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PHARMACOTHERAPY PRESCRIBING PATTERNS IN THE TREATMENT OF BIPOLAR DISORDER IN AN OUTPATIENT POPULATION AT TARA HOSPITAL

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A RESEARCH REPORT SUBMITTED
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IN THE BRANCH OF PSYCHIATRY.

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DECLARATION

I, Eleanor Holzapfel, declare that this research report is my own work. It is being submitted as partial fulfillment for the degree of Master of Medicine in the branch of Psychiatry, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

It has not been submitted for any degree or examination at this or any other University.

Signature:

Date:

DEDICATION

For my dear husband Mark.

ACKNOWLEDGEMENTS

I wish to convey my sincere appreciation to the people who made the preparation of this research report possible. They include but are not limited to the following:

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- My husband Mark for his constant support, encouragement and dedication to helping me with the formatting and completion of my research report.

ABSTRACT

Introduction

Pharmacotherapy is a key component in the management of bipolar disorder. Whilst one might aim for fewer agents, not all patients with bipolar disorder can be stabilized with monotherapy and combination treatment (polypharmacy) is increasingly used to manage patients in clinical practice. Mood stabilizers have traditionally been prescribed as monotherapy, however the use of atypical antipsychotic agents is seen in clinical practice with various such agents approved for such usage. Combination treatment with an antipsychotic, preferably an atypical antipsychotic together with a standard mood stabilizer is also noted in clinical practice as well as recommended by guidelines. Bipolar patients managed in a specialist psychiatric setting have a greater chance of being managed with polypharmacy than in a general practice setting. The use of polypharmacy may also be attributed to receiving treatment in an academic environment.

This current study was based on the application of diagnostic criteria and principles of the Diagnostic and Statistical Manual of Mental Disorders version IV TR (DSM IV TR), published by the American Psychiatric Association and The International Classification of Diseases version 10 (ICD 10), published by the World Health Organisation.

Aims

The study aims to describe the range and frequency of medications used in the management of bipolar bisorder in a specific setting as well as describe the nature and frequency of monotherapy versus polypharmacy use.

Hypothesis

The study hypothesized that the majority of patients attending the specialist / academic psychiatric outpatient clinic at Tara Hospital would be prescribed polypharmacy and that antipsychotics (typical or atypical) would be prescribed in combination with standard mood stabilizers in the majority of cases.

Method

The study took the form of a retrospective patient file review. The clinical files were for patients attending the Tara Hospital psychiatric outpatient clinic. The files of every patient who attended

the clinic at least once in 2009 were screened and included in the study where the recorded ICD 10 code corresponded with a bipolar disorder subtype or a single manic or hypomanic episode. Where the recording of the ICD 10 code was missing or incomplete further scrutiny of the clinical notes enabled the researcher to establish a diagnosis of bipolar disorder using the ICD 10 and/ or DSM IV TR diagnostic criteria and therefore include the patient file in the study. Other necessary information was obtained by reviewing clinical notes as well as the prescription written on the last patient visit for 2009.

Results

The study found that the majority of patients (93.8%) were prescribed polypharmacy, with 3.2 the mean number of psychotropic medications prescribed per patient. Lithium was prescribed in 34.3% of patients. Sodium valproate was prescribed in 37.1% of patients. Eighty three point eight percent (83.8%) of the patients were prescribed at least one standard mood stabilizer. The atypical antipsychotics (46.6%) were prescribed more frequently than the typical antipsychotics (16.5%). Lamotrigine (31.8%) was the preferred novel anticonvulsant and the selective serotonin reuptake inhibitors (SSRI's) were the most commonly prescribed antidepressant (28.9%). Clonazepam (26.8%) was the most frequently prescribed benzodiazepine add-on. The use of combination treatment to manage bipolar disorder was the rule rather than the exception. There was however much variety in the combinations used with no particular combination being prescribed in the majority of patients. Forty seven percent (47%) of the combinations used included a standard mood stabilizer and a typical or atypical antipsychotic.

Conclusion

The current study provides preliminary data on the prescribing patterns in bipolar disorder in a specialist psychiatric clinic within an academic complex in South Africa. The findings are in keeping with international studies and highlights that polypharmacy and combination treatment in the management of bipolar disorder is the norm in such settings. There is a large variation in clinician practices and much variety seen in the combinations of medications used to treat bipolar disorder despite the availability and use of treatment guidelines. This is perhaps because bipolar disorder is such a complex disorder and that most of the treatment recommendations are based on limited data. Treatment guidelines have emerged in order to attempt to standardize treatment and provide clinicians with algorithms to utilize and apply research findings in daily clinical practice. Further study into the effective prescribing principles for bipolar disorder is necessary.

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GLOSSARY OF TERMS

(Terms are listed alphabetically hence references do not appear in numerical sequence in this section)

Add-on medication: anxiolytics and hypnotics that include benzodiadepines (clonazepam, lorazepam, oxazepam) and non-benzodiazepines (propranolol, buspirone, promethazine, hydroxyzine).

Antimanic medication: standard mood stabilizers, atypical and typical antipsychotics.[38]

APA: American Psychiatric Association.[38]

Atypical antipsychotics: olanzapine, quetiapine, ziprasidone, risperidone.[33]

BAP: The British Association for Psychopharmacology.[38]

Borderline personality disorder: the person has a poor sense of self; experiences fears of emptiness and fears abandonment; experiences emotional and mood instability with anger outbursts; is impulsive, chronically suicidal and self- harms.[2]

CANMAT: Canadian Network for Mood and Anxiety Treatment.[38]

Cluster B personality disorders: an enduring pattern of inner experience which is inflexible, pervasive and leads to distress or impairment. The Cluster B personality disorders include: borderline, narcissistic, histrionic and antisocial.[2]

Depressive episode: two weeks or more of a low mood. The mood changes are associated with loss of interest in life, changes in sleep and eating patterns, low energy, poor concentration and memory and suicidal ideation or thoughts of death. The mood disturbance causes significant distress and impairment in functioning.[2]

Hospital classification of fees structure[68]

H0 - people on government pensions and disability grants

H1 - unemployed patients, students and patients with an annual income :< R36000

H2 - patients with an annual income: ≥ R36000 < R72000

Private - patients with an annual income: ≥ R72000

Hypomanic episode: similar presentation as a manic episode however the symptoms do not cause severe impairment in functioning. Hypomanic episodes are not associated with psychosis and usually do not result in hospitalization.[2]

ICD 10 bipolar subtypes: [3]

F30.0 hypomanic episode
F30.1 manic episode without psychosis
F30.2 manic episode with psychosis
F31.0 current bipolar episode hypomanic
F31.1 current bipolar episode manic without psychosis
F31.2 current bipolar episode manic with psychosis
F31.3 current bipolar episode depressed (moderate)
F31.4 current bipolar episode depressed (severe)
F31.5 current bipolar episode depressed (severe with psychosis)
F31.6 current bipolar episode mixed
F31.7 current bipolar episode in remission
F31.8 other bipolar
F31.9 unspecified bipolar

Maintenance phase: the phase of treatment where medication is continued after remission in order to prevent relapse or recurrence of a mood episode.[69]

Manic episode: one week or more of feeling high, an overly happy and outgoing mood or an extremely irritable mood. The mood changes are associated with fast speech, racing thoughts, increased goal directed activity, need for less sleep and impulsivity. The mood disturbance is sufficiently severe to cause marked impairment in functioning or to necessitate hospitalization or there is psychotic features.[2]

NICE: National Institute for Health and Clinical Excellence.[38]

Novel anticonvulsants: the newer anticonvulsants (second generation) - lamotrigine, gabapentin, topiramate, oxcarbazepine.[33,70]

Recovery: if remission continues for six to twelve months.[69,71]

Recurrence: if the patient's symptoms of a mood episode return during or after the recovery phase.[69,71]

Relapse: if the patient's symptoms worsen before remission or if the symptoms of a mood episode return in the remission phase before recovery is achieved.[69,71]

Remission: all the symptoms presenting from the mood episode have resolved for a minimum of a week, sustained remission is twelve weeks or longer.[69,71]

Response: the patient has experienced at least a fifty percent reduction in symptoms from the baseline mood episode as assessed by a standard psychiatric rating scale.[69,71]

Severe episode: this in an episode that causes significant distress and marked impairment in all areas of life. The person may be a danger to themselves and others. They require emergency treatment and hospitalization. A severe episode may be associated with psychosis.[72]

Standard anticonvulsants: sodium valproate, carbamazepine.[33]

Standard mood stabilizers: lithium, sodium valproate, carbamazepine.[33,73]

TMAP: Texas Medication Algorithm Project.[38]

Classification of medication use as per class: *(study specific)*

- Group A: lithium / standard anticonvulsant / novel anticonvulsant / antipsychotic / antidepressant / add-on.
- Group B: sub class of each of the above (where relevant) - typical and atypical antipsychotics / selective serotonin reuptake inhibitors (SSRI's), serotonin noradrenalin reuptake inhibitors (SNRI's), noradrenalin reuptake inhibitors (NRI's), tricyclics (TCA's), mono-amine oxidase inhibitors (MAO's) and other antidepressants / benzodiazepine and non-benzodiazepine add-ons.

Typical antipsychotics: haloperidol, chlorpromazine, flupenthixol, trifluoperazine.[33]

WFSBP: World Federation of Societies of Biological Psychiatry.[38]

INTRODUCTION

(Bolded items appear in the glossary of terms)

Bipolar disorder is a chronic, potentially relapsing mood disorder. This mood disorder is characterized by **manic, hypomanic and depressive episodes**.[1] In psychiatry two major classification and diagnostic systems are used for bipolar disorder.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association is psychiatric specific and is used for clinical purposes. The DSM IV TR was the latest version available at the time the current study was conducted.[2] Since then, the DSM-5 has been released. The International Classification of Diseases (ICD) which is published by the World Health Organization includes all medical conditions with psychiatry being a subset.[3] The version used at the time of the current study was ICD 10, which is still in use at present. The ICD 10 classification system is used by medical information systems that require the ICD 10 codes for record purposes.[3]

The two classification systems differ in their diagnosis and classification of bipolar disorder as follows:

1) The DSM IV TR separates bipolar disorder into bipolar I and II based on at least one episode being **manic or hypomanic** respectively. Where the presentation is not typical of bipolar I or II a diagnosis of not otherwise specified (NOS) is given.[2]
2) The ICD 10 does not differentiate between the bipolar subtypes and requires two mood episodes one of which must be a **manic or hypomanic episode** to make a diagnosis of bipolar disorder.[3]

The goals of treatment in bipolar disorder are many and involve not only the biological aspects but also the psychosocial aspects as well. Pharmacological treatment however is crucial to the care of patients suffering from bipolar disorder. Drug therapy aims to treat an acute exacerbation of either a **manic, hypomanic or depressive episode**; prevent **relapses** / **recurrences** and improve inter-episode functioning (**remission**/**recovery**)[4].

The medications that are often used to treat this condition include mood stabilizers (lithium and anticonvulsants), antipsychotics (**typical** and **atypical**), antidepressants, hypnotics and anxiolytics. These medications may be used on their own or in various combinations.[4]

The term combination therapy includes all the ways in which one medication may be added to another. Polypharmacy refers to the use of two or more medications. Complex polypharmacy refers to the use of four or more medications.[5-8]

The use of polypharmacy can be described as follows:[5-7,9]

- Same-class polypharmacy refers to the use of more than one medication from the same class.
- Multi-class polypharmacy refers to the use of more than one medication from different classes.
- Augmentation polypharmacy implies an additive effect from adding a second medicine to that obtained from prescribing a first.
- Add on therapy refers to adding on to an existing and possibly effective treatment which, for one reason or another cannot or should not be stopped.
- Adjunctive polypharmacy refers to the use of medication to treat the side-effects of another medication.
- Co-therapy refers to the addition of two medications concurrently.

There are many reasons why combination therapy (polypharmacy) is used to treat bipolar disorder.

The clinical reasons are as follows:

- Associated symptoms- psychosis, anxiety, and insomnia (add on or co-therapy pharmacotherapy).[6]
- Inter-episode sub threshold symptoms (add on or augmentation pharmacotherapy).[6]
- Multiple phases of the illness, multiple symptoms need to be addressed (i.e. depression, mania, mixed, rapid cycling) (add on or augmentation or co-therapy pharmacotherapy).[6]
- Partial response to monotherapy (add on or augmentation pharmacotherapy).[6]
- The management of side-effects (adjunctive pharmacotherapy).[7]
- Failure to respond to monotherapy and when this fails guidelines now recommend combination therapies (add on or co-therapy pharmacotherapy).[10]

- Literature reviews demonstrating, in clinical practice and supported by clinical guidelines, that combination treatments provide additional benefits over monotherapy for the management of the various phases of bipolar disorder (augmentation or add on or co-therapy pharmacotherapy).[11]
- Co morbid psychiatric conditions such as personality disorders, substance abuse, anxiety disorders (add on or co-therapy pharmacotherapy).[12]

The Great Debate: Monotherapy versus Polypharmacy

Bipolar disorder is a complex disorder for which in order to achieve and maintain **remission** and **recovery** and prevent **relapse** and **recurrence**, it appears that polypharmacy is needed. The evidence for combination therapy is limited yet the use in clinical practice is common.[13]

A review of controlled studies showed higher response rates in mania when an **atypical antipsychotic** was added to lithium or sodium valproate (60% versus 40%).[14] These studies however have been criticized as a comparator arm i.e. the **atypical antipsychotic** alone has never been included in such studies.[6] The evidence for the use of combination treatment in bipolar depression is present but limited. Studies show the addition of an antidepressant to lithium is more effective than lithium alone.[11] Other studies however refute this and show no benefit to combining an antidepressant with a mood stabilizer or **atypical antipsychotic**.[14] However, it has been noted that the combination of fluoxetine and olanzapine is more effective than olanzapine alone.[19] The addition of lamotrigine to lithium was found to be superior than the addition of a placebo to treat bipolar depression.[15]

It has also been documented that the use of antipsychotics with other medications to treat bipolar disorder is very common in the **maintenance phase** of treatment, however clinical trials supporting this practice are still limited.[6]

Goodwin and Vieta[16] suggest that medication prescribed to treat the acute episode may not necessarily be the treatment of choice for the long term management of bipolar disorder. They state that few studies have attempted to answer the question whether two medicines are better than one in the **maintenance phase**. The BALANCE trial aimed to evaluate combination versus monotherapy in this phase.[16] The BALANCE trial showed a significant advantage of combination with lithium and sodium valproate over sodium valproate monotherapy. The same could not be said for lithium monotherapy however.[15]

Alda and Yatham[17] debate the issue of monotherapy versus polypharmacy in a series of short articles. Alda and Yatham express their opinions individually in separate articles with each author providing rebuttal comments in separate short articles thereafter. Alda supports the use of polypharmacy in treating acute episodes particularly manic episodes but feels the use of polypharmacy in long term treatment (**maintenance phase**) is controversial with data on the effectiveness of combination treatment lacking.[17] Specifically that data is lacking in relation to whether one should initiate treatment with a combination of medication or only where monotherapy

fails use combination treatment (add on or augmentation). Alda[17] notes studies that have shown patients who failed treatment with a single drug improved when a second drug was added to the first drug. Alda further states however that this does not answer the question as to whether the combination of the first and second drug (add on or augmentation) is superior to monotherapy with the second drug (switching).[17]

Yatham, in disagreeing with Alda, states that there is significant clinical trial data to support rational polypharmacy for patients with bipolar disorder.[17] Yatham demonstrates that there are very few medications that treat all phases of the illness and hence the rational for combination treatment.[17] Yatham further notes trials demonstrating combination therapy to be superior to monotherapy in acute **mania, depression** as well as in the **maintenance phase** of bipolar disorder.[17]

Clinical Practice

Studies of clinician prescribing patterns when treating bipolar disorder have described the types of medication prescribed and shown that polypharmacy prescribing is occurring in the majority of cases.[8,12,18-27] Patients with mood and anxiety disorders have been shown to make use of the healthcare services more frequently than those without these disorders and thus have a higher incidence and greater chance of receiving polypharmacy.[28,29] The use of polypharmacy is observed more often in specialist psychiatric settings than in general practice settings.[18,30] Some studies also noted that the majority of patients prescribed an antipsychotic were prescribed this together with a mood stabilizer.[31,32] A noteworthy series of studies are The Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) conducted in American academic centres.[8,33] The STEP-BD was a large scale multicentre study funded by the National Institute of Mental Health. The purpose was to examine the longitudinal course of bipolar disorder; assess the patterns of psychopharmacological treatment and the effectiveness of current treatments.[33]

The STEP-BD study (1998-1999) [33] initially enrolled 500 participants at study entry. Of the participants 73.6% had bipolar I disorder, 23% had bipolar II disorder and 3.4% had bipolar disorder not otherwise specified (NOS). **Standard mood stabilizers** were the most common drugs prescribed on intake (71.9%). The next most common class of agents was antidepressants (40.6%), followed by **novel anticonvulsants** (31.8%), **atypical antipsychotics** (27.2%) and benzodiazepines (25%). **Standard mood stabilizer** monotherapy was used to treat only 11% of patients.[33]

The STEP-BD study (1999-2005)[8] comprised 4035 subjects and found that polypharmacy is exceedingly common in the treatment of bipolar disorder. In this study 40% of the patients were prescribed three or more concurrent medications and 18% of patients were prescribed four or more concurrent medications (complex polypharmacy). The study also showed that lithium, carbamazepine and sodium valproate were the least likely to be used in complex polypharmacy. The antidepressants and **atypical antipsychotics** were used most in combination treatment. The study also demonstrated that patients being treated at tertiary academic centers were prescribed polypharmacy.[8]

International & South African Treatment Guidelines

"Evidence based medicine" refers to the use of up to date evidence and consistent application in clinical practice.[3] The evidence used is provided by original research and systematic reviews.[1] This evidence provides the basis for treatment guidelines.[3] The treatment guidelines include expert interpretation of the evidence as well as consider treatment availability, costs and ethical issues.[3] The treatment guidelines are determined by guideline committees which use expert consensus to reach decisions.[3] There is thus also an element of "experience based medicine" included in the treatment guidelines, with the experts also drawing on their clinical experience, observation and judgement when deciding on which evidence to include.[3]

A perfect treatment scenario would be combination of "evidence based and experienced based medicine" with the patient's own preferences and expectations, to achieve the best possible outcomes.[3]

The pros and cons related to the application of guidelines in clinical practice include:[34-37]

Pros:

- Assists clinicians and policy makers to arrive at decisions concerning treatment and care of patients.
- Sets the standards of care and training.
- Identifies further research areas.
- Is "evidenced and experienced based".
- Helps to improve the cost – effectiveness of treating psychiatric disorders.

