TREATMENT OUTCOME OF PATIENTS WITH BIPOLAR 1 DISORDER FOLLOWING HOSPITALISATION AT MOI TEACHING AND REFERRAL HOSPITAL.

BY

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SM/PSY01/2012

A RESEARCH THESIS SUBMITTED TO THE SCHOOL OF MEDICINE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN PSYCHIATRY.

MOI UNIVERSITY SCHOOLOF MEDICINE.

2016

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This thesis is my original work and has not been presented for a degree in any other university. No part of this thesis may be reproduced without the permission of the author and/or Moi University.

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DEDICATION.

The research thesis is dedicated to Abubakar, Abdallah Mohammed and Rahma the most special people in my life.

ACKNOWLEDGEMENTS.

I wish to thank my supervisors Prof. H.N.K Mengech, Prof. B.N.Gakinya and Dr Anne Mwangi for their guidance and input in the writing of the thesis. I also wish to thank the rest of the faculty and colleagues and the entire department of psychiatry and behavioral sciences, Moi University.

I am greatly indebted to my family for their support and proven patience as I study at Moi University.

I am grateful to the people in different sections of the hospital who facilitated in completion of this research project. My appreciation goes to the records department for their help with data that assisted in calculating my sample size and for their help with patient files retrieval and visit booking .Much gratitude also goes to the statistics department at AMPATH center and for their assistance especially with the research methods and methodology formulation, and data analysis.

I also do appreciate the effort by Dr F. Jaguga and Dr. F.Oguk assisting with proof reading and editing the research thesis.

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LIST OF ABBREVIATIONS.

BD-Bipolar Disorder

BDI-Beck Depression Inventory

CBT- Cognitive Behavior Therapy**.**

DALYS- Disability Adjusted Life Years.

DSM-IV-TR- Diagnostic and Statistical Manual-IV-Text Revision-.

DSM 5- Diagnostic and Statistical Manual fifth (5) edition.

ECT-Electroconvulsive Therapy

GAF --- Global Assessment of Functioning .

HDRS- Hamilton Depression Rating Scale.

WHO - World Health Organization.

YMRS- Young Mania Rating Scale.

MTRH- Moi Teaching and Referral Hospital.

NSRI- Norepinephrine Serotonin Re-uptake Inhibitors

MDD- Major Depressive Disorder.

TCA- Tri Cyclic Antidepressants.

DEFINITION OF KEY TERMS.

Mania.

This will be defined according to DSM 5 (American Psychiatric Association, 2013)

Major Depressive Episode.

Will be defined according to DSM 5 (American Psychiatric Association, 2013) .

Bipolar I Disorder.

This will be defined according to DMS 5 (American Psychiatric Association, 2013).

Recovery- will be defined as:

a) **Syndromal** - DSM-5 criteria for disorder no longer met.
b) **Symptomatic-Young** Mania Rating Scale score ≤12 (Lukasiewicz M, mar 2013) ((R C Young, 1978))and Hamilton Depression Rating Scale score≤8(Bech et al., 1981)
c) **Functional Recovery**- Regaining of premorbid social and occupational and status.

Relapse- new episode of mania and or mixed episode within 8 weeks of syndromal recovery.

Recurrence- New episode of mania or mania with mixed features post remission

Remission- 8 or more weeks of sustained symptomatic and functional recovery.

Syndrome – A group of symptoms that together they are characteristic of a specific disorder, disease or the like.

Symptom – A subjective feeling of departure from normal physiological functioning that is noticed by a patient and that is a reflection of presence of
unusual state or of a disease.

ABSTRACT.

Background. Bipolar 1 disorder is the third leading cause of death in persons aged 15-24 years and if untreated it carries a 15% risk of suicide. The worldwide prevalence is 3-5%. The life time prevalence is 1.3 -1.6%. Drugs used are antipsychotics, mood stabilizers and benzodiazepines in specific cases. Despite the treatment only about 60% of these patients have good recovery after a single episode. Some of the factors that influence outcomes include age of onset, severity of first episode, psychosocial support, drug compliance and co morbid substance use or abuse.

Objective: To assess the 12 month treatment outcomes and levels of recovery in patients admitted for bipolar 1 mania or mania with mixed features and to identify the possible clinical predictors associated with such recovery levels at Moi Teaching and Referral Hospital.

Methods This longitudinal study was carried out at Moi Teaching and Referral Hospital psychiatric wards and outpatient clinics. The study population included all patients aged 18 years and above, admitted to the psychiatric ward at Moi Teaching and Referral hospital with first episode mania and mania with mixed features. Data was collected between November 2013 and December 2014. The patients were interviewed using a structured questionnaire, the Young Mania rating scale, the Hamilton Depression scale and the Global assessment of Functioning scale. Data was obtained within 72 hours of admission. Thereafter assessment was done at 3, 6 and 12 month follow up visits. Analysis was done using STATA version 13 SE. Descriptive statistics such as frequency listings and measures of central tendency were used. Chi square test was used test for association between two categorical variables. In all analysis a p-value less than 0.05 was considered significant. Data was then presented in tables, graphs and p values. Consent was obtained from all study participants. The study was approved by Institutional Research and Ethics Committee and Moi Teaching and referral hospital. Confidentiality of patient record was maintained.

Results. A total of 77 patients were recruited into the study. The median age was 25years (IQR=22, 28). There were 39 females and 38 males. Forty seven (61.0%) were employed and majority (50.6%) were single. Slightly more than half of the participants (51.9%) had co-morbid substance use. Majority of the patients (61.84%) had mania with mixed features while the remaining had a manic episode at presentation. The mean length of stay was 2.29 weeks (IQR 2, 2.89). At 12 month follow-up all the participants had syndromic recovery, 25.6% had symptomatic recovery and 28.3% had functional recovery. The 12 month rates of remission were

2.6% (YMRS) and 10.5% (HMDS). Longer duration of hospital stay was associated with poorer functional recovery ($p<0.001$).

Conclusion. Despite treatment, majority of the patients with bipolar 1 disorder continue to experience persistent, residual, social and occupational dysfunction 12 months after acute manic episode and longer admission duration predict poorer functional recovery.

Recommendations. Longer follow-up and larger studies need to done.

CHAPTER ONE

1.0 BACKGROUND OF THE STUDY.

Mental health is essential for the prosperity of every nation. According to World Health Organization(WHO) and World Bank report on 'Global Burden of disease' 4 out of 10 leading causes of morbidity for persons above 5 years are due to mental disorders(World Health Organization 2001) The leading cause in most developed countries is major depressive illnesses followed closely by bipolar 1 disorder also known as manic-depressive disorders (United States Public Health Service Office of the Surgeon General, 1999).bipolar 1 disorder is also the third leading cause of death in persons aged 15-24 years and the sixth leading cause of morbidity (lost years of healthy life) in those aged 15-44years(United States Public Health Service Office of the Surgeon General, 1999). Bipolar disorder is characterized by mood swings between mania and depression. The disorder has a high rate of recurrence and if untreated carries a 15% risk of suicide(Baldessarini RJ., 2006) .

The prevalence of bipolar disorder is equal between both sexes and worldwide and occurs in all age groups including preschoolers. The worldwide prevalence is 3-5%. No significant differences have been found among races. The life time prevalence is 1.3 -1.6%(American psychiatric association, 2000)

Bipolar 1 disorder has a complex inheritance mode and tends to run in families. Family and twin-twin studies show genetic factors contribute to the disorder. Concordance rate in monozygotic twins is 43% whereas in dizygotic twins is 6%. About 50% of all patients with mood disorder have one of the parents also having a mood disorder. If one parent has Bipolar I Disorder, the child will have a 25% chance of developing a mood disorder. If both parents have Bipolar I Disorder, the child has a 50%-75% chance of developing a mood disorder. First-degree biological relatives of individuals with Bipolar I Disorder have elevated rates of Bipolar I Disorder (4%-24%), Bipolar II Disorder (1%-5%), and Major Depressive Disorder (4%-24%) (Smolin, 2012)

The Pathophysiology of this disorder is poorly understood but some imaging studies have implicated the Amygdalla, the basal ganglia and the prefrontal cortex. The disorder is associated

with abnormal levels of the amine neurotransmitters (dopamine, serotonin and norepinephrine)(Shahana, 2011).

