult to comment on changes in prescription trends over the years. Furthermore, comparisons cannot be made with patients not receiving medications. The findings of this study are restricted to initial prescription patterns, so the overall prescribing patterns over multiple visits at TOCC are not known. This study did not look at dosages, which would have been an additional variable to compare.

This preliminary study has concentrated only on a restricted age range, and it would be more beneficial to conduct a larger study looking at all age groups presenting at TOCC. There are some conditions such as ADHD, occurring more frequently in this particular sample as a result of the age groups chosen for inclusion in the study. This limited age range of sample

population makes it difficult to make accurate comparisons to other studies. Another limitation is that this study did not look at additional socio-economic data in these patients, which would have been helpful in picking up trends in special populations e.g. children in instutions or in foster care. This would have been useful since there is considerable research on psychotropic use in these populations.[52, 53]

Another limitation of the study was the manner in which diagnostic categories were captured. If two diagnoses on Axis I were from the same diagnostic group, they were counted as one diagnosis so as to avoid double counting. This information would have been useful since it could indicate the overall complexity of the psychiatric illness (e.g. if they had PSTD and GAD). This could have been compared to medications prescribed and specifically if more than one medication was prescribed.

Strengths of this study include that this research adds to the already existing research and local knowledge in South Africa.[17,21,34,50] Research that is completed locally could hopefully help validate allocation of resources and need for more training in this mental health field.[81] This research has also pointed out some significant findings at TOCC, of which the prescribing doctors may not be aware. These include the findings with regards to race and psychotropic prescribing differences, as well as the high prescription rates of antidepressants prescribed in the initial encounters in patients diagnosed with mood disorders.

CHAPTER SIX: CONCLUSION

Despite its limitations, this study has described prescribing trends within one public tertiary child psychiatry outpatient clinic in South Africa.

In South Africa, there are no published guidelines for treatment of children with antipsychotics or antidepressants, and the use of these medications is based on the International Association for Child and Adolescent Psychiatry and Allied Professions (ICAPAP) guidelines or NICE guidelines.[8,9,25,26,35,48,49,55,56,81] Psychostimulants were frequently prescribed for the treatment of ADHD according to local guidelines.[13] SSRI's are used predominantly for treatment of mood and anxiety disorders, whilst TCAs were only prescribed for elimination disorders. Due to the limited registered uses of antipsychotics, the majority of their use was off-label. Overall, antipsychotic prescriptions were fewer than those observed in similar international studies and this may demonstrate that the TOCC has adopted a cautious approach.

The main aim of this research report has been fulfilled in that the clinical and demographic features of six to fourteen year old children attending TOCC have been described. It has shown that prescription patterns of psychotropics at TOCC mostly follow international demographic trends and clinical guidelines. Hopefully, this study adds to the small pool of research in South Africa looking at prescribing patterns of psychotropics in children. It is hoped that this study at TOCC may stimulate more in-depth research at South African child psychiatry outpatient units. Future research should look at expanding the sample size by including a wider age range, as this would greatly improve the usefulness of the data, and give a more accurate picture of the prescribing practices with regard to conditions seen at Child Outpatient Psychiatric Services at Tara H Moross Hospital. The patients in this study could be followed to determine changes in prescriptions or whether more concomitant

medication was prescribed. This would allow for comparative analysis with similar studies.

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CHAPTER EIGHT: APPENDICES:

Appendix 1:

DSM-IV explanation.