Cons:

- Not all stakeholders are represented in the guideline committees. These include patients and the pharmaceutical industry.
- Conflicts of interest are not always reported by the guideline committees.
- The treatment guidelines do not always agree and sometimes give conflicting data. The grading systems used to assess the quality of data and effectiveness/safety of an intervention are not standardised.

- The treatment guidelines are not patient centred or individualized. They may not meet the particular features of a clinician's patient population which is a heterogeneous group.
- The treatment guidelines may prevent individual patients and clinicians access to medication as government or private medicine formularies making use of treatment guidelines only include data from a homogenous group of patients.

Given the complexities in the management of bipolar disorder, treatment guidelines have emerged in an attempt to standardize treatment and provide clinicians with algorithms to utilize and apply research findings in daily clinical practice. As discussed earlier these findings however are limited and often conflicting.[38,39] The treatment guidelines have been developed and published by various, international bodies: in North America **(APA, CANMAT, and TMAP)**, in Europe **(NICE, BAP)** and others **(WFSBP)**. According to the literature approaches in managing bipolar disorder in North America and Europe are becoming more congruent.[38,39] The treatment guidelines still recommend the use of monotherapy as first line treatment.[38,39] However, if the **presentation** is **severe** the use of polypharmacy (combination therapy) is supported as first line treatment. In general the use of polypharmacy (combination therapy) is recommended as early as the second line of treatment.[38,39]

The guidelines emphasize the use of **antimanic** / **mood stabilizers** in all phases of bipolar disorder.[38,39] The **atypical antipsychotics** are now established in their use as either monotherapy as an **antimanic** agent or in combination with a **standard mood stabilizer** especially in treating **severe** presentations of **mania**.[38,39] In general the guidelines place increasing emphasis on lamotrigine as an effective medication to treat and prevent depression within the context of bipolar disorder.[38,39] They also recommend cautious use of antidepressants and only in combination with a **standard mood stabilizer** or **antimanic medication**.[38,39] In the European guidelines however lithium and the antipsychotics is emphasized more and the addition of antidepressants occurs earlier on in the treatment algorithm.[38,39]

Both private and state South African psychiatrists make use of international bipolar treatment guidelines. These guidelines however are not always applicable to the South African clinical setting.[40] These guidelines do not take into account the availability of various psychotropics in South Africa, the healthcare settings and availability of resources in South Africa that need to be considered when using certain medications.[40] This is why, The South African Society of

Psychiatrists (SASOP) have developed their own treatment guidelines for psychiatric disorders that address the South African health setting.[40] In 2009 a group of experts was appointed to develop the SASOP treatment guidelines. These experts needed to have both academic and clinical experience.[40] The experts needed to take into account the South African setting, budgetary constraints and "evidence based medicine".[40] Each expert contribution was peer reviewed and all experts needed to disclose conflicts of interest.[40]

The South African National Department of Health and the Council of Medical Schemes has also published standard treatment guidelines for bipolar disorder.[41,42] The South African National Department of Health has included their Essential Drug List (EDL) for psychotropic drugs in their guidelines.[42]

A shortcoming of the SASOP treatment guidelines is that they refer to the current private healthcare setting in South Africa.[40] These guidelines however will still be able to guide public sector psychiatrists and government decision makers to use the most appropriate and cost – effective treatments in the public sector.[40] Access to certain medications mentioned in the guidelines is available to the public sector, as determined by the expanded EDL for psychotropic drugs, for academic tertiary/specialist centres such as TARA hospital.[43]

The South African guidelines follow the principles of the international bipolar guidelines as discussed earlier but overall are most similar to the North American guidelines. South Africa however also includes the use of **typical antipsychotics** in their guidelines as these are easily accessible as well as cost effective in primary and secondary healthcare facilities.[41,42,44]

The clinical treatment guidelines are there to aid and standardise clinician prescribing however there are a number of other factors that informs and determines clinician prescribing practises. These factors include:[45,46]

1) Patient characteristics: age, sex, medical and psychiatric co-morbidity, individual preference, compliance, ability to afford medication, access to healthcare and health resources.

2) Physician characteristics: knowledge, experience, personal preference, values and beliefs, relationship with patient.
3) Illness characteristics: severity, number of previous episodes, response to medication, treatment resistance.
4) Treatment characteristics: medication properties, effectiveness, onset of action, side-effects, drug interactions.
5) Knowledge factors: treatment guidelines, expert consensus, meta-analysis of data, systematic review, medication product information, peer review.
6) Third party factors: government and medical aid medicine formularies, availability of medication in clinical settings.

These characteristics/factors are not only relevant when prescribing medication to treat bipolar disorder but for all psychiatric disorders.

OVERVIEW

The review of the literature shows that not all patients with bipolar disorder can be stabilized with monotherapy and that combination treatment (polypharmacy) is increasingly used to manage these patients in clinical practice.[8,12,18-27] **Standard mood stabilizers** have traditionally been prescribed as monotherapy however the use of **atypical antipsychotic** agents is also seen in clinical practice. The use of an antipsychotic preferably an **atypical antipsychotic** together with a **standard mood stabilizer** is also supported by clinical practice.[14] Bipolar patients managed in a specialist psychiatric setting have a greater chance of being managed with polypharmacy than in a general practice setting.[18,30] The STEP-BD study[8] highlighted the use of polypharmacy in bipolar patients attending tertiary academic centers. All these study results bare testimony to the complexity of the disorder and the need for specialist care. The latest treatment guidelines also indicate that single drug or multiple drug therapy is acceptable based on the severity of the illness.[38-42,44] The guidelines also advocate the use of **atypical antipsychotics** as single agent or in combination with a **standard mood stabilizer** or antidepressant.[38-42,44] There is however great debate in the literature as to whether clinical trials supporting the use of polypharmacy in all phases of bipolar disorder are valid and of high enough standard to provide adequate proof for evidenced based clinical practice.[13,17]

AIM

The current study thus aimed to investigate clinician prescribing patterns for adult patients with bipolar disorder attending an outpatient clinic at a specialist psychiatric hospital within an academic complex.

For the purpose of the study, the medication prescribed was divided into two groups as per class and subclass. This grouping was prompted by the groupings of medications used by most of the articles cited in this research report. The groupings are as follows:

- **Group A**: lithium / **standard anticonvulsant** / **novel anticonvulsant** / antipsychotic / antidepressant / **add-on.**
- **Group B**: sub class of each of the above (where relevant) - typical and atypical antipsychotics / selective serotonin reuptake inhibitors (SSRI's), serotonin noradrenalin reuptake inhibitors (SNRI's), noradrenalin reuptake inhibitors (NRI's), tricyclics (TCA's), mono-amine oxidase inhibitors (MAO's) and other antidepressants / benzodiazepine and non-benzodiazepine **add-on**.

The study objectives were:

1) To describe the range and frequency of medications used, within **Groups A and B** in the management of bipolar disorder.
2) To describe the nature and frequency of monotherapy versus polypharmacy use, within **Groups A and B.**
3) To describe the combinations of medications used, within **Groups A and B.**
4) To assess the association between monotherapy / polypharmacy and all the demographic, biographic and clinical variables, as well as medications used from within **Groups A and B**.
5) To assess the association between bipolar disorder subtype and medications used, from within **Groups A and B**.

This study hypothesized that:

1) Polypharmacy will be prescribed for the majority of patients (> 50%) at the clinic.
2) Where polypharmacy is used antipsychotics (typical or atypical) will be prescribed in combination with a **standard mood stabilizer** in the majority of cases (>50%).
   In respect to the second hypothesis, not to complicate analysis of data unnecessarily it was decided not to distinguish between **typical and atypical antipsychotics**.

METHODOLOGY

Method

The study took the form of a retrospective patient file review.

Setting

The clinical files reviewed were those of adult patients attending the Tara Hospital psychiatric outpatient clinic. The clinic provides secondary, tertiary and quaternary specialist psychiatric care. Tara Hospital outpatient clinic is part of the University of the Witwatersrand's Department of Psychiatry's academic complex. Private (on medical aid) and state patients attend the clinic. The outpatient service caters for the northern suburbs of Johannesburg as well as patients from outside the catchment area who require tertiary and quaternary specialized psychiatric care and are on medication that is not available from their primary or secondary level care community psychiatric outpatient clinics. The patients attending the outpatient clinic will either be assessed and treated by a nurse, principal medical officer, medical officer, registrar, consultant psychiatrist or psychologist. The principal medical officer is a senior qualified doctor and a medical officer is a junior qualified doctor both with a special interest in psychiatry. A registrar is a qualified doctor who is specialising in psychiatry.

Sample

The files of every patient who attended the clinic at least once in 2009 were screened. The files where the recorded ICD 10 code corresponded with a bipolar disorder subtype or a single manic or hypomanic episode were included in the study. Where the recording of the ICD 10 code was missing, or incomplete, further scrutiny of the clinical notes enabled the researcher to establish a diagnosis of bipolar disorder using the ICD 10 and or DSM IV TR diagnostic criteria and therefore include the patient file in the study.

Data

The other necessary information to be included in the study was obtained by reviewing the clinical notes as well as the prescription written on the last patient visit for 2009. The researcher having worked as a consultant in the outpatient clinic, and following discussion with colleagues at the clinic, chose to include only those variables for the study which are known to be reliable and consistently available from the clinical notes.

The following information was obtained from the file and entered onto the data collection sheet (Appendix A):

1) Age.
2) Gender.
3) Socio-economic status as indicated by **hospital fee classification.**
4) Mental health care professional (nurse, registrar / medical officer / principal medical officer, consultant psychiatrist, psychologist) consulted for most of the 2009 visits.
5) Number of clinic visits per year of the study.
6) **ICD 10 bipolar subtypes (F31.0 – F31.9) or single manic episode (F30.0-F30.2).**
7) DSM IV TR bipolar subtypes (I, II, NOS).
8) Evidence of psychiatric comorbidity.

The following information was obtained from the relevant prescription:

1) Total number of medications prescribed as per last prescription for 2009.
2) Classes and subclasses of medication prescribed as per last prescription for 2009.

Ethics

The protocol for this study was approved by the Human Research Ethics Committee at the University of the Witwatersrand (protocol number M120838) (Appendix B). Permission was also obtained from the Chief Executive Officer of TARA Hospital to conduct the study at the hospital (Appendix C).

The patient files included in the study were assigned a study/file number and were entered into a file recruitment log. The log book was kept by the researcher. The log book included the patients name and clinic number and can be readily accessed from the clinic should the researcher require the file in the future.

All the information obtained from the selected clinical files and prescription charts / private scripts was recorded on a data collection sheet. The investigator's data collection sheet included the study / file number. The investigator's research information is kept in a secure place and will be disposed of once the current study has been examined by the University of the Witwatersrand.

DATA ANALYSIS

The data was entered onto an MS Excel spreadsheet (Appendix D). Data Management and Statistical Analysis (DMSA) assisted with the data analysis. The information obtained from the file was sufficient to allow the researcher to achieve the primary aim of the study.

Data Preparation / Cleaning

A variable for therapy type (monotherapy vs. polypharmacy) was derived from the number of psychotropics prescribed. The demographic, biographic and clinical data set was coded. The use / non-use of medication for each **class** / **sub-class of medication** within **Groups A and B** was coded. As a result the total percentages may differ when looking at individual medications, class and subclass of medications as some patients were prescribed more than one medication per class. For example: some patients were prescribed both an **atypical** and **typical antipsychotic**.

Sample Size Calculation

The key research question was regarded as the proportion of patients on polypharmacy. This was measured as a proportion. This proportion was estimated to be 55 to 60%, from the literature.[10,12,23] For sample-size estimation, we used 55% as a worst-case estimate. To estimate this proportion with 5% precision required a sample size of 381, given by the sample size calculation for the estimation of proportions i.e.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where

n = sample size,

Z = Z-statistic for the chosen level of confidence,

P = expected prevalence or proportion,

d = precision

The sample size of 242 used in the study was considerably lower, and thus led to the estimation of a 55% proportion with only an approximately 6.3%, rather than 5% precision. This was deemed reasonable, with the increase in precision requiring the addition of an additional year's bipolar disorder patients which was not felt to be justified given the effort involved.

Analysis: general

Data analysis was carried out using SAS (SAS Institute Inc., *SAS Software, version 9.3 for Windows,* Cary, NC, USA: SAS Institute Inc. (2002-2010)).

Descriptive analysis using tables and graphs to show the continuous variables (age, number of medications, number of visits) and categorical variables (monotherapy, polytherapy, drug class, Bipolar subtype) was included.

The Chi Square (X^2) test was used to assess the relationships between categorical variables. The Fisher's exact test was used for 2 x 2 tables or where the requirements for the X^2 test could not be met. The strength of the associations was measured by Cramer's V and the phi coefficient respectively. The following scale of interpretation was used:

0.50 and above	high/strong association
0.30 to 0.49	moderate association
0.10 to 0.29	weak association
below 0.10	little if any association

The Cochran-Armitage test for trend was used to assess the relationship between an ordinal and a nominal categorical variable.

The 5% significance level was used throughout, unless specified otherwise. *In other words, p-values <0.05 indicate significant results.*

RESULTS

A total of 944 files were screened for the diagnosis of bipolar disorder (I, II, NOS) for the year 2009. Of these files 242 were included in the study.

Descriptive Analysis of the Data Set

- **Demographic Profile**

Age:

The patients were predominantly aged between 18 and 64 years (Table I).

The mean age of the patients was 45.5y (standard deviation 14.0y; median 45y; IQR: 35-55; range18-84y).

The distribution of categorised ages is shown in Figure 1.

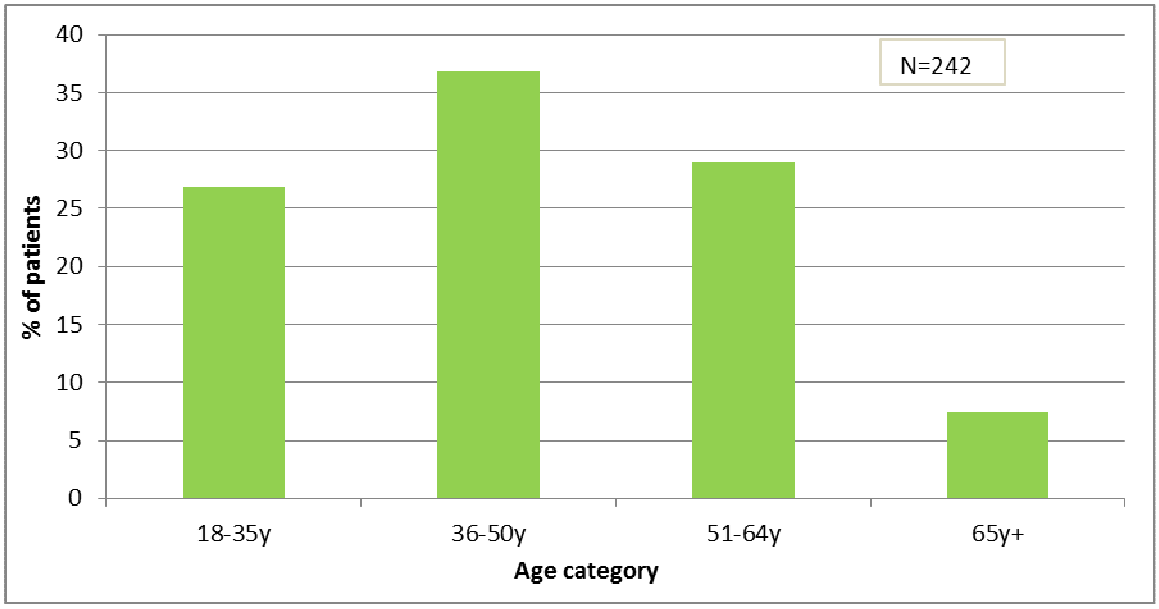


Figure 1 The distribution of categorized ages in the sample

Gender:

The study group was predominantly female (68.2%) (Table I).