The first episode can occur at any age from childhood to old age, but the commonest age of presentation is 21 years. More than 90% of those having a single manic episode will have subsequent episodes. Psychosis may occur in mania or severe depression as well as in mixed episode and usually predicts poor recovery. Manic episodes last between 2 weeks to 4-5 months (GL, 1988)with an average of 4 month duration. Untreated individuals will have 8-10 episodes of mania and depression in a life time. Often 5 years or more may elapse between the first and second episode, but thereafter the episodes become more frequent and more severe(Gitlin MJ, 1995). Up to 60% of the patients experience chronic interpersonal and occupational difficulties or conflicts between the acute episodes and up to 25% of these patients continue to display residual symptoms between episodes(Coryell W, 1993).Diagnosis relies on careful history and mental status examination of the patient. Additional testing for mania is done using validated scales such as the young mania rating scale (YMRS) and the episode is then classified as mild, moderate, severe or with psychotic features (American psychiatric association, 2000). According to the diagnostic and statistical manual fifth edition (American Psychiatric Association, 2013; Association, (2013)) a manic episode is characterized by abnormally elevated and persistent mood for at least one week during which patient have at least three of these features: grandiosity or elevated self-esteem, decreased sleep need, flight of ideas and pressured speech, distractibility, increased goal oriented activities and excessive involvement in pleasurable activities. The symptom mentioned above must not be due to a general medical condition or directly due to use of substance(American Psychiatric Association, 2013).Mania may be accompanied by features of depression interspersed between the elated/expansive mood. If depressive features are present but occur intermittently then the episode will be mania with mixed depressive features. The other specifiers for the manic episode include with or without psychotic features and whether in partial or full remissions. The outcomes of treatment for bipolar disorder focus on the goals of treatment which are to alleviate symptoms and allow for individuals to regain their premorbid levels of social and occupational functioning. Outcomes of interest in this study will include level of recovery; whether syndromic in which the DSM criteria is no longer met, Symptomatic recovery in which the symptom as assessed by Young Mania Rating Scale is less than 12 and functional recovery in which patient will have been able

to regain their premorbid level of social and / occupational functioning(M. W. Tohen, C. M. Tsuang, M, 1990). Biopsychosocial factors of the patient with bipolar 1 have been found to be associated with different outcomes of the disorder in longitudinal studies. Such factors act as predictors of outcome and those that will be assessed in this study will be; age, sex, level of education or academic achievements, occupation and severity of the mania episode. Studies show predictors of an unfavorable outcome to include; poor occupational status prior to index episode, history of previous episodes, history of alcoholism, psychotic features and symptoms of depression during the index manic episode, male gender, and interepisode affective symptoms at 6 months' follow-up(M. W. Tohen, C. M. Tsuang, M, 1990; M. Z. Tohen, Carlos A Hennen, John Khalsa, Hari-Mandir Kaur Strakowski, Stephen M Gebre-Medhin, Priscilla Salvatore, Paola Baldessarini, Ross J, 2003).

The usual treatment for bipolar 1 disorder is life-long mood stabilizer, with lithium, carbamazepine or sodium valproate and an antipsychotic medication. Treatment leads to dramatic decrease in suffering and an 8th fold reduction in the suicide risk. In mania a benzodiazepine may be added to treatment. An antidepressant in combination with an antipsychotic can also be used in depression(Fountoulakis KN., 2005). The most effective therapies include psychopharmacology(Bowden CL, 1998; Bowden CL., 2003; Calabrese JR., 2003) and psychosocial therapy(Colom F., 2006).Since a Manic Episode can quickly escalate and destroy a patient's career or reputation, a therapist must be prepared to hospitalize out-of-control manic patients before they "lose everything". Likewise, severely depressed, suicidal bipolar patients often require hospitalization to save their lives

Although the treatment especially the medication must be life-long, by one year since diagnosis most patients become non-compliant. At 4 years follow-up, 41% have good recovery and 4% have died. Studies done previously on bipolar manic patient have shown that only 50-60% of patient achieved good recovery after a manic episode(Eduard Vieta, 2008 June).

Better operational criteria to define outcome and newer medications have produced new data on the outcome of management of mania in bipolar 1 disorder. Moi teaching and referral hospital serves the western Kenya region as the referral facility as well as a teaching hospital for Moi University. The hospital has a psychiatry department which offers both outpatient and inpatient facilities. The inpatient facility has a capacity of 25 patients. The ward accommodates both adult

males and females. The pediatric patients are managed in the general pediatric wards. Currently there is no data on the treatment outcomes for the patients who are admitted to the MTRH psychiatric unit with diagnosis of bipolar 1 disorder. This study aimed at establishing these outcomes and making recommendations that will help improve patient care in the inpatient unit as well as during follow-up care.

1.2Problem statement.

Mental illnesses are among the leading causes of morbidity for persons over 5 years of age all over the world (WHO) and are ranked 6th top ten cause of morbidity for those aged 15-44 years of age. Mental illness is the 3rd cause of mortality in those aged 15-24 years. Since the prosperity of all nations relies on the productivity of people in this age group, mental health is therefore essential for the development of the nation. Bipolar I disorder is the second leading mental health disorder with associated morbidity and occur equally among males and female of all races. The disorder is associated with a 15 % risk of suicide and significant social and occupational dysfunction with huge losses of human resources. These factors have economic implications as well as the large amount of resources used to treat and rehabilitate such individuals. Proper diagnosis and treatment as early as possible will help reduce the morbidity associated with mania and or depression and significantly increase efficient use of limited resources. Furthermore there has been a steady increase in the number of patients admitted with bipolar 1 disorder at MTRH, as well as a notable increase in the levels of non-compliance leading to multiple admissions for some patients. There is no established treatment protocol at MTRH and no data available on the outcomes of treatment as well the course of illness for bipolar 1 disorder in the western region of Kenya. A knowledge gap therefore exists.

1.3 Study justification.

Treatment of bipolar 1 markedly improves the individuals' recovery outcome. Most of the research data available was collected prior to the introduction of new diagnostic criteria and treatment. There is ready availability of new treatment modes and medication. These changes have brought about changes in treatment outcomes elsewhere in the world. No information exists on the treatment modes, outcomes of treatment or the association of clinical predictors and

treatment outcomes for bipolar 1 disorder in the western region of Kenya. The study therefore seek to obtain data that will help determine whether the disorder's outcomes corresponds or is different from that reported in other regions of world. Furthermore data will help the clinician to predict possible outcomes for patients to ensure individualized care plan are set from the first encounter with the patient. This will reduce relapses and enhance recovery. Moreover he availed data will be used by clinicians and the policy makers to formulate treatment guidelines and improve care for patients with bipolar 1 disorders in this region.

1.4 Research questions.

1. What is the treatment outcomes and for patients admitted with bipolar 1 disorder at Moi Teaching and Referral Hospital?
2. What factors are associated with treatment outcomes for patients admitted with bipolar 1 disorder at Moi Teaching and Referral hospital?

1.5 Research objectives.

1.5.2 Main Objective

The main objective of this study is to assess the treatment protocols used at MTRH and the 12 month levels of recovery of patients admitted for first episode bipolar 1 mania or mania with mixed features and to identify the association between clinical predictors and the recovery outcomes.