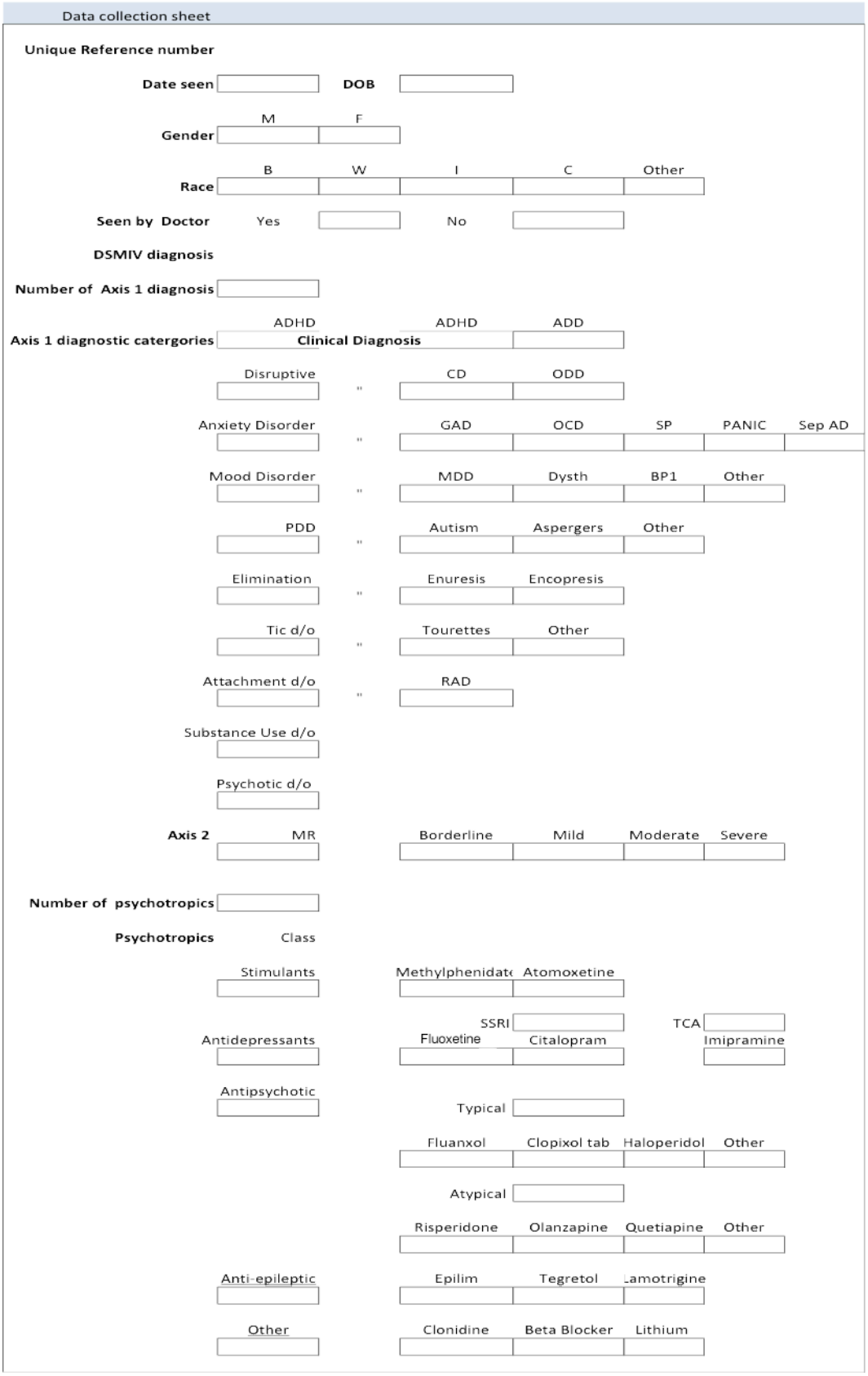
DSM-IV TR. (Diagnostic and Statistical Manual of Mental Disorders – Text revision)

The sample will have an Axis I disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The DSM-IV is a multiaxial classification system, comprising of 5 axes.[3]

Axis I consists of clinical disorders and other conditions that may need attention. (V codes)
Axis II consists of personality disorders and mental retardation
Axis III refers to any general medical or physical condition that the patient may have.
Axis IV is used to code any current stressors. (Psychosocial or environmental)
Axis V is used to record the global assessment of functioning (GAF) scale.