Hospital Fee Classification:

The majority of the patients (65.7%) were in the H1 classification. Only 5.8% were private patients (Table I).

Variable	Category	Overall		Monotherapy		Polypharmacy	
N		**242**		**15**		**227**	
Variable	**Category**	**N**	**%**	**N**	**%**	**n**	**%**
Age	18-35y	65	26.86	6	40.00	59	25.99
	36-50y	89	36.78	5	33.33	84	37.00
	51-64y	70	28.93	4	26.67	66	29.07
	65y+	18	7.44	0	0.00	18	7.93
Gender	Male	77	31.82	5	33.33	72	31.72
	Female	165	68.18	10	66.67	155	68.28
Hospital Fee Classification	H0	19	7.85	1	6.67	18	7.93
	H1	159	65.70	11	73.33	148	65.20
	H2	42	17.36	2	13.33	40	17.62
	Private	14	5.79	0	0.00	14	6.17
	Other	8	3.31	1	6.67	7	3.08

Table I Demographic characteristics of study patients

- **Clinic Visit Profile**

Health Care Professional:

The patients were seen predominantly by a registrar / medical officer (MO) (43.0%) or a principal medical officer (PMO) (36.8%) (Table II).

Number of Clinic Visits:

Thirty two point two percent of the patients have had five or more visits, while the rest have had fewer visits (Table II).

The distribution of the number of clinic visits is shown in Figure 2.

Variable	Category	Overall		Monotherapy		Polypharmacy	
N		**242**		**15**		**227**	
Variable	**Category**	**N**	**%**	**n**	**%**	**n**	**%**
Health Care Professional	Nurse	32	13.22	3	20.00	29	12.78
	Registrar/MO	104	42.98	6	40.00	98	43.17
	PMO	89	36.78	5	33.33	84	37.00
	Consultant	17	7.02	1	6.67	16	7.05
Number of Clinic Visits	1	37	15.29	5	33.33	32	14.10
	2	44	18.18	3	20.00	41	18.06
	3	40	16.53	1	6.67	39	17.18
	4	43	17.77	5	33.33	38	16.74
	5+	78	32.23	1	6.67	77	33.92

Table II Clinic visit profile of patients in the sample

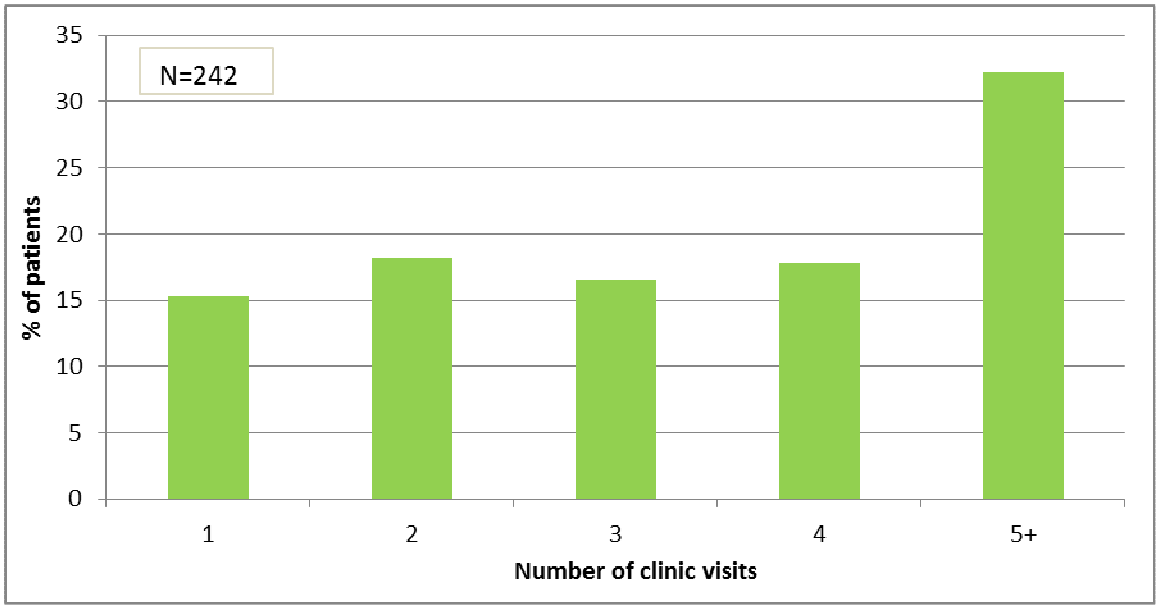


Figure 2 The distribution of number of clinic visits in the sample

- **Diagnostic Profile**

Bipolar Disorder Subtype:

Type I predominated with 68.6% of patients. Type II and NOS was 23.1% and 8.26% respectively (Table III).

Psychiatric Comorbidity:

Fourty eight point three percent of the patients were diagnosed with a comorbid psychiatric condition (Table III).

Variable	Category	Overall		Monotherapy		Polypharmacy	
N		**242**		**15**		**227**	
Variable	**Category**	**N**	**%**	**n**	**%**	**n**	**%**
Bipolar disorder subtype	Type I	166	68.60	12	80.00	154	67.84
	Type II	56	23.14	3	20.00	53	23.35
	NOS	20	8.26	0	0.00	20	8.81
Psychiatric comorbidity	Yes	117	48.35	5	33.33	112	49.34
	No	125	51.65	10	66.67	115	50.66

Table III Diagnosis of patients in the sample

- **Medication Profile**

Monotherapy / Polypharmacy:

Only 6.2% of the patients were prescribed monotherapy. Thirty six point three percent were prescribed four or more psychotropic medications (Table IV).

Estimates with 95% confidence intervals:

- Monotherapy: 6.2% (3.5-10.0%).
- Polypharmacy: 93.8% (90.0-96.5%).

Variable	Category	Overall		Monotherapy		Polypharmacy	
N		**242**		**15(6.2%)**		**227(93.8%)**	
Variable	**Category**	**N**	**%**	**N**	**%**	**n**	**%**
Number of psychotropics	1	15	6.20	15	100.00	0	0.00
	2	55	22.73	0	0.00	55	24.23
	3	84	34.71	0	0.00	84	37.00
	4	52	21.49	0	0.00	52	22.91
	5+	36	14.88	0	0.00	36	15.86

Table IV Number of psychotropics prescribed to patients in the sample

The mean number of psychotropic medications prescribed per patient was 3.2 (standard deviation 1.2; median 3; IQR: 2-4; range 1-6). The distribution of the number of psychotropic medication prescribed per patient is shown in Figure 3.

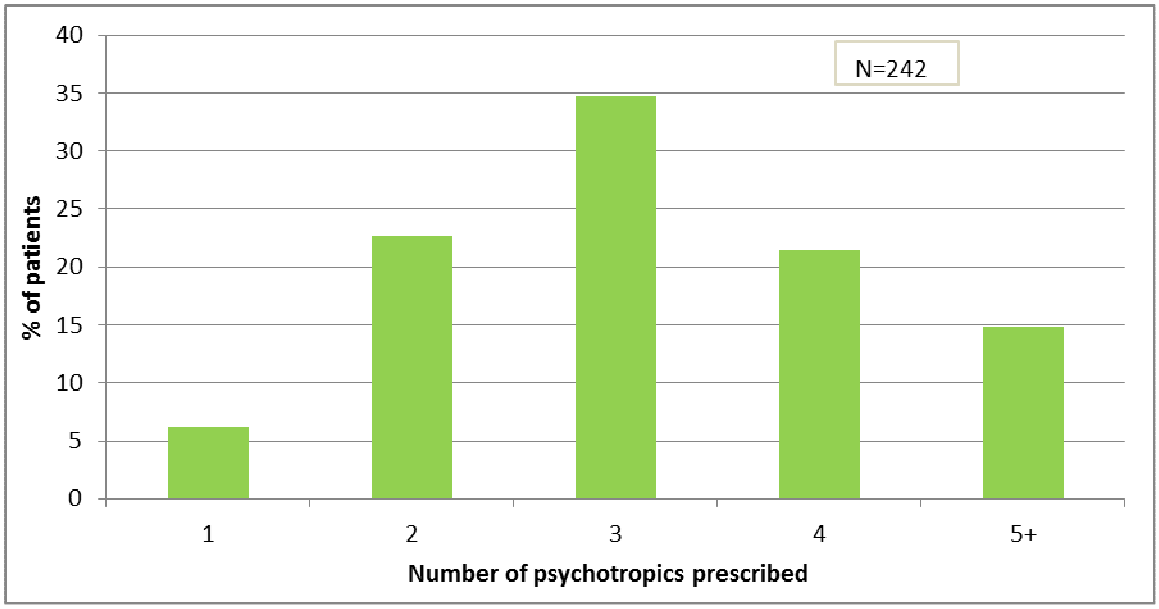


Figure 3 The distribution of the number of psychotropic medication prescribed per patient in the sample

Medication:

- The proportion of patients in the sample who had one or more psychotropic medications prescribed in each of the medication classes as per **Group A** is shown in Figure 4. Eighty three point eight percent of the patients were prescribed at least one **standard mood stabilizer**. The prescription of antipsychotics (61.1%) predominated followed by **add-ons** (53.7%), **standard anticonvulsants** (49.5%) and antidepressants (48.7%).

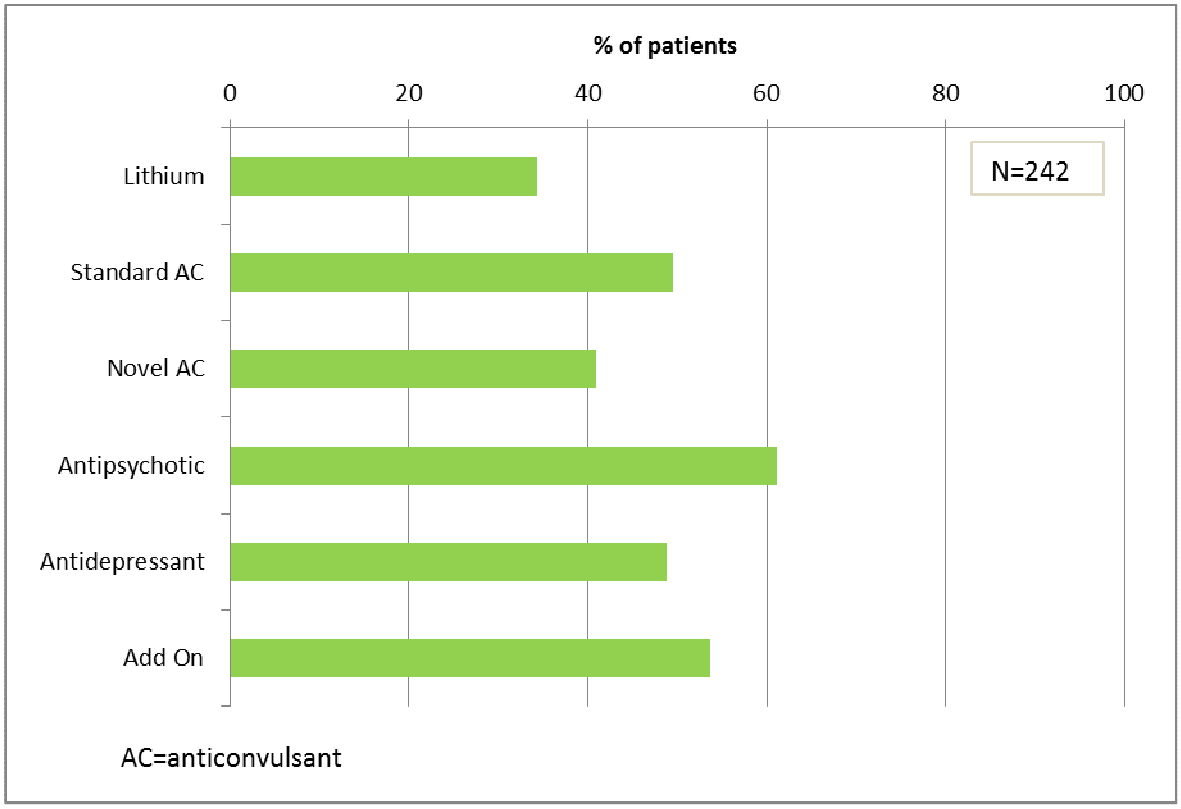


Figure 4 The proportion of patients in the sample who had one or more psychotropic medications prescribed in each class as per Group A

- The proportion of patients in the sample who had one or more psychotropic medications prescribed in each of the medication classes as per **Group B** is shown in Figure 5. The prescription of **standard anticonvulsants** (49.5%) predominated, followed by **atypical antipsychotics** (46.6%) and **novel anticonvulsants** (40.9%).

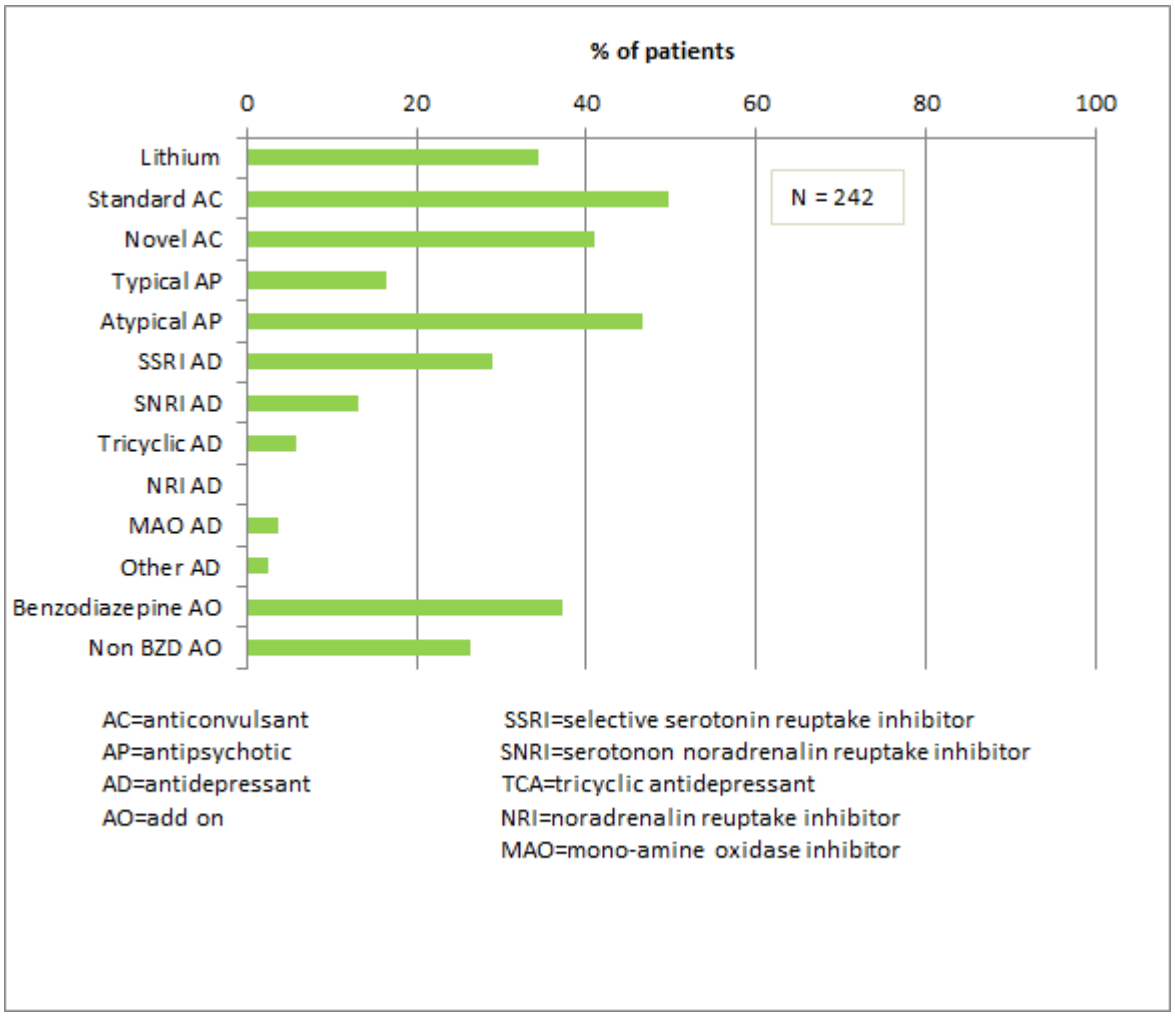


Figure 5 The proportion of patients in the sample who had one or more psychotropic medications prescribed in each class as per Group B

- The psychotropic medication classes prescribed as per **Group B** for each bipolar subtype is shown in Table V.