1.5.2 Specific objectives.

1. To assess the one year relapse rate for bipolar 1 mania and or depression.
2. To assess the proportion of patients that achieves syndromic, symptomatic and functional recovery after first episode bipolar 1 mania or mixed episode at MTRH as a measure of treatment outcome.
3. To determine the association that exists between the clinical predictors the level of recovery

CHAPTER TWO:

2.0 LITERATURE REVIEW.

2.1 Introduction

Despite substantial advances in pharmacological treatment of bipolar 1 disorder, most longitudinal studies show that the course of this disorder remains unfavorable for the patients. The one year relapse rates in these studies were found to range between 37% and 44%. Moreover the patient continued to endure psychological and social impairment despite having symptomatic recovery(Colom F., 2006). In another study patients with bipolar 1 first mania or mixed episode were followed for 2-4 years post admission and three aspects of recovery were assessed; symptomatic, syndromic and functional recovery. By 2 years, most subjects achieved syndromal recovery (98%, with 50% achieving recovery by 5.4 weeks); 72% achieved symptomatic recover and only 43% achieved functional recovery. Within 2 years of syndromal recovery, 40% experienced a new episode of mania (20%) or depression (20%), and 19% switched phases without recovery. Moreover some of the predictors of syndromic recovery included, sex (50% females had shorter time of recovery), shorter index hospitalization, and lower initial depression ratings. Older patients recovered faster and stayed for shorter admission periods. Predictors of mania recurrence were initial mood-congruent psychosis, lower premorbid occupational status, and initial manic presentation. Antidepressant treatments were marginally related to longer time to recovery and earlier relapse. In conclusion the authors found that all but 2% of patients had syndromic recovery, 28% remained symptomatic and only 47% had functional recovery and 57% of the patients either had a new illness or switched from mania to depression or vice versa during the 2 year follow up(M. Z. Tohen, Carlos A Hennen, John Khalsa, Hari-Mandir Kaur Strakowski, Stephen M Gebre-Medhin, Priscilla Salvatore, Paola Baldessarini, Ross J., 2003). Results from the EBLEM study (European Mania in Bipolar Longitudinal Evaluation of Medication) a prospective multinational observational longitudinal study, 28% and 68% of the

3,681 patients studied had low and high work impairment respectively in the preceding year. The authors assessed baseline characteristics of patients including Socio-demographic variables, psychiatric history, clinical status and information on pharmacological treatment for bipolar disorder. The distribution of the baseline characteristics was analyzed with descriptive statistics and variables hypothesized as risk factors for functional impairment were analyzed using logistic regression models. The authors concluded that Work impairment is significant in the year prior to an acute episode of mania (Goetz, 2007). In addition studies have shown that even during symptomatic recovery patients with bipolar 1 disorder have residual psychosocial impairments. One such study used Functioning Assessment Short Test (FAST) to assess multiple areas of functioning such as autonomy, occupational functioning, cognitive functioning, interpersonal relationships, financial issues, and leisure time. Multivariate analysis was used to determine the global and specific clinical predictors of outcome. Sixty percent ($n = 42$) of the patients had overall functional impairment (defined as a FAST total score > 11) compared to 13.1% ($n = 8$) of the control group ($p = 0.001$). Previous mixed episodes, current subclinical depressive symptoms, previous hospitalizations, and older age were identified as significant potential clinical predictors of functional impairment(Rosa, 2009). Furthermore a total of 252 patients from the Maritime Bipolar Registry with DSM-IV diagnoses of bipolar I or bipolar II disorder had their GAF ratings during maintenance treatment compared across clinical and demographic variables. The mean GAF score in this sample was 67 ± 17 (range 10–100). The GAF scores followed bimodal distribution with mean values of 50.5 ± 10.3 and 79.0 ± 10.3. Decreased functioning was found in patients with chronic illness course, history of rapid cycling, suicidal behavior, psychiatric co morbidity, hypothyroidism, and diabetes mellitus, regardless of treatment of these conditions. There were no differences in the level of functioning between men and women. The authors concluded that other than the bipolar disorder co morbidities also lower level of functioning (Hajek, 2005). On assessment of time to recurrence since the first episode, one study found that residual affective symptoms were the strongest predictor of recurrence.

Compulsory admission and treatment is often required in the acute stage of illness. This may take a few days or weeks depending on the severity of the illness. Combination therapy is mostly utilized. When taking decisions about treatment, tolerability should also be a major concern, as differences in safety and tolerability may exceed differences in efficacy for most compounds,

Psychoeducation of patients and caregivers is a powerful tool that should be used in combination with medication for optimal long-term outcome. Functional recovery should be the ultimate goal.

2.2Treatment approach for acute mania.

Achieving rapid control of aggression, agitation and impulsivity is the first step in management of acute mania. Recently it has become evident that the best approach to management is integrative where the acute symptom are controlled while keeping in perspective the long term issues as well as the functional outcome (2). Some of the long term issues include the predominant polarity of the episodes and regular cross sectional assessment of the patients (3).

The published consensus on recommendations for pharmacological first-line and second-line treatment of mania differ invariably but most recommend lithium as monotherapy, although in some cases antipsychotics such as olanzapine and mood stabilizer like valproate are added to the treatment. Most patients eventually will receive more than one drug (4). Psychotherapy has been shown to help patients especially during the recovery period as observed by Schöttle et.al. They noted that psychotherapy for caregiver and family as well as to the patients was positive in regard to decreasing the recurrence rates, improved quality of life, improved functioning and more favorable symptom improvement. (Schottle D, Nov 2011). Bauer and colleagues suggest 2 approaches depending on whether the patient has been on mood stabilizers or not. Patient with acute episode of mania who are already on optimum treatment suggest continuing the mood stabilizer and adding lamotrigine to treatment. Patient who have not been on mood stabilizers and are having their first episode should be given quetiapine or olanzapine in combination with carbamazepine and lamotrigine as alternative. There was no additional benefit of using antidepressants if patients were already on mood stabilizers.(R. P. Bauer M, Grunze H, Pfennig A May 2012; Swann AC., 2005). Furthermore Post and colleagues found that the more different antidepressant trials the patient with bipolar disorder has received, the less responsive they become to treatment (Post RM, 2012).

2.3 Specific pharmacotherapy.

2.3.1 Lithium.

Lithium is the drug commonly used for prophylaxis and treatment of manic episodes. A recent study suggests that lithium may also have a neuroprotective role. Lithium therapy may serve to protect and preserve the hippocampal volumes, in contrast to patients with major depression, who show diminished hippocampal volumes.(A. M. Bauer M, Priller J, Young LT, Nov 2003; Hajek T, Apr 2012).At optimal doses lithium reduces the rates of recurrence by 50% .the drug is more effective with mania as opposed to depressive episodes. Lithium has demonstrated superiority over other drugs in mania in well controlled clinical trials and in these studies 40%-80% of patients showed improvement by 2-3 weeks. Moreover lithium has been shown to have anti- suicidal effects and is well tolerated when combined with antipsychotic drugs and remains the gold standard for mania treatment(Bowden CL, 1998). Lithium may decrease the concentrating ability of the kidneys but studies have shown that it is implicated only in few cases of renal failure and the risk for end stage renal failure is low (McKnight RF, Feb 2012).