Appendix 2:

Data collection sheet:



Data collection sheet

Unique Reference number

Date seen **DOB**

Gender M F

Race B W I C Other

Seen by Doctor Yes No

DSMIV diagnosis

Number of Axis 1 diagnosis

Axis 1 diagnostic catergories ADHD **Clinical Diagnosis** ADHD ADD

Disruptive " CD ODD

Anxiety Disorder " GAD OCD SP PANIC Sep AD

Mood Disorder " MDD Dysth BP1 Other

PDD " Autism Aspergers Other

Elimination " Enuresis Encopresis

Tic d/o " Tourettes Other

Attachment d/o " RAD

Substance Use d/o

Psychotic d/o

Axis 2 MR Borderline Mild Moderate Severe

Number of psychotropics

Psychotropics Class

Stimulants Methylphenidat Atomoxetine

Antidepressants SSRI Fluoxetine Citalopram TCA Imipramine

Antipsychotic Typical Fluanxol Clopixol tab Haloperidol Other

Atypical Risperidone Olanzapine Quetiapine Other

Anti-epileptic Epilim Tegretol Lamotrigine

Other Clonidine Beta Blocker Lithium

Appendix 3:	
VARIABLES:	
Demographic:	Age at appointment
	Gender
	Race
Clinical:	
Axis 1 category:	Attention Deficit Hyperactivity disorder
	Disruptive disorders
	Anxiety disorders
	Mood disorders
	Pervasive developmental disorder
	Elimination disorder
	Tic disorder
	Substance use disorder
	Attachment disorder
	Psychotic disorder
Axis 2:	Mental Retardation
Axis 3:	Medical Condition
Medication class:	Psychostimulant
	Anti-depressant
	Antipsychotic

Appendix 4:

Table showing components of each diagnostic category:

Diagnostic Category	Specified diagnosis
Attention deficit-hyperactivity disorder	Attention deficit-hyperactivity disorder Attention deficit-hyperactivity disorder-Combined Attention deficit-hyperactivity disorder-Hyperactive Attention deficit-hyperactivity disorder-Inattentive
Anxiety disorder	Adjustment disorder with anxiety features Anxiety disorder Generalised Anxiety disorder Post Traumatic Stress disorder Seperation Anxiety disorder Specific phobia Panic Attack School Refusal
Attachment disorder	Reactive attachment disorder
Disruptive disorder	Conduct disorder Oppositional defiant disorder
Elimination disorder	Enuresis-nocturnal Enuresis- primary Encopresis
Learning disorder	Learning disorder - not otherwise specified Learning disorder - Disorder of written expression Learning disorder - Reading disorder
Mood disorder	Mood disorder not otherwise specified Dysthymic disorder Major depressive disorder Adjustment disorder with depressed mood
Pervasive developmental disorders	Aspergers syndrome Autism
Psychotic disorder	Psychosis not otherwise specified
Selective Mutism	Selective Mutism
Somatoform disorder	Somatoform disorder

Appendix 5:
Table showing components of each medication category:

Treatment Category	Specified diagnosis
Selective serotonin re-uptake inhibitor	Citalopram Fluoxetine
Tricyclic antidepressant	Imipramine
Psychostimulant	Methylphenidate IR Methylphenidate LA Methylphenidate Extended- Release Tablets Atomoxetine*
Anti-psychotic	Risperidone

*Atomoxetine- although this is not a psychostimulant it was included in this group since it was prescribed for ADHD

Appendix 6:

Ethics clearance:

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Antoinette Miric

CLEARANCE CERTIFICATE	**M111106**
PROJECT	Demographic and Clinical Features of Children Receiving Pschiatric Medication at a Specialist Pschiatric Clinic
INVESTIGATORS	Dr Antoinette Miric.
DEPARTMENT	Department of Psychiatry
DATE CONSIDERED	25/11/2011
DECISION OF THE COMMITTEE*	