Category	Variable	Bipolar disorder N=242					
		Type I		Type II		NOS	
		n=166		n=56		n=20	
		N	%	N	%	n	%
Lithium	Lithium	73	43.98	6	10.71	4	20.00
Anticonvulsant	Standard	98	59.04	16	28.57	6	30.00
	Novel	50	30.12	37	66.07	12	60.00
Antipsychotic	Typical	26	15.66	6	10.71	8	40.00
	Atypical	92	55.42	16	28.57	5	25.00
Antidepressant	SSRI	31	18.67	28	50.00	11	55.00
	SNRI	12	7.23	15	26.79	5	25.00
	TCA	7	4.22	6	10.71	1	5.00
	NRI	0	0.00	0	0.00	0	0.00
	MAO	7	4.22	2	3.57	0	0.00
	Other	2	1.20	3	5.36	1	5.00
Add On	Benzodiazepine	56	33.73	24	42.86	10	50.00
	Non-Benzodiazepine	38	22.89	18	32.14	8	40.00

SSRI=selective serotonin reuptake inhibitor
SNRI=serotonon noradrenalin reuptake inhibitor
TCA=tricyclic antidepressant
NRI=noradrenalin reuptake inhibitor
MAO=mono- amine oxidase inhibitor

Table V The psychotropic medication classes prescribed (Group B) for each bipolar subtype

- Thirty four point three percent of the patients in the sample were prescribed lithium (Table VI).
- After sodium valproate (37.1%), the most commonly prescribed psychotropic medications were lamotrigine (31.8%), clonazepam (26.8%), risperidone (21.9%) and citalopram (14%) (Table VI).

Psychotropic Class	Psychotropic	N	%
Lithium	Lithium	83	34.30
Anticonvulsants-standard and novel	Valproate	90	37.19
	Carbamazepine	32	13.22
	Oxcarbazepine	4	1.65
	Lamotrigine	77	31.82
	Topiramate	11	4.55
	Gabapentin	17	7.02
	Other	0	0.00
Antipsychotics-typical	Flupenthixol	14	5.79
	Chlorpromazine	12	4.96
	Trifluoperizine	7	2.89
	Haloperidol	5	2.07
	Zuclopenthixol	3	1.24
	Fluphenazine	0	0.00
Antipsychotics-atypical	Risperidone	53	21.90
	Quetiapine	22	9.09
	Olanzepine	13	5.37
	Clozapine	12	4.96
	Sulpiride	10	4.13
	Amisulpiride	7	2.89
	Ziprazidone	0	0.00
	Aripiprazole	0	0.00
Antidepressant-SSRI	Citalopram	34	14.05
	Escitalopram	2	0.83
	Fluoxetine	29	11.98
	Sertraline	1	0.41
	Paroxetine	4	1.65
	Fluvoxamine	0	0.00
Antidepressant-SNRI	Venlafaxine	31	12.81
	Duloxetine	1	0.41
Antidepressant-TCA	Imipramine	1	0.41

Table VI The proportion of patients in the sample prescribed the various psychotropic medications (N=242)

Psychotropic Class	Psychotropic	N	%
Antidepressant-TCA	Clomipramine	1	0.41
	Amitriptaline	9	3.72
	Mianserin	3	1.24
	Lofepramine	0	0.00
	Other	1	0.41
Antidepressant-NRI	Reboxetine	0	0.00
Antidepressant-MAO	Maclobemide	7	2.89
	Tranylcypromine	2	0.83
Antidepressant-Other	Mirtazepine	1	0.41
	Trazadone	4	1.65
	Bupropion	1	0.41
Add On – Benzodiazepine	Clonazepam	65	26.86
	Diazepam	6	2.48
	Lorazepam	12	4.96
	Oxazepam	9	3.72
	Midazolam	3	1.24
	Bz Other	0	0.00
Add On - Non-benzodiazepine	Zolpidem	4	1.65
	Zopiclone	5	2.07
	Promethazine	9	3.72
	Buspirone	9	3.72
	Propranolol	24	9.92
	Hydroxyzine	21	8.68
	Non Bz Other	1	0.41

SSRI=selective serotonin reuptake inhibitor

SNRI=serotonon noradrenalin reuptake inhibitor

TCA=tricyclic antidepressant

NRI=noradrenalin reuptake inhibitor

MAO=mono- amine oxidase inhibitor

Table VI (continued) (N=242)

- The proportion of patients in the sample prescribed the various anticonvulsants is shown in Figure 6 (in these results, percentages do not sum to 100% since some patients were prescribed more than one of these medications). Sodium valproate (37.1%) and lamotrigine (31.8%) were the most popular **standard** and **novel anticonvulsants** respectively.

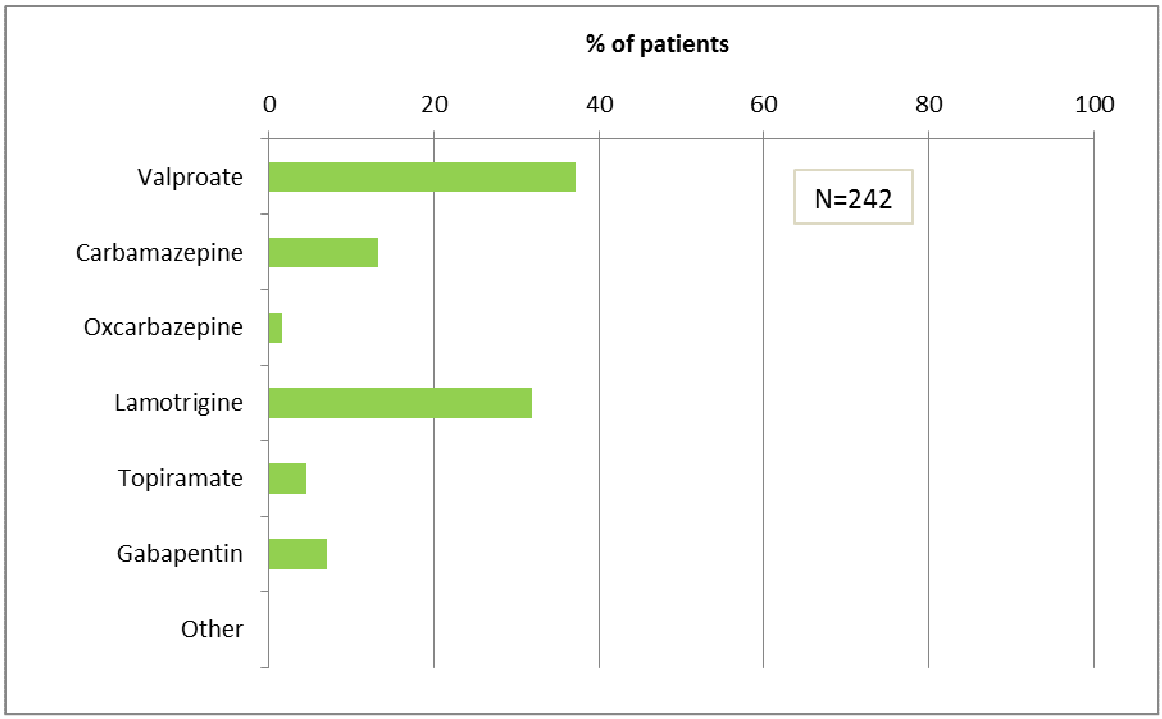


Figure 6 The proportion of patients in the sample prescribed the various anticonvulsants

- Forty six point six percent of patients were prescribed **atypical antipsychotics** and 16.5% were prescribed **typical antipsychotics**. The proportion of patients in the sample prescribed the various **typical** and **atypical antipsychotics** is shown in Figure 7 (in these results, percentages do not sum to 100% since some patients were prescribed more than one of these medications). Risperidone (21.9%) was the most frequently prescribed antipsychotic.
- The proportion of patients prescribed each antipsychotic in the sample of patients prescribed antipsychotics is shown in Figure 8 (in these results, percentages do not sum to 100% since some patients were prescribed more than one of the medications).

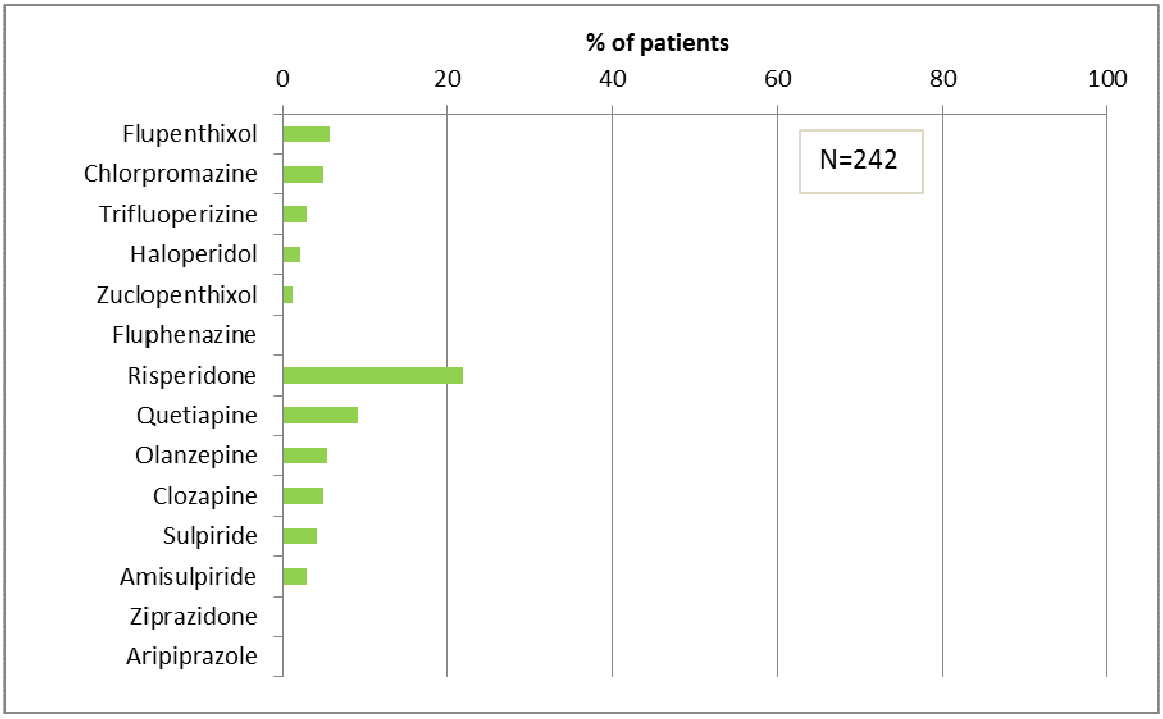


Figure 7 The proportion of patients in the sample prescribed the various antipsychotics

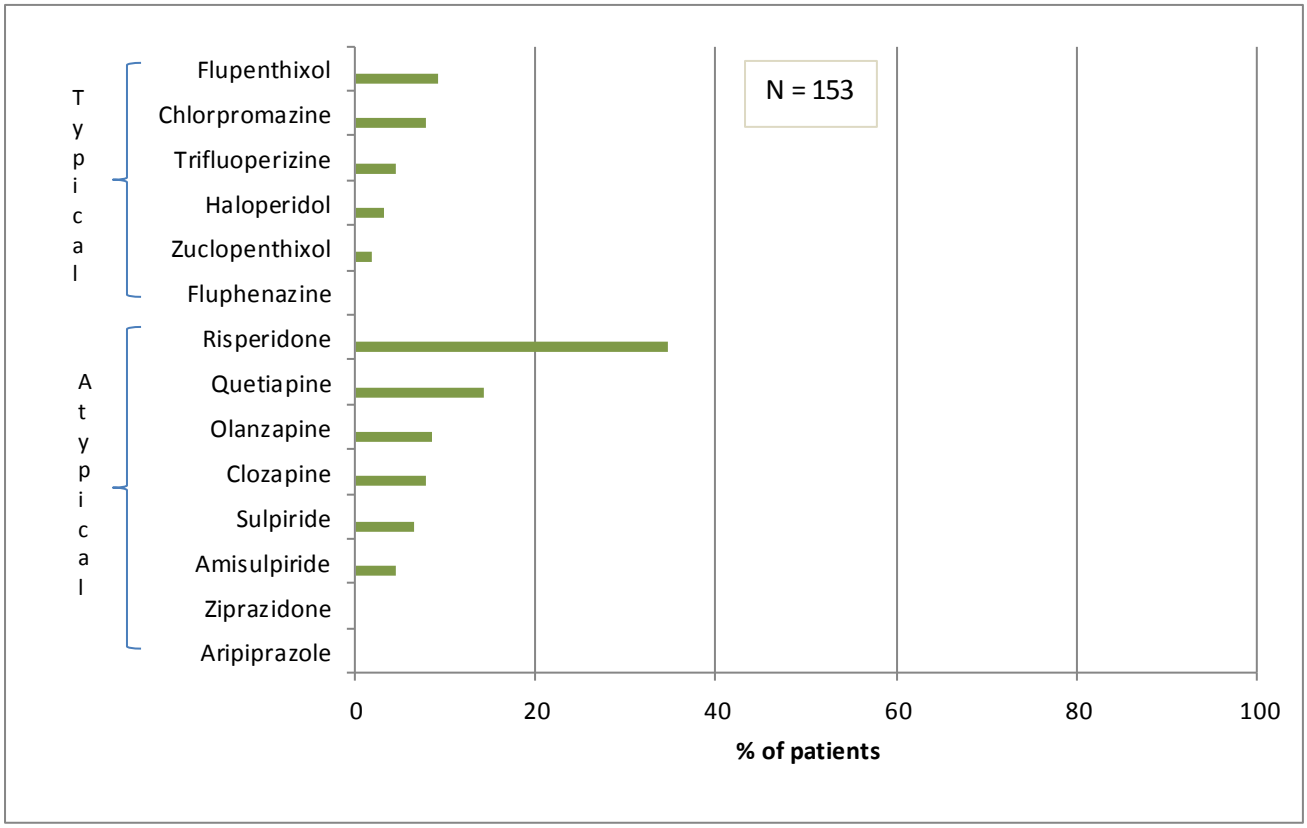


Figure 8 The proportion of patients prescribed each antipsychotic in the sample of patients prescribed antipsychotics

- The proportion of patients in the sample prescribed the various antidepressants is shown in Figure 9 (in these results, percentages do not sum to 100% since some patients were prescribed more than one of these medications). Citalopram (14%), fluoxetine (11.9%) and venlafaxine (12.8%) were the most frequently prescribed antidepressants.
- The proportion of patients prescribed each antidepressant in the sample of patients prescribed antidepressants is shown in Figure 10 (in these results, percentages do not sum to 100% since some patients were prescribed more than one of the medications).

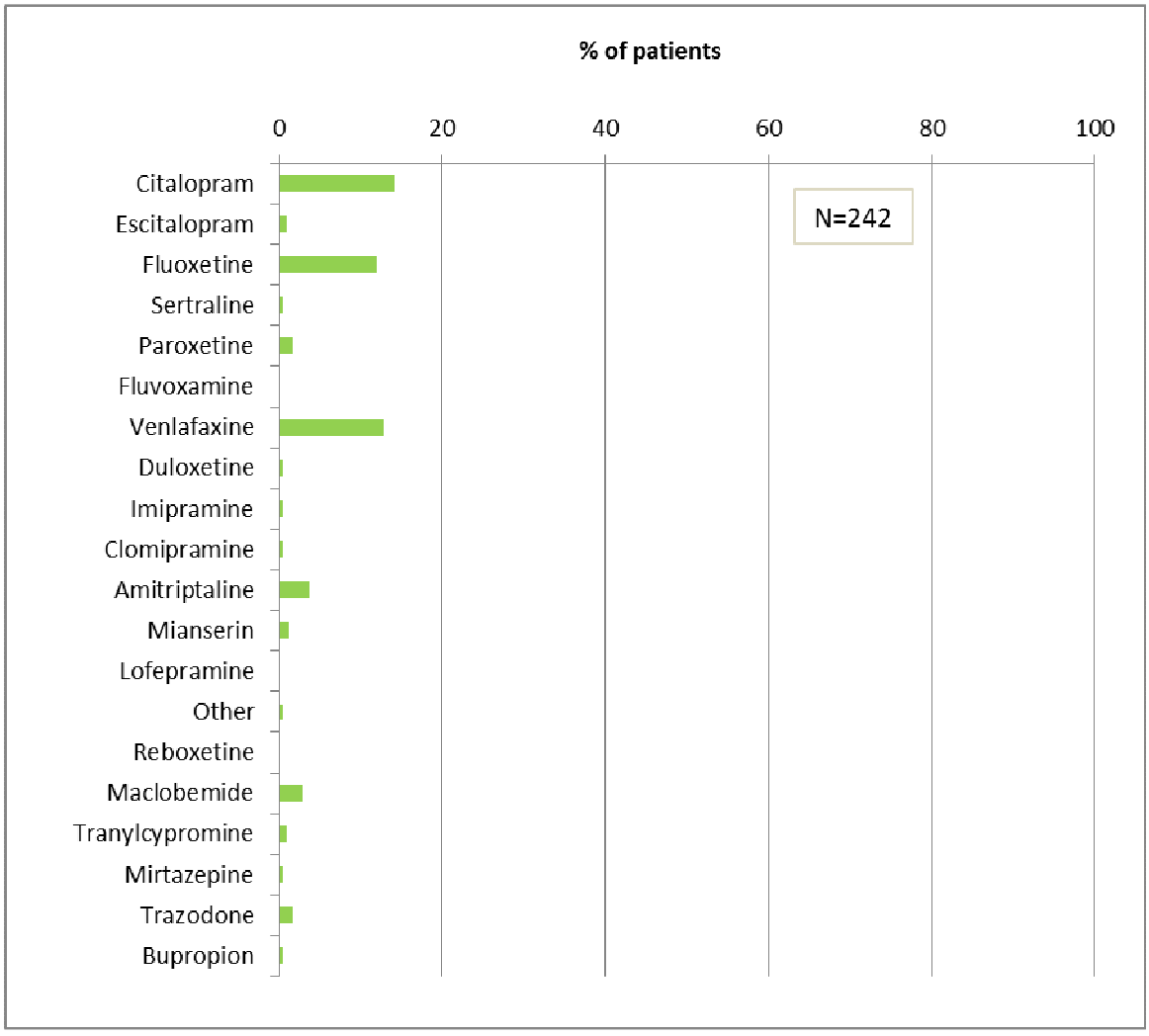


Figure 9 The proportion of patients in the sample prescribed the various antidepressants