2.3.2 Antipsychotic drugs.

Antipsychotic drugs are increasingly being used to treat bipolar disorder. This is especially so with the newer drugs. These drugs are used both for acute mania and also for mood stabilization. This is despite the concern of the effect that some of the antipsychotics may have on lipids and glucose metabolism. A study done on effect of Ziprasidone did not show any significant difference in plasma lipid profile compared with placebo (Pappadopulos E, Jun 2012). Moreover in a study of Aripiprazole in young patient aged 10-17years with mania and mixed episodes Aripiprazole demonstrated significant improvement in Young Mania Rating Scale (YMRS) scores. In this study 10mg and 30mg dosages were used and both groups tolerated drugs well although those on 30mg had a shorter duration to all-cause discontinuation mostly due to side effects.(Swann AC., 2005). The role of antipsychotic in controlling and maintenance phase of bipolar disorder is well documented and studies have identified olanzapine, risperidone and haloperidol as the most efficacious treatment ,significantly out performing other antipsychotics and the primary mood stabilizers (Cipriani A, 2011).

2.3.3 Carbamazepine.

Studies done on carbamazepine as a mood stabilizing drug shows that it is effective as a mood stabilizer but failed to prevent rapid cycling. Two trials found carbamazepine together with a typical antipsychotic more effective than an antipsychotic alone. Furthermore the symptoms reduction was quicker in the first week following co- administration of risperidone and carbamazepine or with lithium(Weisler, 2005; Yatham, 2003).

2.3.4 Valproate.

Valproic acid and the salts or amides have been used in the acute and maintenance phases of bipolar 1 disorder and have shown efficacy. One study by Keck et.al found that an oral loading of sodium valproate to achieve a serum level of 50mg /L were effective in significant reduction in the Young Mania Rating scale and was associated with minimal side effects.(Keck Jr, 1993). A double blind controlled randomized clinical trial where valproate was combined with a neuroleptic medication showed that the use of valproate led to marked decrease in the neuroleptic dose needed to control the acute phase of mania. The proportion of responders (a 50% improvement rate shown on the YMRS) was higher for the combination with valproate than for the group receiving only neuroleptic (70% vs. 46%; $p = 0.005$). Valproate is beneficial because it allows the administration of fewer neuroleptic medications and produces improved and quicker remission of manic symptoms (Müller-Oerlinghausen, 2000).

2.3.5 Benzodiazepines and other drugs.

Benzodiazepines have a sedative effect which makes them useful as adjunct therapy in acute mania. As outlined by the guidelines from the American Psychiatric Association (APA), these medications should be used only in addition either to mood stabilizers or antipsychotics. The guidelines recommend that chlorpromazine may be used to control psychotic symptoms and to calm the patient through sedation. It was noted that chlorpromazine was superior to placebo and as equally effective as lithium monotherapy (American Psychiatric Association).

2.4 Non pharmacological treatment.

2.4.1 Electroconvulsive therapy.

Electroconvulsive therapy is useful in treatment of a number of psychiatric disorders. It is highly effective in mania. Often, the severity of the symptoms, the lack of response to medications, or the presence of contraindications to certain medications necessitates the use of ECT. Recent

technological development have made the procedure safe and easy.(Valenti Marc 2008). In a naturalistic study of patients treated with lithium and ECT there was a clinically significant difference in response seen in those given ECT ($p>0.05$) and 78% of non-responders to lithium showed marked improvement of symptoms when ECT was administered furthermore unilateral and bilateral ECTs were equally effective however the unilateral ECT was associated with fewer cognitive deficits. The dose of electricity used had an effect on the rate of response with higher doses giving faster responses(Black DW, 1987 April; Sackeim, 1993). The mechanism of action of ECT is not fully understood but functional magnetic resonance imaging (fMRI) has shown decreases in the global connectivity of the left dorsolateral prefrontal region of the brain in patient treated with ECT. This region has been implicated in depression and cognitive dysfunction in mood disorders. This realization may allow for the use of ECT without much invasive techniques (Hampton, 2012).

2.4.2 Psychotherapy.

Bipolar disorder is often only partially treated by medication alone and this has led to recent developments in the adjunctive psychological treatment of disorder. Most studies show that individual cognitive behavior therapy is of especially much help to the bipolar patient when given during symptom remission. CBT seems to impact on symptoms, social functioning and the risk of relapse(Jones, 2004). An example of another individual psychotherapy is the interpersonal and social rhythm therapy that is specifically designed for the treatment of bipolar disorder. Patient are taught to regularize their biological cycles such as the circadian cycle with their daily routines and this helps to diminish interpersonal problems, and adhere to medication regimens. It modulates both biological and psychosocial factors to mitigate patients' circadian and sleep–wake cycle vulnerabilities, improve overall functioning, and better manage the potential chaos of bipolar disorder symptomatology (E. S. Frank, Holly A. Kupfer, David J., 2000). In a review study of the different psychotherapy approaches used, family therapy, interpersonal therapy, and systematic care appeared to be most effective in preventing recurrences when initiated after an acute episode, whereas cognitive-behavioral therapy and group Psychoeducation appeared to be most effective when initiated during a period of recovery. Individual psycho educational and systematic care programs were more effective for manic than depressive symptoms, whereas family therapy and cognitive-behavioral therapy were more effective for depressive than manic symptoms(Miklowitz, 2008). In a randomized controlled

study the author found that changing the therapy type assigned to a patient during and after the illness led to more relapse compared to those who were maintained on the same type of therapy (40% versus 20%) respectively. This is in support of the observation that patients with bipolar disorder perform better if their daily routines remains relatively regular.(E. S. Frank, Holly A Mallinger, Alan G Thase, Michael E Weaver, Elizabeth V Kupfer, David J, 1999).

CHAPTER THREE.

3.0 RESEARCH DESIGN AND METHODOLOGY.

3.1 Research design.

A longitudinal design was be used. The study included all patients aged above 18 years who were admitted to the psychiatric ward at Moi Teaching and Referral Hospital (MTRH) with first time manic or mixed features episodes of bipolar 1 disorder. All those who meet the inclusion criteria were recruited to the study and were followed up for a total of 12 months at 3, 6 and 12 months. Data obtained from the study subjects include demographics, clinical data, social and occupational data. Clinical data obtained included the symptom scores and level of functioning at the various review visits.

3.2 Study area.

The recruitment of the study subjects was carried out in the psychiatric wards of MTRH and thereafter the follow –up of patients was done at the outpatient psychiatric clinics of MTRH. The hospital is a regional referral Centre for western Kenya and serves a population of about 16.7 million people. The hospital also serves as the teaching facility for Moi University School of medicine. At the time of formulating the research proposal, the psychiatric unit constituted a male inpatient ward and a female inpatient ward with a bed capacity of 25 patients although the bed occupancy was more than 200 at times. The hospital however completed a new psychiatric unit during the study period. This unit has an inpatient bed capacity of about 100 patients; both male and female wards. The bed occupancy for bipolar 1 during the period of the study was

between 10-15 patients per month. The hospital also runs a once weekly outpatient psychiatry clinic.

3.3 Study population.

These included all patients 18 years and above admitted to the psychiatric ward with first episode of bipolar 1 mania or mixed features episodes and who meet the inclusion criteria. The patients were selected from a pool of all patients that were admitted to the mental health unit both from the accident and emergency department as well as those transferred from other general hospital wards.

3.4 Eligibility criteria

3.4.1 Inclusion criteria.

Patients were included in the study if:

1. 18 years and above.
2. Meet criteria for DSM-5 bipolar 1 mania or mixed features episode.
3. Reside within a radius of 100 kilometers from the study site for ease of follow up and tracing in cases of loss to follow up.
4. Provide an informed consent when the procedures of the study had been explained. The consent was provided for by a relative in cases of severely ill patients

3.4.2 Exclusion criteria.

Patients were excluded from the study if:

1. Mania or mixed symptoms resulted entirely from acute substance or drug intoxication or from substance or drug withdrawal as determined by resolution of symptoms within expected period of acute withdrawal and intoxication for the abused substance.
2. Mania or depressed symptoms resulted entirely from medical illness determined by medical evaluation.