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

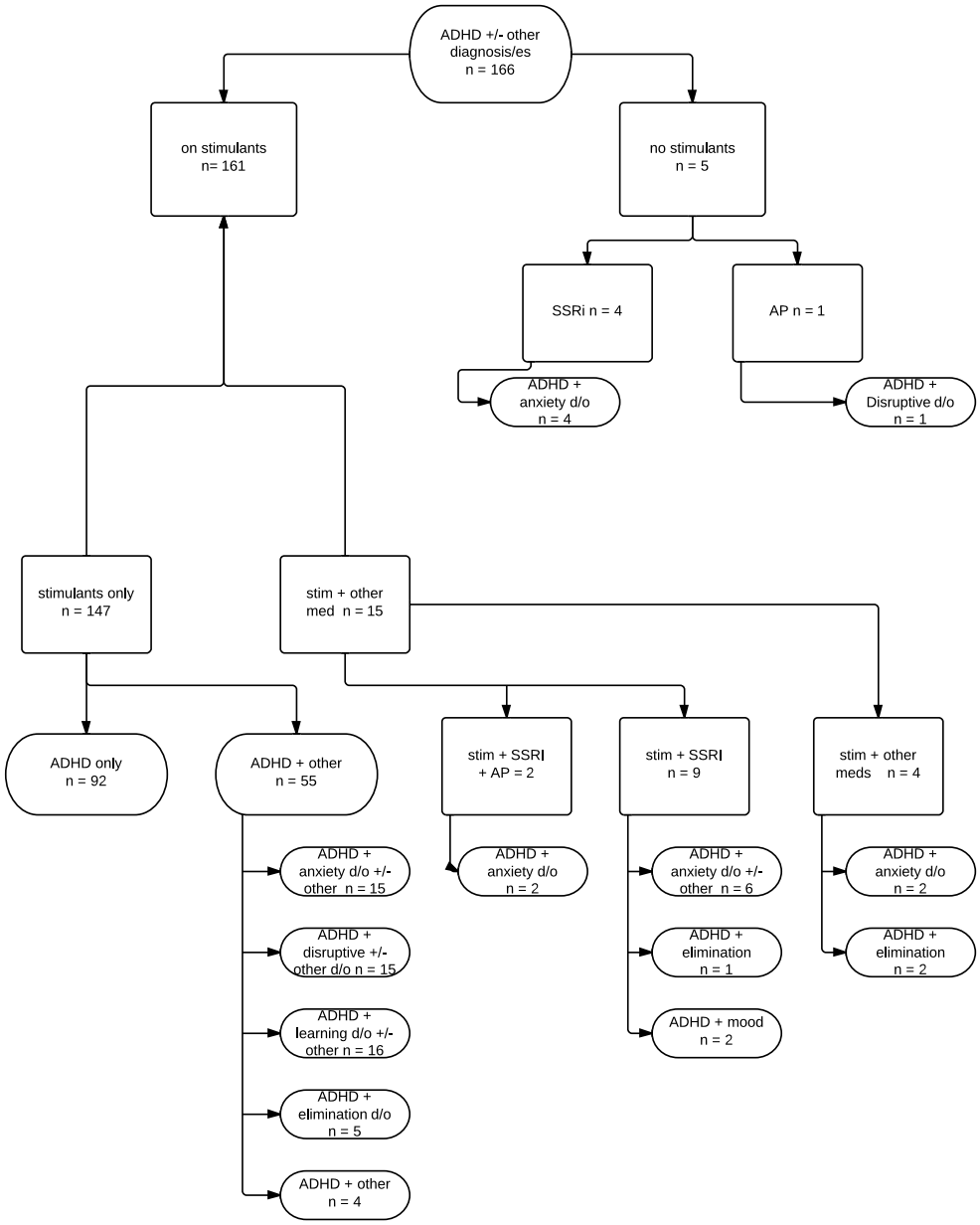
*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr M Motlana