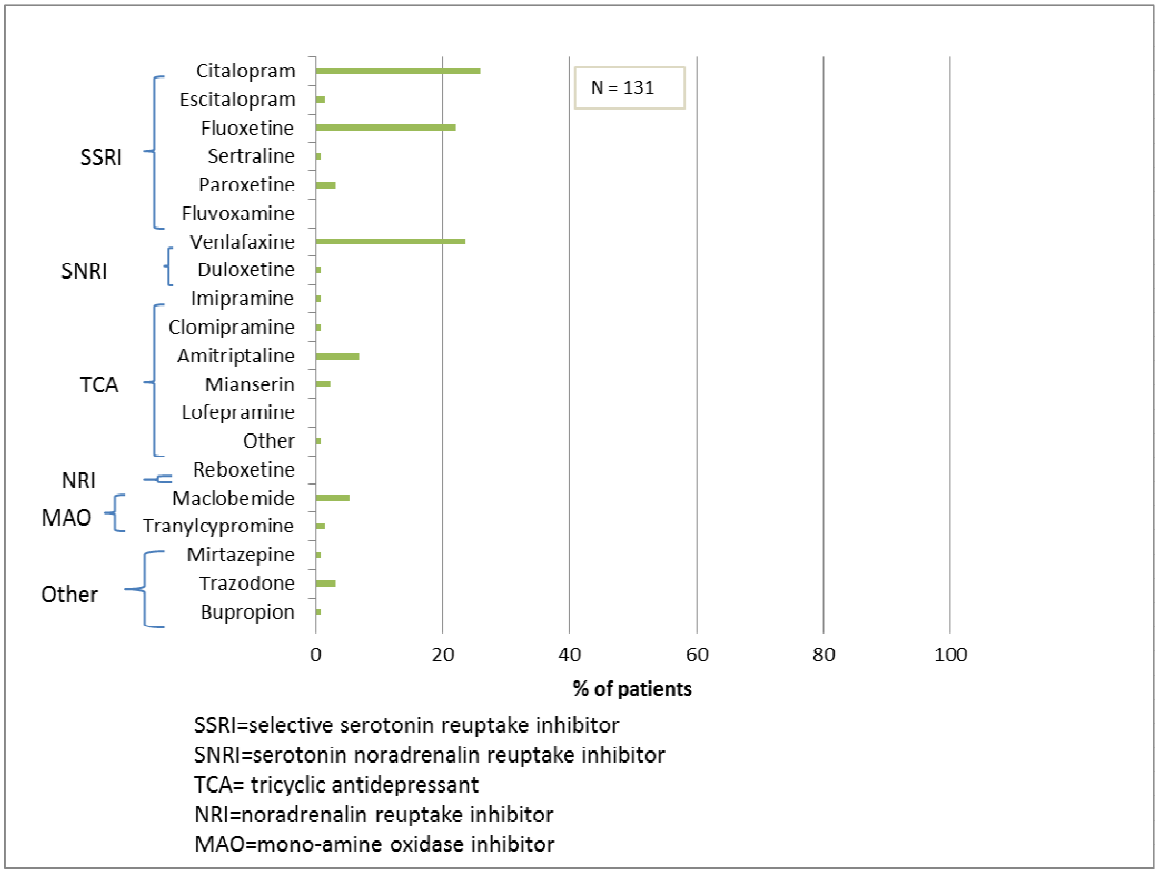


Figure 10 The proportion of patients prescribed each antidepressant in the sample of patients prescribed antidepressants

- The proportion of patients in the sample prescribed the various **add-ons** is shown in Figure 11 (in these results, percentages do not sum to 100% since some patients were prescribed more than one of these medications). Clonazepam (26.8%) was the most frequently prescribed **add- on**.
- The proportion of patients prescribed each **add-on** in the sample of patients prescribed **add-ons** is shown in Figure 12 (in these results, percentages do not sum to 100% since some patients were prescribed more than one of the medications).

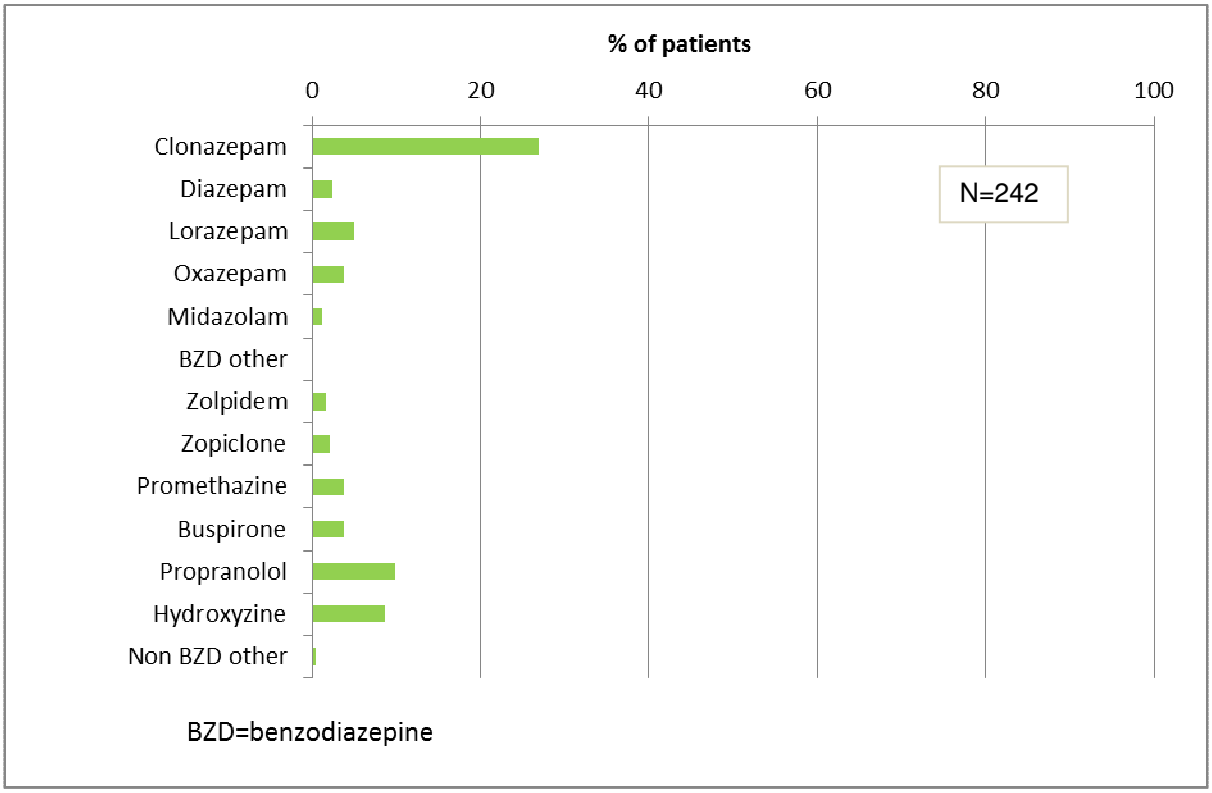


Figure 11 The proportion of patients in the sample prescribed the various add-ons

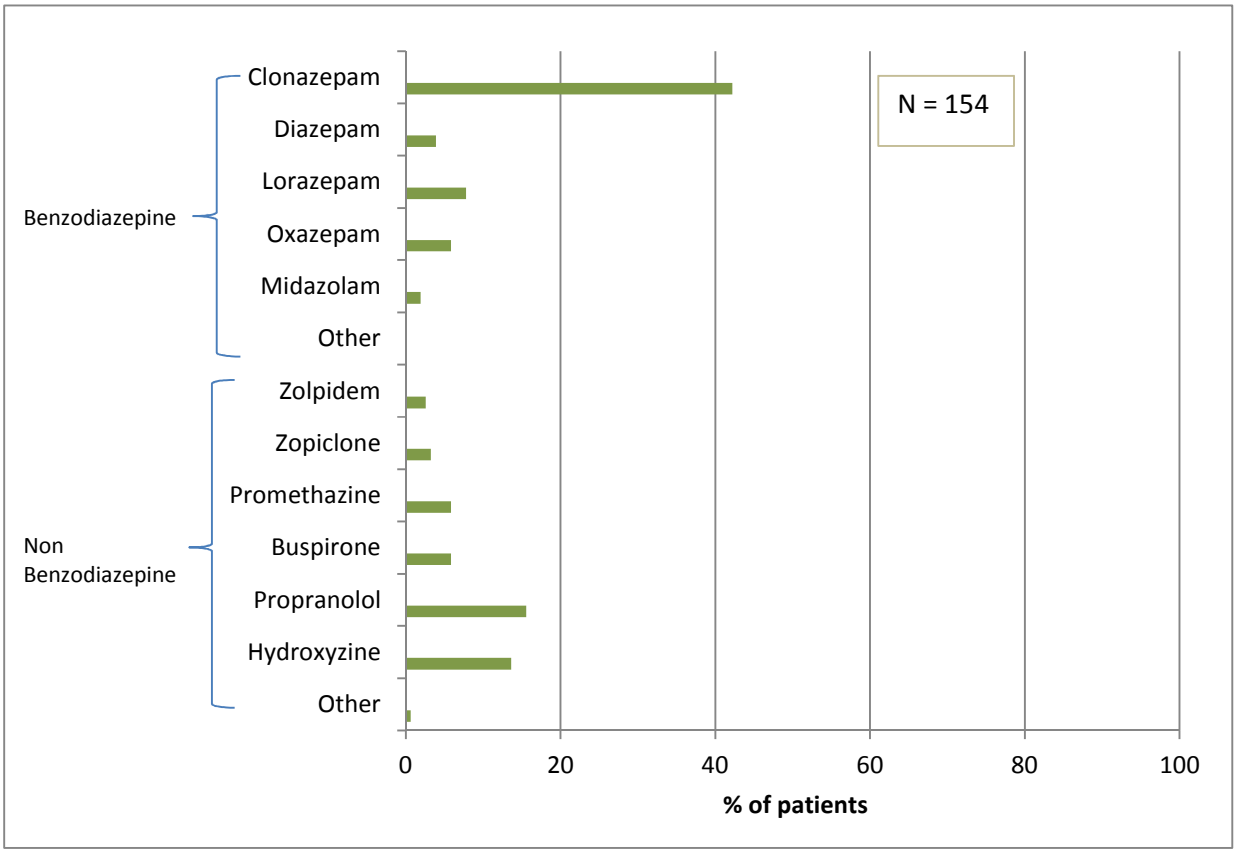


Figure 12 The proportion of patients prescribed each add-on in the sample of patients prescribed add-ons

Combinations of Medication Used as per **Group A.**

A total of fifteen patients were prescribed monotherapy (4 were prescribed Lithium; 4 were prescribed a **standard anticonvulsant**; 5 were prescribed a **novel anticonvulsant** and 2 were prescribed an antipsychotic). Three percent were treated with **standard mood stabilizer** monotherapy.

The distribution of the number of classes of medications prescribed per patient in the sample (combining **standard** and **novel anticonvulsants** into one class) is shown in Figure 13.

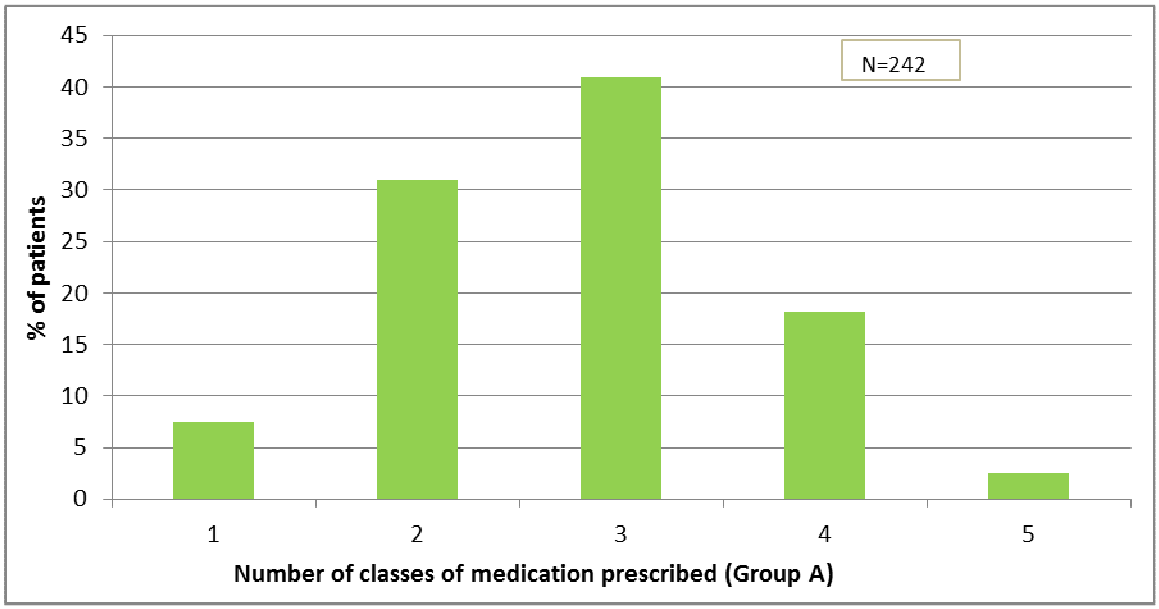


Figure 13 The distribution of the number of classes of psychotropic medication prescribed per patient in the sample according to Group A
(combining standard and novel anticonvulsants into one class)

The mean number of classes prescribed in combination was 2.8 (standard deviation 0.9; median 3; IQR: 2-3; range1-5).

The total number of medication combinations obtained was 52. Of these combinations the most frequently prescribed combination was a **standard anticonvulsant** with an antipsychotic (9.1%). The antipsychotics were prescribed together with **standard mood stabilizers** in 114 of the 242 patients (47%). Antipsychotics were prescribed with other classes of medication combinations in 34 of the 242 patients (14%). Antidepressants were prescribed together with a **standard mood stabilizer** and or antipsychotic in 91 of the 242 patients (38%). Antidepressants were prescribed with a **novel anticonvulsant** and or **add-ons** in 27 of the 242 patients (11%).

Combinations of Medication Used as per **Group B**.

The total number of medication combinations obtained was 132. The combination of an **atypical antipsychotic** and a **standard anticonvulsant** was the most frequently prescribed combination (7.02%).

Association between Monotherapy / Polypharmacy & all the Demographic, Biographic & Clinical Variables, as well as Medication Classes as per Groups A / B

We note at the outset that the monotherapy group is very small (n=15).