3.5 Sampling technique

3.5.1 Sampling method.

Consecutive sampling technique was applied. Every patient admitted during the study recruitment period who meet inclusion criteria was sampled.

3.5.2 Sample size.

In order to attain a precision of 5% for the proportion of patients who attain syndromic recovery in such a single cohort we estimated the sample size using the following formula(W., 1977)

$$n_0 = \left(\frac{Z_{1-\alpha/2}}{\delta}\right)^2 P(1-P)$$

$$= \left(\frac{1.96}{0.05}\right)^2 \times 0.44 \times 0.56 ,$$

$$= 378$$

Where

$z_{1-\alpha/2} = 1.96$ At $\alpha = 0.05$

Level of Significance, $\alpha = 0.05$

Absolute precision δ = 5%

P is expected proportion of individuals in the sample with the characteristic of interest, in this case syndromic recovery, at the $100(1-\alpha/2)\%$ confidence interval. Anticipated population proportion (p) = 60% (Paul et al., 1998). Since the recruitment of subjects will be done within four months and the expected total number of bipolar-1 patients is 20 patients per month we adjust for finite population.

$n_f = \underline{n\_\_\_\_\_} = \underline{378}$

1+n/N 1+378/80

= 66 patients. This was the minimum number of participants required for statistical power. However the study design is longitudinal and as such we expected some attrition. We expected close to15 % to drop out at 12 months. Thus to cushion against that we adjusted for drop outs as follows

$$. n = \left(n_0 \Big/ (1 - dropoutrate) \right) = \frac{66}{0.85} = 77$$

This gave us 77 subjects as the valid sample size at the start of the study but due to the small and finite study population, we recruited all the patients that met the inclusion criteria for this study.

3.5 Study procedures.

Recruitment of patients was carried out within 72 hours of admission to the wards. A total of 78 participants were eligible for the study during the recruitment period. One of these participants decline give consent and was excluded. Another patient (1) died study at the 6th month follow up due to a suicide. The principal investigator recruited two research assistant to help with identification of newly admitted patients and retrieving of patients files. Demographic data such as age, sex and residential area as well as the highest level of education and occupation achieved was recorded. Axis 1 Diagnosis was determined using Structured Clinical Interview for DSM 5, as well as the treatment the patient was receiving and this information was obtained from the patient interview, review of patient medical records, treating clinicians and family members. The diagnostic interview was done at admission and at the follow-up visits .The assessment of the episode symptoms was done within 72 hours of admission using standardized questionnaires. These were; Young Mania Rating Scale for manic episode. The scale is an eleven item clinician administered questionnaire, which was used to assess the severity of the manic episode as follows; a score of > 12 indicated full criteria Manic episode ,YMRS ≤12 indicates syndromic recovery ,YMRS =5 symptomatic remission YMRS = 3), or euthymic (YMRS = 2) (R C Young, 1978; Young RC, 2000). At a score of 25 YMRS has a positive predictive value of 83%(Lukasiewicz M, mar 2013).

The 17-item Hamilton Depression Rating Scale was used to assess for depression in a mixed episode. Those who had a mixed feature episode had to meet the YMRS score of > 12 as well as a depressive score (HMD) of >7. The questionnaire is designed for adults and is used to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. A score of 0-7 was considered to be normal. Scores of 20 very severe depression(Bech et al., 1981) The Global Assessment of Functioning Scale was used to assess the level of social and occupational

dysfunction. The Global Assessment of Functioning (GAF) assigns a clinical judgment in numerical fashion to the individual's overall functioning level. Impairments in psychological, social and occupational/school functioning are considered, but those related to physical or environmental limitations are not. The scores range from 0-100 depending on severity of social occupational dysfunction or based on severity of symptoms whichever is more severe. Score of less than 50 indicated severe impairments and/or symptoms, scores of 51-71 indicate moderate to mild symptoms or dysfunction, scores of 71 to 81 indicate transient symptom or very mild dysfunction while scores above 81 indicate satisfactory functioning and absence of symptoms. All patient received treatment as usual regardless of their willingness to participate in the study. Patients were reviewed twice weekly until they were discharged. Thereafter patients were scheduled for review visits at 3, 6 and 12 months and recovery was assessed as: syndromic, symptomatic and functional as indicated in the appendix on longitudinal interval follow-up.

3.6 Data collection and management

3.6.1 Data collection.

Patient recruitment was done between November 2013 and April 2014. Data was collected between November 2013 and March 2015. Average length of follow-up was 12.5 months.

3.6.2. Data management

Data was collected using formatted questionnaire which contained patient unique numbers for identification. The data collection forms were checked at the end of each day for completeness and inconsistencies were ruled out before data entry. Data obtained was maintained in the study computer under a password for protection. On completion of study data was cleaned and transferred to a computer database for analysis. Descriptive statistics was used. For continuous data, means and median was used and for categorical data frequencies and percentages was used. Inferential statistics such as Chi square and Fischer's exact tests (if the expected cell count is >10) were used. Logistic regression was used to adjust for confounders and to assess trends; methods that adjust for correlation between measurements over time were employed. Analysis was done at 95% significance level.

3.8 Ethical consideration.

Approval was sought from the institutional research and ethics committee to carry out the study. Permission and approval was also obtained from the director Moi teaching and referral hospital. Patients were fully informed on all the procedures of the study and an informed consent was obtained from the entire study population before enrolment. The procedures involved in the study and the length of the interview was explained to each patient and their guardians. For those patients who were too sick to either understand or make good judgment about participating in the study, consent was obtained from their relative or spouse or guardian caring for the patient. Those who had consented or consent given on their behalf by their proxy, were enrolled to the study. All patients' records were kept confidential and patients received all necessary and indicated care regardless of their willingness or unwillingness to participate in the study.

CHAPTER FOUR.

4.0 RESULTS:

4.1 Demographic data.

The demographic data of the study subjects in Table 1, shows that there was no gender predominance among the study population (49.4% females and 50.6% males (n=76). The mean age of the patients was 25(22, 28), of these, 23(29.99%) subjects were married, 39 (50.6%) single, 11 (14.3%), separated and 4 (5.2%, divorced. Most of the study subjects had attained a secondary level of education (n=39(50.6%) followed by those who had attained primary level education and only a small number had tertiary education (n=12(15.6%). However 61% of the patients were unemployed at the time of initial admission to the mental health unit.

4.2 Substance use.

There was no marked difference in the number of patients who did and those who did not use substance (51.9% versus 48.1% respectively). The substance that was mostly abused was alcohol with tobacco and cannabis being second and third respectively.

4.3 Axis 1 diagnosis.

Majority of the patients (61.84%) had initial mania with mixed features at recruitment. There was no major difference in the distribution of males and females in both sub- categories (mania versus mania with mixed features). Those with a mixed features episode had a longer hospital stay. (2.29 weeks versus 2.14 weeks)

4.4 Length of stay.

The mean length of stay for the patients was 2.29 weeks (2, 2.86).

Table 1 demographic data

Variable	Mixed N=47	Mania N=29
Gender		
Female	25 (65.8)	13 (34.2)
Male	22 (57.9)	16 (42.1)
Marital status		
Single/Divorced/Separated	34 (64.2)	19 (35.8)
Married	13 (56.5)	10 (43.5)
Education level		
Primary	14 (56)	11 (44)
Secondary	24 (61.5)	15 (38.5)
Tertiary	9 (75)	3 (25)
Employment		
Employed	18 (60)	12 (40)
Unemployed	29 (63)	17 (37)
Substance use		
No	23 (57.5)	17 (42.5)
Yes	24 (66.7)	12 (33.3)
Age in years	24 (21, 28)	26 (22,28)
Length of stay (in weeks)	2.29 (2, 3)	2.14(1.86, 2.43)

4.4 Clinical characteristics.

Data from this study show that all the patients were severely ill at admission with low scores on the Global Assessment of Function (GAF=<50) and that all 76 patients had YMRS scores more than 12 (100%). Forty seven patients (60.5%) had an initial manic with mixed features episode on admission compared to twenty nine patients (39.5%) that had mania.