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

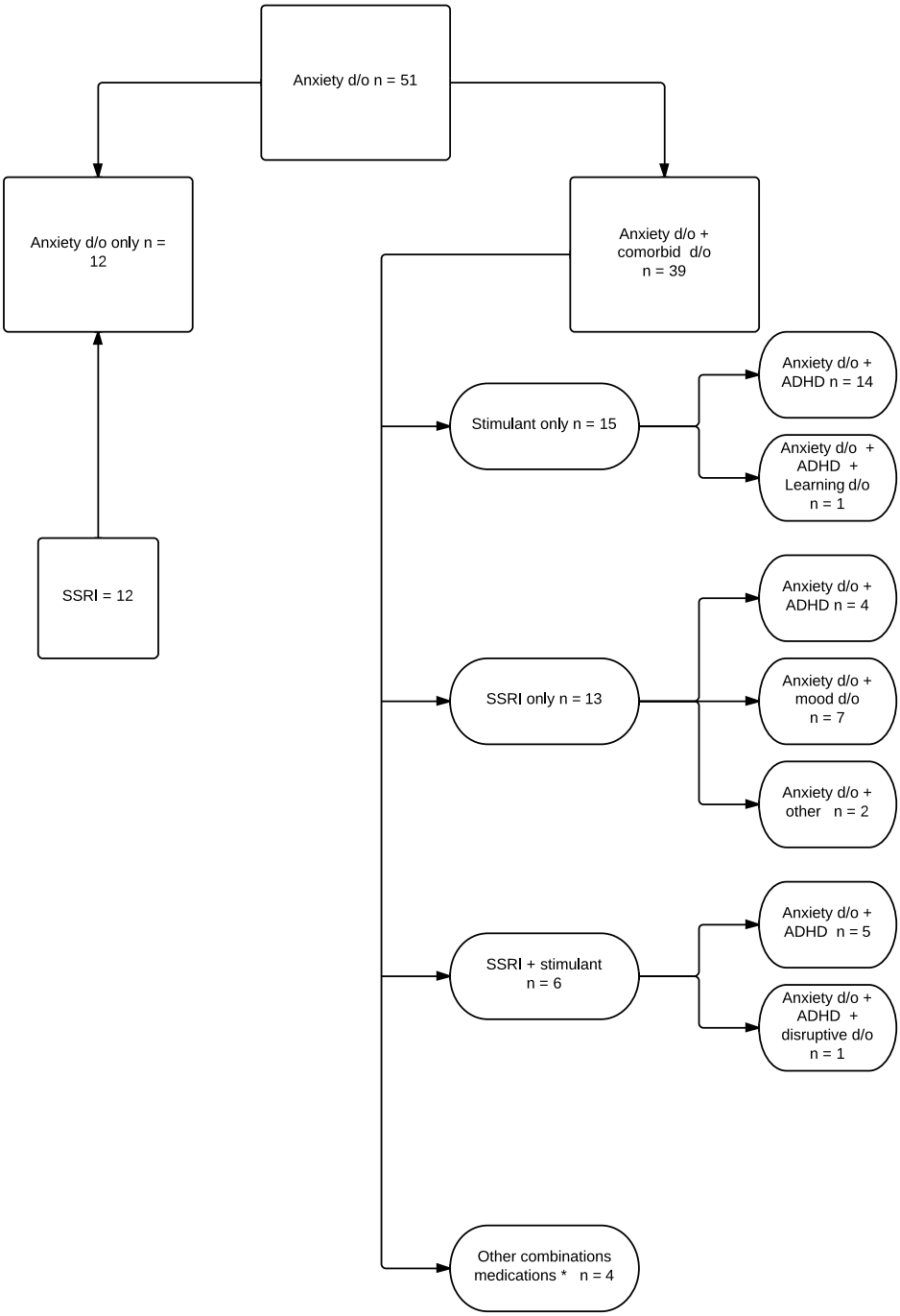
Appendix 7:

Flow chart showing patients who were diagnosed with Attention deficit hyperactivity disorder, the medication they were treated with and diagnositic co-morbidities:



Appendix 8:

Flow chart showing patients who were diagnosed with Anxiety disorders, the medication they were treated with and diagnostic co-morbidities:



Appendix 9:

Flow chart showing patients who were diagnosed with Disruptive disorder, the medication they were treated with and diagnostic co-morbidities