The following significant differences were found:

- Number of clinic visits (Cochran-Armitage test for trend; p=0.046): it appears that the monotherapy patients had had fewer visits than the polypharmacy patients. (Figure 14)

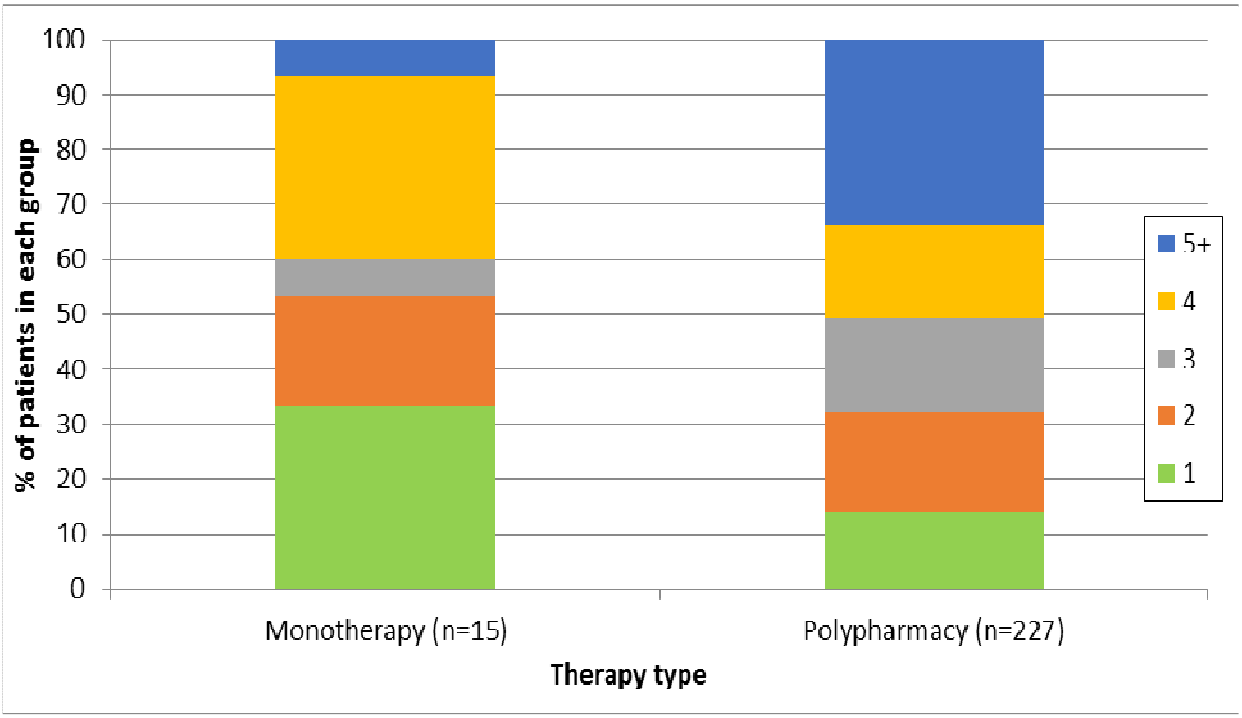


Figure 14 Number of clinic visits

(N=242)

- Medication as per **Group A**:

1. **Antipsychotics** : a larger proportion of polypharmacy patients (64.3%) were prescribed one or more antipsychotics, compared to monotherapy patients (13.3%)(Fisher's exact test; p<0.0001; phi=0.25).
2. **Antidepressants**: a larger proportion of polypharmacy patients (52.0%) were prescribed one or more antidepressants, compared to monotherapy patients (0.0%)(Fisher's exact test; p<0.0001; phi=0.25).
3. **Add-ons:** a larger proportion of polypharmacy patients (57.3%) were prescribed one or more add-ons, compared to monotherapy patients (0.0%)(Fisher's exact test; p<0.0001; phi=0.28).

- Medication as per **Group B**:

1. **Atypical antipsychotics:** a larger proportion of polypharmacy patients (48.9%) were prescribed one or more atypical antipsychotics, compared to monotherapy patients (13.3%) (Fisher's exact test; p=0.0074; phi=0.17).
2. **SSRI antidepressants:** a larger proportion of polypharmacy patients (30.8%) were prescribed one or more SSRI antidepressants, compared to monotherapy patients (0.0%) (Fisher's exact test; p=0.0069; phi=0.16). .
3. **Benzodiazepine** and **non-benzodiazepine add-ons:** a larger proportion of polypharmacy patients (39.7 and 28.2% respectively) were prescribed one or more of these add-ons, compared to monotherapy patients (0.0% in both cases) (Fisher's exact test; p=0.0013; phi=0.20 and p=0.013; phi=0.15 respectively).

Association between Bipolar Disorder Subtype & Medication Classes as per Groups A / B.

The following significant differences were found:

- **Group A**: there were significant differences for lithium**, standard** and **novel anticonvulsants**, antipsychotics and antidepressants (Fisher's exact test; p<0.0001 in all cases; phi=0.30, 0.28, 0.33, 0.24, 0.46 respectively). The prescription of lithium was favoured for type I, compared to the other two types. The prescription of one or more **standard anticonvulsants** was favoured for type I. The prescription of one or more of the **novel anticonvulsants** was favoured for type II and NOS. The prescription of one or more antipsychotics was favoured for type I and NOS. The prescription of one of more antidepressants was favoured for type II and NOS (Figure 15).

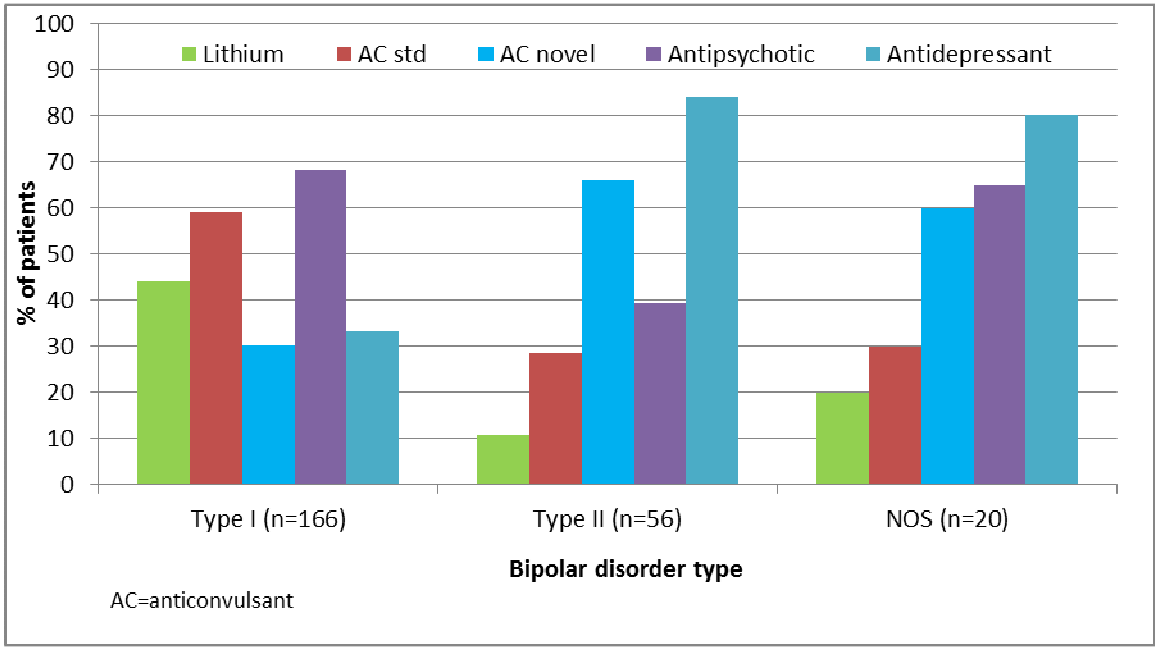


Figure 15 Bipolar Disorder subtype and psychotropic medication classes as per Level A (N=242)

- **Group B***:* there were significant differences for lithium, both **standard** and **novel anticonvulsants**, both **typical** and **atypical antipsychotics** and for SSRI and SNRI antidepressants (Fischer' exact test; p<0.0001 in all cases; phi=0.30, 0.28, 0.33, 0.20, 0.26, 0.33, 0.26 respectively). The prescription of lithium was favoured for type I, compared to the other two types. The prescription of one or more **standard anticonvulsants** was favoured for type I. The prescription of one or more of the **novel anticonvulsants** was favoured for type II and NOS. The prescription of one or more **typical antipsychotics** was favoured for NOS, while the prescription of **atypical antipsychotics** was favoured for type I. The prescription of one or more antidepressants (of either type) was favoured for type II and NOS (Figure 16).

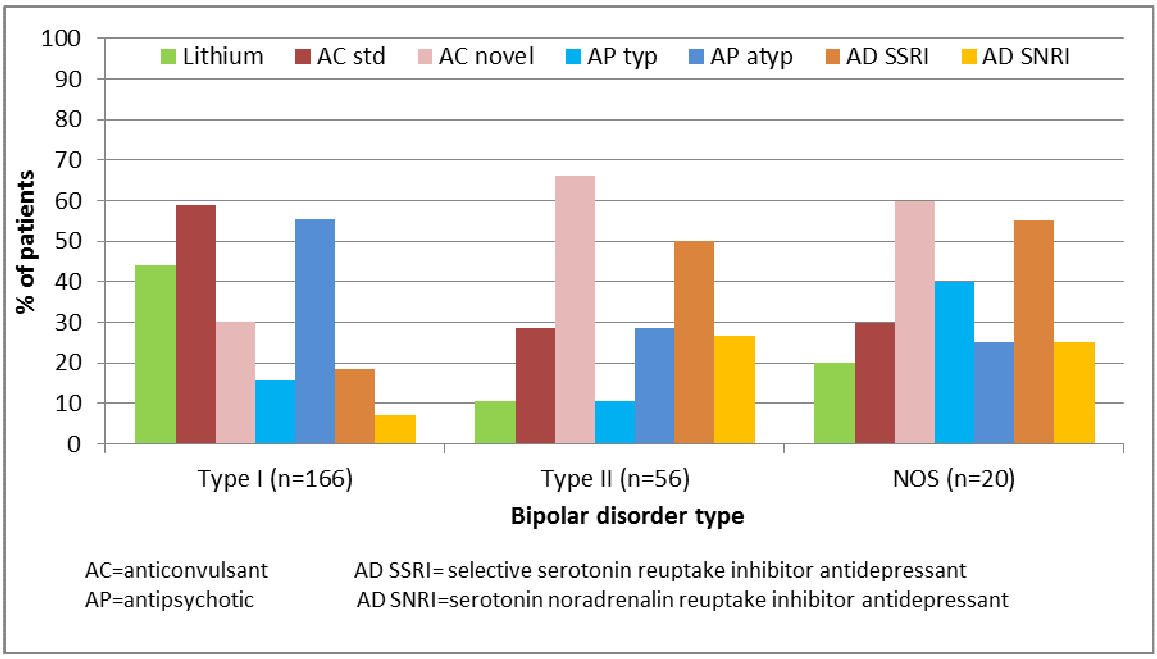


Figure 16 Bipolar disorder subtype and medication classes as per Group B (N=242)

- The prescription of lamotrigine was favoured for type II (51.8%) and NOS (50.0%), compared to type I (22.9%) (chi-square test; p<0.0001; Cramer's V=0.28).

Comorbidity & Selected Variables:

The following significant differences were found:

- **Bipolar disorder subtype**: the presence of a psychiatric comorbidity was lower in type I (34.9%) compared to type II (75%) and NOS (85%) (chi-square test; $p<0.0001$; phi=0.24).
- **Number of medications prescribed**: those with a psychiatric comorbidity were more likely to have five or more medications prescribed. Of those patients with a psychiatric comorbidity, 78% were prescribed more than two medications versus 65% of those without a psychiatric comorbidity (chi-square test; $p=0.031$; Cramer's V=0.21).
- **Lamotrigine**: lamotrigine was prescribed more in patients with a psychiatric comorbidity (43.6%) than those without a psychiatric comorbidity (20.8%) (Fisher's exact test; $p<0.0001$; phi=0.24).

DISCUSSION

Bipolar disorder is a condition with a broad spectrum, and diverse set, of symptoms. It is thus a complex disorder, with patient's that are complex. It is therefore inevitable that treatment will not always conform to standard options and guidelines. The discussion will look at findings and factors that are relevant and important in relation to the treatment of bipolar disorder.

Demographic Profile

- ### Age & Gender

Epidemiological studies show that bipolar disorder affects males and females equally, however bipolar disorder II is more prominent in females.[47] The current study has shown a predominantly female population. This may be because females usually predominate in treated samples of patients with mood disorders.[19] It has also been reported that female patients tend to ask for help more readily than males and also tend to be more compliant with their medication treatment.[25] Hence this may explain the higher number of female patients in the sample. The majority of the patients' age was between 18 and 64. This is in keeping with prevalence studies that report a one year prevalence of bipolar disorder among adults aged 65 and older to be 0.4%. This is significantly lower than in younger adults which is 1.4%.[47]

The data highlights that increasing age appears to be associated with a higher likelihood of polypharmacy (see table II). The older patient with bipolar disorder usually presents with rapid cycling and mixed moods, a decrease in cognitive functioning and a more severe presentation than younger patients with a lower treatment response.[48] Medical comorbidity is also seen in the older patient.[49,50] Age related tolerance and metabolism of medications need to be considered.[48] Thus for reasons mentioned, bipolar disorder in the older patient changes into a more complex illness with the association of polypharmacy in such patients.[49,50]

- ### Socio- economic Status

Bipolar disorder is associated with high rates of unemployment.[51] This is also reflected in the current study. Most of the patients in the current sample (65.7%) were classified as falling into a lower socioeconomic group. These patients were either unemployed or earning less than R36 000 a year. Bipolar disorder is a potentially relapsing condition and with each episode comes loss of earning and periods spent unemployed. This leads to a deterioration in their overall financial situation. TARA Hospital is a government hospital and thus patients who could afford private care would likely be serviced by the private sector.

Clinic Visit Profile

The current study did not include which phase of bipolar disorder was being treated as it was surmised that being an outpatient population the majority of patients would be stable and in the maintenance phase. This was supported by the data which demonstrated that the majority of patients consulted with a health care professional less specialised than the consultant psychiatrist and the majority of patients had four or less visits to the clinic a year. This would equate to a consultation every three months, at the most, for these patients. The data however demonstrates that for some patients monotherapy is not seemingly a consistent predictor of fewer clinic visits (see Table II). This may be due to clinicians choosing to use polypharmacy as first step management even in stable patients.

Diagnostic Profile

An American population study conducted between 2001 and 2003 revealed that a lifetime prevalence of bipolar disorder I was 1%, bipolar disorder II was 1.1% and bipolar disorder not otherwise specified (NOS) was 1.4%.[52] Some studies estimate that bipolar disorder NOS might affect up to 6% of the general population.[52] In this current study bipolar disorder I was the most common diagnosis and bipolar disorder NOS was the least common diagnosis. This could be representative of the under-detection and under-treatment of bipolar spectrum disorders in psychiatric clinic settings.[52]

McElroy[53] refers to bipolar disorder with comorbidity as 'complicated bipolar' and states that comorbidity is the rule, not the exception in bipolar disorder. A Stanley Foundation Bipolar Treatment Outcome Network study showed 65% of the 300 patients had at least one psychiatric comorbidity.[54] Psychiatric comorbidity includes anxiety, sleep, substance and personality disorders as well as attention deficit hyperactivity disorder. The current study showed that almost half of the patients had a psychiatric comorbidity. The presence of psychiatric comorbidity is one of the reasons given for the use of polypharmacy in bipolar disorder.[12,15] The current study supports this association and demonstrated a statistically significant difference when comparing the number of psychotropics prescribed where psychiatric comorbidity was present or absent i.e. the presence of comorbidity was associated with a greater number of psychotropics prescribed.

Medication Profile

- ### Specific Medication

The Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[8,33] is the largest treatment study conducted for bipolar disorder to date. It was also conducted in academic centres, like the current study, and is also a North American study. South African bipolar disorder treatment guidelines tend to follow the American Psychiatric Association guidelines.[38-42,44] The STEP-BD study[8,33] is thus a useful reference point for discussing the prescribing patterns of bipolar patients in the current study.

In the STEP-BD study lithium (38.4%) and sodium valproate (36.8%) were shown to be most commonly prescribed.[33] In the current study lithium (34.3%) and sodium valproate (37.1%) were also shown to be the two most common medications prescribed. In keeping with the STEP-BD study[33] lamotrigine (31.8%) and clonazepam (26.8%) were the next most frequently prescribed medications. In the STEP-BD study however lamotrigine was prescribed in 15.4% of patients and clonazepam in 15% of patients.[33] The higher percentage of lamotrigine use in the current study may reflect clinician preference and relative ease of use as it does not require blood monitoring and is a generally safe medication to use notwithstanding recognized dermatological side effects.[55,56] The latter consideration is particularly useful in an outpatient population. The higher percentage of clonazepam use may reflect that clinicians are perhaps overprescribing benzodiazepines in this patient sample however the study did not specifically explore clinician motivation for prescribing. In the current study the SSRI's were the most common antidepressant prescribed (18.6%) and lamotrigine the most common **novel anticonvulsant** prescribed (31.8%). This was also seen in the STEP-BD study (21.6% and 15.4% respectively).[33] In the STEP-BD study bupropion was prescribed in 14.6% of patients.[33] In the current study bupropion was used in 0.41% of patients. This finding likely reflects that the use of certain medications is limited by what is available to the clinic, based on the Government's essential drug list at the time of the study.