Table 2 clinical characteristics

Variable	**Mixed**				**Mania**			
Score	**Visit**				**Visit**			
	0	**3**	**6**	**12**	**0**	**3**	**6**	**12**
HMD						19	19	
<=7					29	(65.52)	(65.52)	23
>7	0 (0)	22 (47.83)	28 (62.22)	28 (62.22)	(100)	10	10	(79.31)
	47 (100)	24 (52.17)	17 (37.78)	17 (37.78)	0 (0)	(34.48)	(34.48)	6 (20.69)
YMR					0 (0)		4 (13.79)	5 (17.24)
<=12	0 (0)	2 (4.35)	8 (17.78)	14 (31.11)	29	2 (6.9)	25	24
>12	47 (100)	44 (95.65)	37 (82.22)	31 (68.89)	(100)	27 (93.1)	(86.21)	(82.76)
GAF						0 (0)	1 (3.45)	0 (0)
<50	47 (100)	5 (10.87)	2 (4.44)	0 (0)	29 (100	28	28	21
51-80	0 (0)	38 (82.61)	40 (88.89)	32 (71.11)	0(0)	(96.55)	(96.55)	(72.41)
>80	0 (0)	3 (6.52)	3 (6.67)	13 (28.89)	0(0)	1 (3.45)	0 (0)	8 (27.59)

At 12th week visit which was the first visit after discharge 22(47.8%) of the patients who had a mixed episode had syndromic but not symptomatic recovery with the reminder still having significant depressive symptoms (HMD score>7) and 10(34.8%) of those who had mania as the initial presentation had depression at the same period of time. At 12 months follow-up visit, those patient with depressed symptoms had decreased to 17(37.7%) for the mixed features group and 6(20.69%) for the manic group. There was notable minimal improvement on the symptoms scores (HMD, YMRS, GAF) for most patients beyond the 6th month. On the mania symptom scores at 12th week visit 44(95.65%) patients with mixed feature episode still had not achieved

syndromic recovery compared to 27(93.1%) of those who had a manic episode. The level of functioning however increased up to 6th month throughout the 12 month follow-up. There were only 3(6.67%) patient who had a mixed episode with normal functioning at 12 week visit and 1(3.45%) manic patient. Compared to 13 (28.89%) and 8(27.6%) at 12 month visit. Most patients however, 32 (71.11%) for mixed and 21(72.41%) for manic episode, had residual social economic dysfunction at 12 months following admission for a manic or mania with mixed features episode. From the data it is clear that all patients achieved syndromic recovery but not all had full symptomatic and / or functional recovery. The relapse rates for patients in this study were found to be 25 %(YMRS>) 12) and 28 %(HMDs>7) among those patients with mixed episode. There was no relapse among those with an initial manic episode.

Table 3 relapse rates

	YMRS		HMD	
	Mania N=29	Mixed N=47	Mania N=29	Mixed N=47
Recovery	4	8	0	28
No-recovery	25	37	0	11
Relapses	0 (0%)	2 (25%)	0	8 (28%)

4.5. Treatment.

From the data obtained, all 76(100%) patients received an antipsychotic at the initial assessment. Majority of the patient were on more than one antipsychotic medication during the period of study. This study did not assign patients to any treatment modes or alter patients' medications. Some possible reason for change in the medication may have been due to side effects , non-response and medication availability The most widely prescribed antipsychotic was olanzapine (89.5% n=68), followed by chlorpromazine (25% n=19) and haloperidol (9.2% n=7). Only one (1.37%) of the patients was on an antipsychotic other than the three types listed. There was no particular criterion that was found to have been used to decide on the treatment applied to individual patients.

The study also found that benzodiazepines were prescribed and to 47.4% of the patients and these patients were found to have had higher scores on the Young Mania Rating Scale compared to those patients who did not get benzodiazepines.

Mood stabilizing medications were prescribed to 93.4% (n=71) of the study group. Carbamazepine was the most frequently prescribed mood stabilizer in this study, with a total of 82.9% of the patients receiving this drug. Only 10.5% were on sodium valproate. None of the patients was on lithium or any other mood stabilizer. There were no patients in this study who had been put on an antidepressant medication and none of the patients in this study had electroconvulsive therapy during the 12 months follow-up

Furthermore more than three quarters (81.6%) of the patients received non-pharmacological treatments. These treatment modalities included; psychotherapy (36.8%), counseling (21.1%) and Psychoeducation (30.3%). Again the investigator did not find any criteria used to select which patients received what type of psychological treatment.