The STEP-BD study showed that olanzapine and risperidone were the most frequently prescribed **atypical antipsychotics**, with only 4% of patients prescribed **typical antipsychotics**.[33] The current study showed that risperidone was the most commonly prescribed **atypical antipsychotic** (22%). Olanzapine was only prescribed in 5% of patients and **typical antipsychotics** were prescribed in 17% of patients. These differences could reflect that although the patients received treatment at a tertiary institution not all the **atypical antipsychotics** are readily available and some require detailed motivation at consultant psychiatrist level in order to access or are not included for use on the Government's essential drug list. The higher percentage

use of **typical antipsychotics** may reflect their cost effectiveness for use in a State sector outpatient setting, with depot formulations of **typical antipsychotics** being available for improved compliance. It should be noted that the South African bipolar guidelines[41,42,44] do include the use of **typical antipsychotics** for manic / hypomanic episodes as do one of the North American treatment guidelines (**CANMAT**) which mentions the use of **typical antipsychotics** in the maintenance phase of bipolar disorder.[38,39]

- **Medication Classes**

Overview

In the current study the **standard mood stabilizers** were prescribed in 83.8% of patients. The next most common class prescribed was antidepressants (48.7%) followed by **atypical antipsychotics** (46.6%), **novel anticonvulsants** (40.9%) and benzodiazepines (37.1%). These results are similar to the STEP-BD study, where **standard mood stabilizers** were prescribed in 71.9% of patients, antidepressants in 40.6% of patients but with **novel anticonvulsants** being prescribed more frequently than **atypical antipsychotics** (31.8% versus 27.2%) and benzodiazepines being prescribed in 25% of patients.[33]

Standard mood stabilizers

The current results revealed that **standard mood stabilizers** are prescribed in the majority of patients and still have an important role to play in the management of bipolar disorder. Sodium valproate was prescribed slightly more frequently than lithium. This may be due to the fact that sodium valproate is easy to prescribe and well tolerated.[57] The **standard mood stabilizers** are often used as first line treatments.[58] The **standard mood stabilizers** have sometimes been referred to as the 'chocolate, vanilla and strawberry' of bipolar disorder.[59] This is reference to the fact that these medications are the foundation or staples of bipolar disorder treatment. The treatment guidelines are very clear in their support of the use of these psychotropic medications and consider them to be first line treatment.[38,39,41,42,44]

Novel anticonvulsants and atypical antipsychotics

Both the current study and the STEP-BD study[33] show the use of **atypical antipsychotics** and **novel anticonvulsants** by clinicians to manage bipolar disorder. The STEP-BD study suggests that clinicians are recognizing these medications to have mood stabilizing properties with fewer side-effects, based on their own clinical experience as well as randomized clinical trials supporting their use in bipolar disorder.[33] The treatment guidelines are also encouraging the use of **atypical**

antipsychotics in all phases of bipolar management.[38,39,41,42,44] Lamotrigine is recommended to manage bipolar depression and bipolar maintenance in the treatment guidelines.[38,39,41,42,44]

Antidepressants

The use of antidepressants in managing bipolar depression is controversial. Some studies show some benefit to the addition of an antidepressant to a **standard mood stabilizer** whilst others show no positive effect.[60,61] Bipolar treatment guidelines[38,39,41,42,44] suggest cautious use of antidepressants; use in combination with an **antimanic medication** and careful / selective choice of an SSRI in order to prevent a manic switch or rapid cycling. The prescribing of antidepressants in the STEP-BD study[33] and the current study was noted for between 40 - 50% of patients.

Another study looking at prescribing patterns in bipolar I patients showed that over 50% of patients were prescribed antidepressants.[25] The antidepressant use in all three studies is high given the concerns around treating bipolar patients in the depressed phase with antidepressants. Such prescribing can however be justified given that patients are treated in specialist, academic settings potentially implying both complexity as well as an understanding of the risks and benefits. That 15-20% of bipolar patients relapse into depression after antidepressant discontinuation suggests the need for antidepressants.[61]

Baldessarini[19] suggests that the high observed rates of antidepressant use may reflect the residual symptoms of depression that are seen in bipolar patients. Levine et al[25] suggests that mania is a lot easier to treat than bipolar depression and this could be one reason for the high rates of antidepressant use. Both statements are perhaps implying that mood stabilizers and antipsychotics are often not effective enough to treat bipolar depression and require augmentation/add-on therapy with an antidepressant. Not with standing concerns regarding the use of antidepressants in this patient population, there is a high percentage of use which likely reflects the complexity of such patients.

Benzodiazepine add-ons

The STEP-BD[33] study together with the current study demonstrate the frequent use of benzodiazepines. This is also reflected in a study of bipolar I patients which showed high rates of benzodiazepine use in the sample studied.[25] Levine et al, the authors of this study suggested that this may be due to comorbid anxiety disorders; certain benzodiazepines having antimanic effects in add-on treatment or evidence of the extent of polypharmacy.[25] The authors however caution their use as bipolar patients often have comorbid substance use disorders.[25]

Monotherapy / Polypharmacy

One of the stated hypotheses of the current study was that the use of polypharmacy would be found in the majority of patients i.e. the norm rather than the exception.[8,12,18-27] This was indeed proven in that of the 242 patient files reviewed the majority of patients (>50%) were prescribed polypharmacy (93.8%). The patients were prescribed a mean number of 3.2 medications. This is in keeping with other studies which showed the average number of medications prescribed to be 3.31 and 2.98 and 2.6 respectively.[22-24] Levine et al[25] showed in their study that less than 20% of bipolar patients received monotherapy and over 80% received two or more medications, of whom nearly 50 % received three or more medications. The STEP-BD study[8] showed that 40% of the patients were prescribed three or more concurrent medications and 18% of patients received four or more medications (complex polypharmacy). Weinstock[28] demonstrated in a study that 36% of the patients were prescribed 'complex polypharmacy'. Levine et al[25] indicated in their study that nearly 25% of patients were prescribed 'complex polypharmacy' which was found in 36.3% of patients in the current study. The current study together with the above mentioned studies show a higher rate of 'complex polypharmacy' use than the STEP-BD study.[8] Weinstock[28] surmised that the STEP-BD study[8] perhaps under reported the use of 'complex polypharmacy' as they did not include the use of benzodiazepines, hypnotics and stimulants when considering 'complex polypharmacy'.

The current study highlights and is supported by many studies[8,12,18-27] that bipolar disorder is more commonly treated with polypharmacy than monotherapy. The current study also demonstrates that patients being treated within a specialist academic psychiatric setting are being prescribed polypharmacy. This finding was congruent with the STEP-BD study[8] and with Ventimiglia's[18] comment: 'the majority of individuals receiving care in tertiary and speciality centres will require a polytherapeutic regimen'. Nichol et al[30] looked at factors predicting the use of multiple psychotropic medications and found that patients consulting psychiatric specialists are much more likely to be prescribed combination therapy than those who consulted general practitioners. The patients consulting psychiatrists were six times more likely to receive multiple psychotropic medications. Nichol et al[30] also found that manic patients were four times more likely to be treated with polypharmacy. These findings suggest that complicated mental health problems require polypharmacy and are more likely to be supervised by specialist psychiatrists than general practitioners/primary care physicians.[62]

Combinations

The majority of patients were prescribed more than two classes of medication. There was no combination of medication classes prescribed that predominated and 52 combinations were shown as per **Group A.** The most common combination being a **standard anticonvulsant** and antipsychotic (**typical** or **atypical**), although this was only prescribed in 9.1% of patients. These findings are in keeping with two other studies[58,63] which looked at prescribing patterns in bipolar disorder. Bauer et al[63]showed 52 and Rossenbaum et al[58] showed 38 combinations of classes of medication prescribed. The most popular combination prescribed as per **Group B** was an **atypical antipsychotic** together with a **standard anticonvulsant** (7.02%) and a total of 132 different combinations were prescribed. This current study hypothesised, that where polypharmacy is used antipsychotics (**typical** or **atypical**) will be prescribed in combination with a **standard mood stabilizer** in the majority of cases (>50%). This hypothesis was not proven as the results demonstrated that there is not one combination of medication that is prescribed in the majority of cases. The study did however find that 47% of the combinations did include at least a **standard mood stabilizer** and antipsychotic (**typical** or **atypical**). This finding is consistent with the data that suggest the use of a mood stabilzer together with an antipsychotic (**typical** or **atypical)** may be more effective than either class of medication on their own.[57]

The wide variation and numerous possible medication combinations demonstrated in the current study could reflect the complexity of the patient and the disorder being treated, clinician preference, clinician skill and experience, socioeconomic factors, lack of evidence base and specific treatment guidelines / guidance for the use of medication combinations.[15,25,58,63]

It has been recognized that the treatment of bipolar disorder is complex and often requires the use of multiple medications and complex combinations, whilst acknowledging that such approaches may be potentially harmful, given the various drug interactions, and also costly.[15] Many bipolar patients however do not respond to combinations of treatments consistent with evidence-based guidelines.[15] The literature to date has not adequately addressed the efficacy of polypharmacy involving more than two medications to treat bipolar patients.[15] Sachs[15] raises concerns that this leads to personalized and individualised care that is uncontrolled and does not meet the standards of evidence based medicine. Sachs[15] defines 'ineffective complex chronic care' as patients who remain ill despite receiving five or more medications for six months or more. Sachs[15] advocates that where personalized and individualized treatment is necessary that clinicians practice 'effective complex chronic care', defining this as polypharmacy given to patients for whom excellent results might be attributed to a skilful treatment regime of four or more medications.

Gelenberg[64] advocates that clinicians should match a particular patient with the optimal regimen or customize treatment to each patient's needs. He encourages clinicians to look at previous response to treatment, polarity of an episode, psychiatric and medical comorbidity and drug interactions.[64] He echoes the recommendation of Sachs[15] to practice 'effective complex chronic care' for bipolar patients.[64]

The bipolar treatment guidelines are there to guide clinicians in providing evidence-based treatment. These guidelines unfortunately do not adequately address the problems that clinicians face such as: when to start / stop or change a medication; for how long a trial of medication should last; how quickly to titrate up a medication; which medication to prescribe first, when to add or switch to a second medication; which mood stabilizer to use first; which antipsychotic to use first and what treatment for a particular patient should be prioritized or deferred.[59] This is where the skill and experience of the clinician comes in and plays a vital role in the management of bipolar patients. Sir William Osler said 'the true polypharmacy is the skilful combination of remedies'.[5]

The current study is South African based. The results from the study are congruent with independent conclusions of numerous international studies highlighted throughout the discussion. The conclusion is that polypharmacy use in bipolar disorder is the norm and there is a diverse spectrum of medication combinations used to treat bipolar disorder. This may be a consequence of the complexity of bipolar disorder, inadequate guidelines and studies with respect to recommended combinations, in particular when more than two medications are involved. From the current study it appears that many combinations of medication prescribed may be due to clinician personal preference as well as the need to individualize treatment according to the needs of each patient. The evaluation and validity or otherwise of this hypothesis would be an interesting basis for further study.

Association between Monotherapy / Polypharmacy & the Demographic, Biographic & Clinical Variables

It is difficult to make inferences or discuss the association between monotherapy / polypharmacy and the demographic, biographic and clinical variables as the monotherapy group is very small. This could be motivation then for a future study that involves a larger sample size. Of statistical significance however, is that the monotherapy group had fewer clinic visits over the year of study. This supports what one might intuitively surmise i.e. that the monotherapy group is perhaps more stable and less complex group than the polypharmacy group.

Association between Bipolar Disorder Subtype & Medication Classes

In the current study bipolar I patients were prescribed **standard mood stabilizers** and **atypical antipsychotics** more often than the other bipolar types. Bipolar I patients experience **mania** and clinical trials and bipolar treatment guidelines[38,39,41,42,44] advocate the use of these medications for **manic** episodes and **maintenance** of bipolar I disorder. The favouring of antipsychotics, in particular the **typical agents**, in the bipolar NOS group may suggest the comorbidity of **Cluster B personality disorders** with bipolar disorder.

Prevalence studies show that bipolar disorder patients have a significantly higher prevalence of personality disorder than the general population.[65] Ehret demonstrated in a bipolar study that 53.4% had a comorbid personality disorder and most had borderline personality disorder.[56] The antipsychotics are used to treat mood instability, aggression and impulsivity in **Cluster B personalities**.[55] The researcher's personal experience as a consultant psychiatrist at Tara Hospital outpatient's department highlighted the utility of fluphenthixol depot - a **typical antipsychotic** - usage in low doses because of its effectiveness, low side effects and low cost. The current study did not address the spectrum of comorbidity and association with bipolar type, but it did demonstrate that bipolar II and NOS have a higher presence of comorbidity.

Bipolar II disorder often has more depressive episodes than the other types of bipolar disorder while bipolar disorder, especially bipolar II and borderline personality disorder often co-occur.[33,66] This could then explain the preference of antidepressants and **novel anticonvulsants** in the current study's bipolar II and NOS groups. Lamotrigine and antidepressants are recommended to manage depression, mood instability and impulsivity in borderline personality disorders and depressive episodes and maintenance treatment in bipolar disorder.[38,39,41,42,44,55] The current study revealed that lamotrigine was favoured in those patients with comorbidity.

Adherence to Guidelines

The results of the current study indicate that the clinicians working at TARA Hospital's outpatient clinic prescribe in a manner that is congruent with both North American and South African bipolar treatment guidelines.[38,39,41,42,44] This is evidenced by the majority of patients being prescribed **standard mood stabilizers** and the preferred use of **atypical antipsychotics** over **typical antipsychotics** especially when treating bipolar I patients; the preferred use of lamotrigine in bipolar II patients and the prescribing of an antidepressant in most cases an SSRI together with a **standard mood stabilizer** or antipsychotic (**typical** or **atypical**).

Although this was not an objective of the study it is interesting to note that this finding supports a North American study that looked at clinician concordance with treatment guidelines in a tertiary specialist outpatient setting.[67] The results showed a 50%-80% concordance rate. There was a higher concordance rate for patients experiencing a manic and manic/psychotic phase than a depressed or mixed phase.[67] This acknowledges once again that bipolar depression/mixed episode may be more resistant to treatment and require a far more individualised approach to treatment.

Limitations

The study is a retrospective file review and relies on the information documented in the files. This information may not always be reliable or recorded in sufficient detail. The study also presumes that mental health care professionals have sufficient knowledge of the DSM IV TR and ICD 10 and have used it correctly when making diagnoses, undertaking assessments and recording clinical information in the file. When it came to the data analysis however the ICD 10 codes for bipolar disorder were not utilised as they were not consistently or correctly recorded. The researcher relied on the DSM IV TR diagnosis recorded together with the clinical notes in the file documenting DSM IV TR diagnostic criteria to provide and record the bipolar type. The comorbidity was not documented in detail as the clinical notes did not adequately document this.

The monotherapy group was small and whilst proving one of the hypotheses, the ability to make inferences for this group was limited. As the study was cross sectional the information gathered pertains to a particular period i.e. patients seen at the clinic in 2009 with their last prescription for 2009. The data cannot be therefore generalized beyond this environment/period.

The current study did not consider a specific bipolar disorder episode but rather considered a general approach to prescribing in bipolar disorder. The study made an assumption that the majority of patients would be in the **maintenance phase** of bipolar disorder given that the study population were outpatients. The study could not exclude that some patients may have been in an acute **relapsing** / **recurring** phase but that they could be managed in an outpatient setting.

CONCLUSION

The current study provides preliminary data on the prescribing patterns in bipolar disorder in a specialist psychiatric outpatient clinic within an academic complex in South Africa. The results are in keeping with international literature that states that polypharmacy use in bipolar disorder particularly in a specialist setting is the rule rather than the exception.[8,12,18-27,30,62] The current study, in keeping with the STEP-BD study[8], also highlights that patients receiving treatment within an academic complex are likely to be prescribed polypharmacy.

The number of medications available to treat bipolar disorder is increasing. **Atypical antipsychotics** and **novel anticonvulsants** in particular lamotrigine have now been recognized to have mood stabilizing properties.[14,33,38,39,41,42,44] The current study and other studies looking at the prescribing patterns in bipolar disorder show that clinicians are now utilizing these medications.[24,33]

Treatment guidelines aim to improve the quality, appropriateness and cost- effectiveness of health care. They can also be used as valuable educational tools.[62] This study illustrates that the practice of South African clinicians is congruent with both National (South African) and North American bipolar disorder guidelines.[38,39,41,42,44] The current study however highlights that despite the availability of and apparent adherence to treatment guidelines there is still large variation in clinician practices. The current study echoes other studies that show combination treatment is the rule in the management of bipolar disorder, however there is much variety in the combinations used.[22-25,58,63] This is perhaps because bipolar disorder is such a complex disorder and that most of the treatment recommendations are based on limited data.[14]

There is definitely scope for further study of prescribing patterns in bipolar disorder. The current study was a retrospective file review which was limited by a small monotherapy group, assumed maintenance phase of bipolar and poor recording of clinical notes in some of the files. Future studies should aim for a larger bipolar population. A prospective study with a detailed assessment of patient characteristics, clinician characteristics, bipolar episode, clinical outcomes and psychiatric comorbidity would address the limitations noted. Such data could provide insights into particular prescribing combinations and uses and their effectiveness in bipolar disorder as well as highlight factors associated with psychotropic medication prescription profiles and choices.

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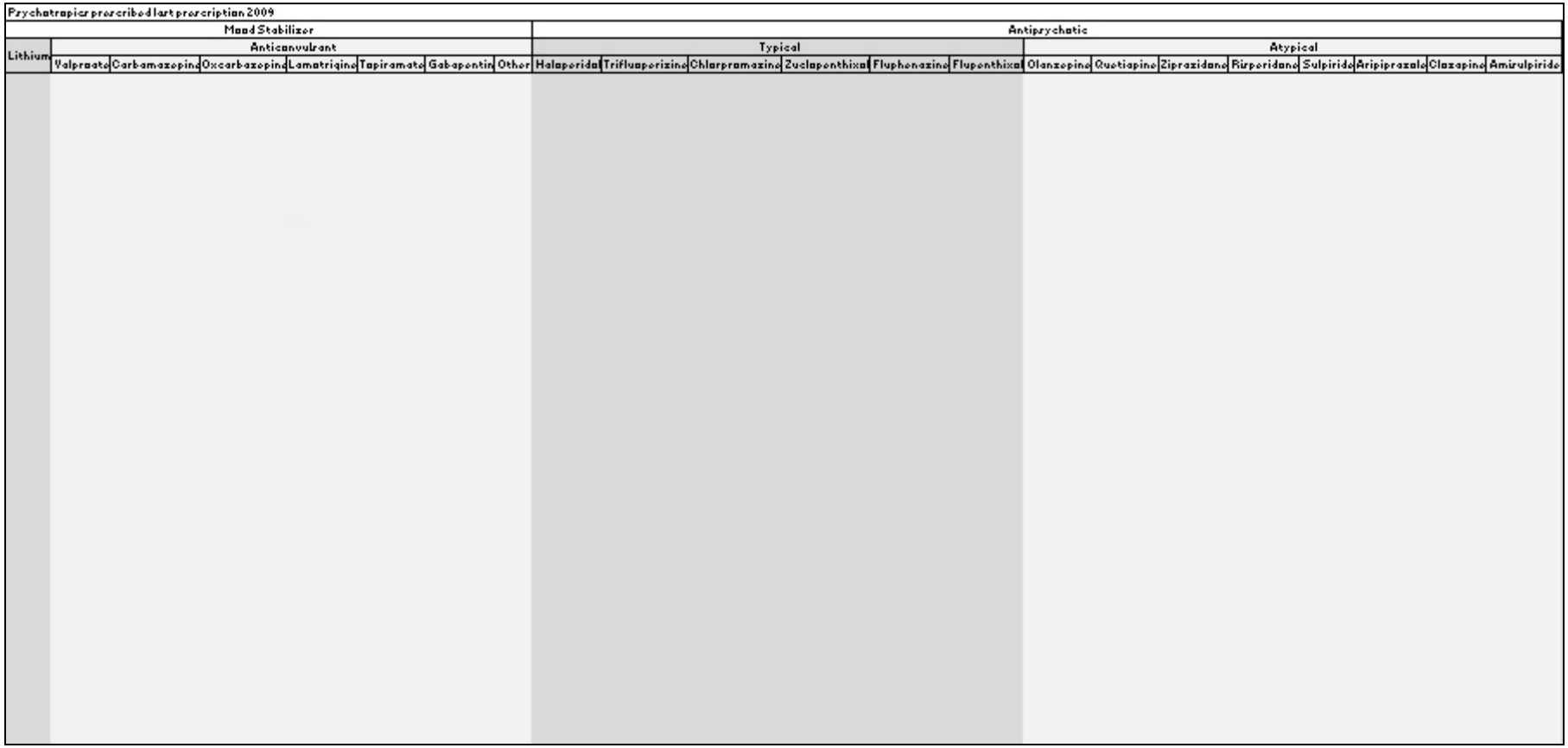
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APPENDIX A

Data collection sheet

Name				Date of Birth			Age					Sex		Hospital fee classification				Health care professional				Number of clinic visits					Type of Bipolar			Bipolar ICD 10																Psychiatric co-morbidity			Number of psychotropics prescribed				
First name	Surname	Tara file number	Study number	Year	Month	Day	<=35	36-50	51-64	>=65		Male	Female	H1	H2	Private	Other	Nurse	Registrar / MO	PMO	Consultant	1	2	3	4	>=5	Type 1	Type 2	NOS	F30.0	F30.1	F30.2	F31.0	F31.1	F31.2	F31.3	F31.4	F31.5	F31.6	F31.7	F31.8	F31.9	Not recorded	Yes	No	Condition	1	2	3	4	>=5

Data collection sheet



Psychotropics prescribed last prescription 2009																							
Mood Stabilizer								Antipsychatic															
Lithium	Anticonvulsant							Typical						Atypical									
	Valproate	Carbamazepine	Oxcarbazepine	Lamotrigine	Topiramate	Gabapentin	Other	Haloperidol	Trifluoperizine	Chlorpromazine	Zuclopenthixol	Fluphenazine	Flupenthixol	Olanzepine	Quetiapine	Ziprazidone	Risperidone	Sulpiride	Aripiprazole	Clozapine	Amirulpiride		

Data collection sheet

Psychotropics prescribed last prescription 2009																				
Antidepressant																				
SSRI							SNRI		TCA						NRI	MAO		Other		
Citalopram	Escitalopram	Fluoxetine	Sertraline	Paroxetine	Fluvoxamine	Venlafaxine	Duloxetine	Imipramine	Clomipramine	Amitriptaline	Mianserin	Lofepramine	Other	Reboxetine	Maclobemide	Tranylcypromine	Mirtazepine	Trazodone	Bupropion

Data collection sheet

Psychotropics prescribed last prescription 2009													
Anxiolytics									Hypnotics			Other
Buspirone	Propranolol	Antihistamine			Benzodiazepine					Zolpidem	Zopiclone	Other	
		promethazine	promethazine	other	clonazepam	diazepam	lorazepam	oxazepam	other				

APPENDIX B

Ethics certificate

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Eleanor Holzapfel

CLEARANCE CERTIFICATE	**M120838**
PROJECT	Pharmacotherapy Prescribing Patterns in the Treatment of Bipolar Disorder in an Outpatient Population at Tara Hospital
INVESTIGATORS	Dr Eleanor Holzapfel.
DEPARTMENT	Department of Psychiatry
DATE CONSIDERED	31/08/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 31/08/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Chris Szabo

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 C

Permission from the CEO of Tara Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

To: Dr Motlana and Dr Otieno

Clinical Head and CEO Tara Hospital

7 August 2012

Dear Drs

Re: Approval Request to conduct Research

I hereby request permission for the following researcher, Dr Eleanor Holzaphel to conduct research at Tara. She is a psychiatrist who previously worked at Tara. She intends to do a retrospective record review, entitled, **"Pharmacotherapy patterns in the treatment of bipolar disorder in an outpatient population at Tara Hospital".**

The study is towards her MMed(psych) at the University of Witwaterstrand. The proposal has been sent electronically to you. She requires our permission in order to apply Ethics approval. She is aware that research may only commence once we have received documentation indicating her Ethics Approval.

Yours sincerely

.....

Date: 7/8/12

Dr Jow'hara Chundra

Secretary- Tara research Committee

Recommended/~~Not Recommended~~

.....

Dr Mashadi Motlana

Clinical Head

Date: 2012/08/07

Approved/~~Not Approved~~

.....

Dr Florence Otieno

CEO

Date: 08/08/2012

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APPENDIX D

MS Excel spreadsheet (statistical analysis)

Variable	Category	Overall		Therapy type					BD Type							Psychiatric comorbidity				
				Monotherapy		Polypharmacy		p-value for between-group test (effect size in brackets)	Type I		Type II		NOS		p-value for between-group test (effect size in brackets)	Yes		No		p-value for between-group test (effect size in brackets)
n		**242**		**15**		**227**			**166**		**56**		**20**			**117**		**125**		
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**		**n**	**%**	**n**	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Age	18-35y	65	26.86	6	40.00	59	25.99	0.64												
	36-50y	89	36.78	5	33.33	84	37.00													
	51-64y	70	28.93	4	26.67	66	29.07													
	65y+	18	7.44	0	0.00	18	7.93													
Sex	Male	77	31.82	5	33.33	72	31.72	1.00												
	Female	165	68.18	10	66.67	155	68.28													
Hospital Fee Classification	H0	19	7.85	1	6.67	18	7.93	0.75												
	H1	159	65.70	11	73.33	148	65.20													
	H2	42	17.36	2	13.33	40	17.62													
	Private	14	5.79	0	0.00	14	6.17													
	Other	8	3.31	1	6.67	7	3.08													
Health Care Professional	Nurse	32	13.22	3	20.00	29	12.78	0.84												
	Registrar/MO	104	42.98	6	40.00	98	43.17													
	PMO	89	36.78	5	33.33	84	37.00													
	Consultant	17	7.02	1	6.67	16	7.05													
Number of Clinic Visits	1	37	15.29	5	33.33	32	14.10	0.046												
	2	44	18.18	3	20.00	41	18.06													
	3	40	16.53	1	6.67	39	17.18													
	4	43	17.77	5	33.33	38	16.74													
	5+	78	32.23	1	6.67	77	33.92													
BD type	Type I	166	68.60	12	80.00	154	67.84	0.63								58	49.57	108	86.40	<0.0001 (V=0.40)
	Type II	56	23.14	3	20.00	53	23.35									42	35.90	14	11.20	
	NOS	20	8.26	0	0.00	20	8.81									17	14.53	3	2.40	
Psychiatric Comorbidity	Yes	117	48.35	5	33.33	112	49.34	0.29	58	34.94	42	75.00	17	85.00	<0.0001 (V=0.40)					
	No	125	51.65	10	66.67	115	50.66		108	65.06	14	25.00	3	15.00						
Number of psychotropics	1	15	6.20	15	100.00	0	0.00	-								5	4.27	10	8.00	0.031 (V=0.21)
	2	55	22.73	0	0.00	55	24.23									21	17.95	34	27.20	
	3	84	34.71	0	0.00	84	37.00									43	36.75	41	32.80	
	4	52	21.49	0	0.00	52	22.91									23	19.66	29	23.20	
	5+	36	14.88	0	0.00	36	15.86									25	21.37	11	8.80	
Monotherapy / Polypharmacy	Monotherapy	15	6.20	15	100.00	0	0.00	-												
	Polypharmacy	227	93.80	0	0.00	227	100.00													

MS Excel spreadsheet (statistical analysis)

Variable	Category	Overall		Therapy type			BD Type				Psychiatric comorbidity		
				Monotherapy	Polypharmacy	p-value for between-group test (effect size in brackets)	Type I	Type II	NOS	p-value for between-group test (effect size in brackets)	Yes	No	p-value for between-group test (effect size in brackets)
n		**242**		**15**	**227**		**166**	**56**	**20**		**117**	**125**	
Lithium	Lithium	83	34.30										
Anticonvulsants	Valproate	90	37.19										
	Carbamazepine	32	13.22										
	Oxcarbazepine	4	1.65										
	Lamotrigine	77	31.82										
	Topiramate	11	4.55										
	Gabapentin	17	7.02										
	Other	0	0.00										
Antipsychotics-typical	Flupenthixol	14	5.79										
	Chlorpromazine	12	4.96										
	Trifluoperizine	7	2.89										
	Haloperidol	5	2.07										
	Zuclopenthixol	3	1.24										
	Fluphenazine	0	0.00										
Antipsychotics-atypical	Risperidone	53	21.90										
	Quetiapine	22	9.09										
	Olanzepine	13	5.37										
	Clozapine	12	4.96										
	Sulpiride	10	4.13										
	Amisulpiride	7	2.89										
	Ziprazidone	0	0.00										
	Aripiprazole	0	0.00										
Antidepressant-SSRI	Citalopram	34	14.05										
	Escitalopram	2	0.83										
	Fluoxetine	29	11.98										
	Sertraline	1	0.41										
	Paroxetine	4	1.65										
	Fluvoxamine	0	0.00										
Antidepressant-SNRI	Venlafaxine	31	12.81										
	Duloxetine	1	0.41										
Antidepressant-TCA	Imipramine	1	0.41										
	Clomipramine	1	0.41										
	Amitriptaline	9	3.72										
	Mianserin	3	1.24										
	Lofepramine	0	0.00										
	Other	1	0.41										
Antidepressant-NRI	Reboxetine	0	0.00										
Antidepressant-MAO	Moclobemide	7	2.89										
	Tranylcypromine	2	0.83										
Antidepressant-Other	Mirtazepine	1	0.41										
	Trazodone	4	1.65										
	Bupropion	1	0.41										
Add On - Benzodiazepine	Clonazepam	65	26.86										
	Diazepam	6	2.48										
	Lorazepam	12	4.96										
	Oxazepam	9	3.72										
	Midazolam	3	1.24										
	BZD other	0	0.00										
Add On - Non-Benzodiazepine	Zolpidem	4	1.65										
	Zopiclone	5	2.07										
	Promethazine	9	3.72										
	Buspirone	9	3.72										
	Propranolol	24	9.92										
	Hydroxyzine	21	8.68										
	Non BZD other	1	0.41										

MS Excel spreadsheet (statistical analysis)

Variable	Category	Overall		Therapy type					BD Type						Psychiatric comorbidity				
				Monotherapy		Polypharmacy		p-value for between-group test (effect size in brackets)	Type I		Type II		NOS	p-value for between-group test (effect size in brackets)	Yes		No		p-value for between-group test (effect size in brackets)
n		**242**		**15**		**227**			**166**		**56**		**20**		**117**		**125**		
Group A (Combining Anticonvulsants)																			
Number classes of drugs	1	18	7.44																
	2	75	30.99																
	3	99	40.91																
	4	44	18.18																
	5	6	2.48																
Psychotropic type	Lithium	83	34.30	4	26.67	79	34.80	0.59	73	43.98	6	10.71	4	20.00	<0.0001 (phi=0.30)				
	Anticonvulsant	192	79.34	9	60.00	183	80.62	0.09	129	77.71	46	82.14	17	85.00	0.71				
	Antipsychotic	148	61.16	2	13.33	146	64.32	<0.0001 (phi=0.25)	113	68.07	22	39.29	13	65.00	<0.0001 (phi=0.24)				
	Antidepressant	118	48.76	0	0.00	118	51.98	<0.0001 (phi=0.25)	55	33.13	47	83.93	16	80.00	<0.0001 (phi=0.46)				
	Add On	130	53.72	0	0.00	130	57.27	<0.0001 (phi=0.28)	84	50.60	32	57.14	14	70.00	0.24				
Group A																			
Psychotropic type	Lithium	83	34.30	4	26.67	79	34.80	0.59	73	43.98	6	10.71	4	20.00	<0.0001 (phi=0.30)				
	Standard AC	120	49.59	4	26.67	116	51.10	0.11	98	59.04	16	28.57	6	30.00	<0.0001 (phi=0.28)				
	Novel AC	99	40.91	5	33.33	94	41.41	0.60	50	30.12	37	66.07	12	60.00	<0.0001 (phi=0.33)				
	Antipsychotic	148	61.16	2	13.33	146	64.32	<0.0001 (phi=0.25)	113	68.07	22	39.29	13	65.00	<0.0001 (phi=0.24)				
	Antidepressant	118	48.76	0	0.00	118	51.98	<0.0001 (phi=0.25)	55	33.13	47	83.93	16	80.00	<0.0001 (phi=0.46)				
	Add On	130	53.72	0	0.00	130	57.27	<0.0001 (phi=0.28)	84	50.60	32	57.14	14	70.00	0.24				
Group B																			
Lithium	Lithium	83	34.30	4	26.67	79	34.80	0.59	73	43.98	6	10.71	4	20.00	<0.0001 (phi=0.30)				
Anticonvulsant	Standard AC	120	49.59	4	26.67	116	51.10	0.11	98	59.04	16	28.57	6	30.00	<0.0001 (phi=0.28)				
	Novel AC	99	40.91	5	33.33	94	41.41	0.60	50	30.12	37	66.07	12	60.00	<0.0001 (phi=0.33)				
Antipsychotic	Typical AP	40	16.53	0	0.00	40	17.62	0.14	26	15.66	6	10.71	8	40.00	0.0014 (phi=0.20)	24	20.51	16	12.80	0.12
	Atypical AP	113	46.69	2	13.33	111	48.90	0.0074 (phi=0.17)	92	55.42	16	28.57	5	25.00	<0.0001 (phi=0.26)	48	41.03	65	52.00	0.10
Antidepressant	SSRI AD	70	28.93	0	0.00	70	30.84	0.0069 (phi=0.16)	31	18.67	28	50.00	11	55.00	<0.0001 (phi=0.33)				
	SNRI AD	32	13.22	0	0.00	32	14.10	0.23	12	7.23	15	26.79	5	25.00	<0.0001 (phi=0.26)				
	Tricyclic AD	14	5.79	0	0.00	14	6.17	1.00	7	4.22	6	10.71	1	5.00	0.19				
	NRI AD	0	0.00	0	0.00	0	0.00	-	0	0.00	0	0.00	0	0.00	-				
	MAO AD	9	3.72	0	0.00	9	3.96	1.00	7	4.22	2	3.57	0	0.00	1.00				
	Other AD	6	2.48	0	0.00	6	2.64	1.00	2	1.20	3	5.36	1	5.00	0.11				
Add On	Benzodiazepine AO	90	37.19	0	0.00	90	39.65	0.0013 (phi=0.20)	56	33.73	24	42.86	10	50.00	0.21				
	Non BZD AO	64	26.45	0	0.00	64	28.19	0.013 (phi=0.15)	38	22.89	18	32.14	8	40.00	0.13				

APPENDIX E

Turnitin Originality Report

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