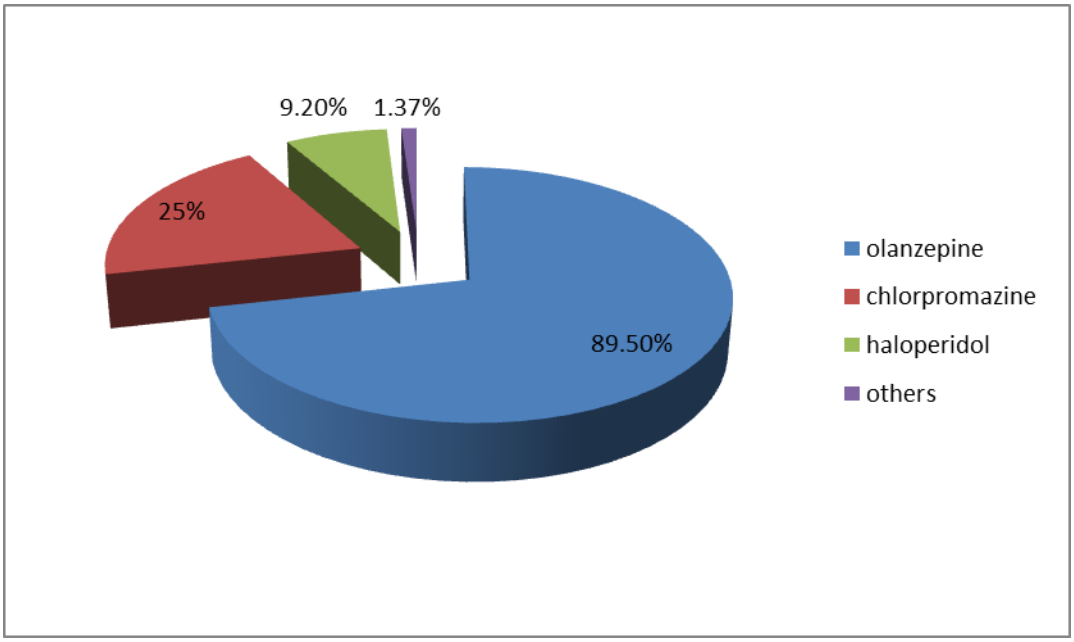

Figure 1 antipsychotics

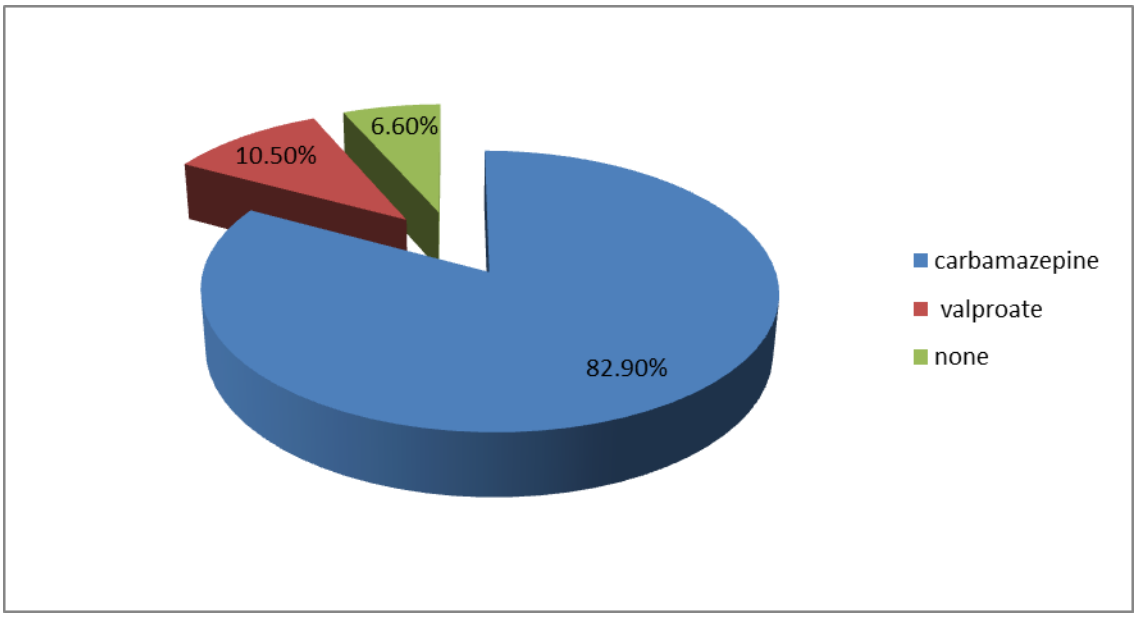

Figure 2 Mood stabilizers

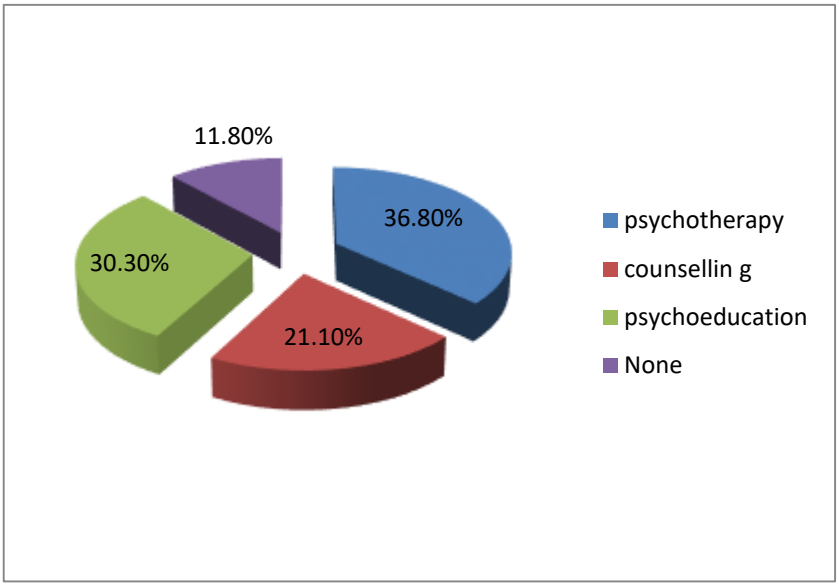

Figure 3 Non pharmacological treatment

4.6 Factors associated with recovery

There was a strong association between the scores on the YMRS and the overall length of hospital stay (p=0.001) as well as on the depressive score scale HMD (p=0.03). There was an association between functional recovery and the marital status (p=0.05) and employment with functional recovery (p=0.047).However, there was no association between the level of education and both symptomatic and functional recovery in this study

Table 4. Demographic factors associated with recovery

	GAF			YMR			HMD		
Variable	**Symptomatic**	**Functional**	**p-value**	**<=12**	**>12**	**p-value**	**<=7**	**>7**	**p-value**
Sex			0.439	24.3 (28)	75.7 (37)	0.79			
Female	25 (67.6)	12 (32.4)					25 (67.6)	12 (32.4)	0.802
Male	28 (75.7)	9 (24.3)		27 (27)	73 (37)		26 (70.3)	11 (29.7)	
Marital status			0.072	50 (2) 30.4 (16)		0.476			
Divorced	2 (50)	2 (50)			50 (4)		3 (75)	1 (25)	0.637
Married	18 (78.3)	5 (21.7)		30 (7)	69.6 (23)		17 (73.9)	6 (26.1)	
Separated	10 (100)	0 (0)		18.9 (30)	70 (10)		8 (80)	2 (20)	
Single	23 (62.2)	14 (37.8)			81.1 (37)		23 (62.2)	14 (37.8)	
Education level			0.653	29.2 (17)		0.858			
Primary	16 (66.7)	8 (33.3)		23.1 (30)	70.8 (24)		18 (75)	6 (25)	0.478
Secondary	28 (71.8)	11 (28.2)			76.9 (39)		27 (69.2)	12 (30.8)	
Tertiary	9 (81.8)	2 (18.2)		27.3 (8)	72.7 (11)		6 (54.5)	5 (45.5)	
Employment			0.065	33.3 (20)		0.213			
Employed	25 (83.3)	5 (16.7)		20.5 (35)	66.7 (30)		20 (66.7)	10 (33.3)	0.73
Unemployed	28 (63.6)	16 (36.4)			79.5 (44)		31 (70.5)	13 (29.5)	
Substance use			0.394	30 (28) 20.6 (27)	70 (40) 79.4 (34)	0.356			
No	27 (67.5)	13 (32.5)					30 (75)	10 (25)	0.22
Yes	26 (76.5)	8 (23.5)					21 (61.8)	13 (38.2)	
Age	26 (22,28)	24 (21,26)	0.298	26 (21,29)	24 (22,28)	0.746	26 (22,28)	24 (21,28)	0.6155
Length of stay in weeks	2.29 (2,23)	2.29 (2,2.71)	0.918	3.14 (2.43, 3.71)	2.14 (1.86,2.71)	0.001	2.14 (1.86,2.71)	2.71 (2.14,3.29)	0.0366

Table 4 Treatment association with recovery

Axial 1 diagnosis	Treatment	HMD		YMR		GAF		
		<=7	>7	<=12	>12	<50	51-80	>80
Mixed	1	11 (68.75)	5 (31.25)	2 (12.5)	14 (87.5)	0 (0)	12 (75)	4 (25)
	2	15 (60)	10 (40)	11 (44)	14 (56)	0 (0)	17 (68)	8 (32)
	3	1 (50)	1 (50)	0 (0)	2 (100)	0 (0)	2 (100)	0 (0)
	4	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Mania	1	12 (85.71)	2 (14.29)	2 (14.29)	12 (85.71)	0 (0)	11 (78.57)	3 (21.43)
	2	9 (69.23)	4 (30.77)	3 (23.08)	10 (76.92)	0 (0)	8 (61.54)	5 (38.46)
	3	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	2 (100)	0 (0)
	4	23 (79.31)	6 (20.69)	5 (17.24)	24 (82.76)	0 (0)	21 (72.41)	8 (27.59)

1=Antipsychotic + mood stabilizer+ benzodiazepines**,** 2**=** Antipsychotic + mood stabilizer, 3= Antipsychotic benzodiazepines and 4=Antipsychotics alone

Different treatment was associated with different recovery outcomes as shown in table 4 above. Majority of the patients were on more than one drug at the initial assessment. Those with

significant score on the YMRS scale (YMRS>12), majority were on an antipsychotic a benzodiazepine and a mood stabilizer i.e. 14 patients with mixed episode and 12 patients with mania. Most Patients with depressive symptoms (HMDs>7) in a mixed episode had been put on an antipsychotic and a mood stabilizer. Majority of patient with normal functioning were either on an antipsychotic alone or in combination with a mood stabilizer. The above result show that use of benzodiazepines was preferred if the patient had more severe symptoms on the YMRS and that both antipsychotics alone and antipsychotic in combination were effective in syndromic and functional recovery.

CHARPTER FIVE

5.0 DISCUSSION:

Bipolar 1 disorder is one of the top ten causes of morbidity and mortality among individual aged 15-45. It's a significant cause of disability and social economic dysfunction in approximately 1-2 % of the general population(World Health Organization, 2001). This study undertook to identify the levels of recovery among those patient admitted for their first episode bipolar 1 mania and the factors that have an association to such levels of recovery. In this study we limited recruitment to first episode mania/mania with mixed features in order to limit bias that may be caused by prolonged illness course. The study was a hospital based longitudinal follow-up and this may have an impact on the result as only very severely ill patients tend to be admitted to the in –patient unit.

The study recruited a total of 78 patients. The data included for analysis was that of 76 patients with mania or mania with mixed features, who had completed the 12 months follow-up. During this study we did not find any specific treatment protocols used by the clinicians for the treatment of bipolar 1 disorder and we did not assign patients to any treatment cohorts. Treatment as usual was continued during the follow-up. There were varying proportions of patient who had received different treatment options despite having a similar diagnosis. Furthermore all 76 (100%) patients had received antipsychotics at admission regardless of whether or not they were experiencing significant psychotic symptoms. Some authors have recommended use of antipsychotic in treating bipolar 1 especially in acute episodes.(American Psychiatric Association; Cipriani A, 2011).Mood stabilizing medications were prescribed to 93.4% (n=71) of the study group.

Recovery on the three levels (syndromic symptomatic and functional) proceeded in a linear fashion with syndromic recovery preceding both symptomatic and functional recovery respectively (Table1). It is notable that all the patients had experienced syndromic recovery at some point during the follow-up which occurred before discharge but not all patients achieved symptomatic and functional recovery even at 12 months follow up. At 8 weeks visit only 5.33% of the patients had symptomatic recovery and another 5.4% had achieved functional recovery. These figures are much lower than those found in several studies(lack DW, 1987 April;

McElroy SL, 1995).(Mauricio Tohen et al., 2005). However the number of patients with symptomatic (YMRS <12) and functional (GAF=/> 80) recovery increased to 25.68% and 28.38% at 12 months respectively. In a Cincinnati sample, 35% of manic patients recovered functionally by 12 months and in the McLean-Harvard First-Episode Mania Study these rates of recovery were found to be 39-43%.(Rosa, 2009; M. Tohen et al., 2003). Furthermore A total of 252 patients from the Maritime Bipolar Registry with DSM-IV diagnoses of bipolar I or bipolar II disorder had their GAF ratings during maintenance treatment compared across clinical and demographic variables and their initial score were 68.6±15.8.The data shows that despite recovery, only about one third of patients with bipolar 1 disorder who have regained full premorbid level of functioning. Majority of the patients (71.62%) still had some social and or occupational dysfunction even after discharge. Moreover patients in our study had 12 months relapse rates of 2.6 %. This was so because we had few numbers of patient had actually achieved remission of symptoms by 12 months (YMRS <12 = 25% n=19).

Age was not associated with recovery levels in this study. The findings are similar those by A Martinez-Aran et.al and Wingo et.al. in which the authors found no significant association between age of onset and psychosocial recovery(Martinez-Aran et al., 2007) (Wingo, Baldessarini, Holtzheimer, & Harvey, 2010). Tohen et al. found earlier age of onset (<30 years) to correlate with poorer outcomes of treatment(Mauricio Tohen et al., 2000). Very early or early onset of bipolar disorder was found to herald a more severe disease course in terms of recurrence and comorbidity by (Perlis et al., 2004). Level of education was not associated with recovery in our study. Contrary, some studies have shown association between level of education and treatment outcomes(Wingo et al., 2010). The same authors found higher education level to be associated with shorter illness periods and higher functional recovery

There was a high rate of substance use among the patient in our study (N=37) comprising of 48.1% of the study population. Majority of the patients who had co-morbid substance use had initial high scores on the Young Mania Rating Scale and had worse social occupational functioning at the admission assessment. In this study we however we did not find statistically significance association between substance use and any level of recovery (GAF p=0.394, YMRS p=0.356, HMD p=0.22). There was no significant association between substance use and the initial scores of mania or depression. In contrast some authors have found a positive association

between substance use and initial depression score in patients with bipolar disorder.(Regier et al., 1990). The average length of stay for patients in our study was 2.29 weeks (IQR 2, 2.89). Longer stay was associated with poorer scores on two of the assessment scales (Young Mania Rating Scale p= 0.001, Hamilton Depression Rating scale p=0.03).Similarly in a cohort study comparing two groups of patient on treatment for mania, the authors found the average length of stay for 1230 patients to be18.0 days (IQR 12.0, 28.0) in one cohort and 20.0 days (IQR 12.0, 34.0) in the other cohort, respectively and this was associated with poorer treatment outcomes (Addisu, Wondafrash, Chemali, Dejene, & Tesfaye, 2015; Karamustafalioglu et al., 2014). Moreover a longitudinal study assessing a 4 year outcome in bipolar mania found that the length of stay was inversely associated with both symptomatic and functional recoveries but not to syndromic recovery (M. W. Tohen, C. M. Tsuang, M, 1990).

There was no significant association between the type of episode and the level of recovery. This finding was similar to the finding of one study(McElroy SL, 1995). However other studies have reported better outcomes with index pure manic episodes(M. Z. Tohen, Carlos A Hennen, John Khalsa, Hari-Mandir Kaur Strakowski, Stephen M Gebre-Medhin, Priscilla Salvatore, Paola Baldessarini, Ross J, 2003).The differences in methodology may have accounted for the differences in outcome observations. There was no significant association between the gender and levels of recovery (YMRS p=0.79, HMD p=0.8)

There was a notable association between marital status and functional recovery (p=0.07) and between employment status and functional recovery (p=0.06). The associations however failed to reach significance level. Wingo et.al found marital status to be positively associated with functional recovery as measured using verbal fluency , a measure of executive functioning.(Wingo et al., 2010)

CHAPTER SIX:

6.0 RECCOMMENDATIONS AND CONCLUSIONS

6.1: LIMITATIONS.

In this study the sample size was limited by a finite population and this may have reduced the power of the study. The study was a hospital based study involving severely ill patients and as such may be difficult to infer the results to the general population.

6.2 CONCLUSIONS.

Despite treatment interventions, only 29% of the patient with an initial bipolar 1 mixed episode and 27.6% of those with mania regained normal occupational functioning at 12 months. Majority of patients with bipolar 1 disorders continue to exhibit residual symptoms and social – occupational dysfunction in the 12 months following admission for an acute manic or mixed episode. The factor with most significant association with functional recovery was the length of stay ($p=0.001$). Employment status and marital status are also associated with functional recovery ($p=0.06$, $p= 0.07$). This association however did not reach statistical significance.

6.3 RECCOMMEDATIONS.

Treatment guidelines for management of patients with bipolar 1 disorder need to be established at Moi Teaching and Referral Hospital. This would allow more standardized treatment for bipolar 1 patients. A longer community based naturalistic study need to be done so that results can be generalized to the community.

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APPENDICES

APPENDIX I: CONSENT FORM

Patient Number……..……

I, DR FELICITA WANGECI MWANGI, a student in the department of mental health, Moi University, under the guidance of my supervisors (Prof. H.N.K Mengech, Dr B, Gakinya, Dr Anne Mwangi), am carrying out a study on the treatment outcomes of patients with first episode bipolar 1 mania or mania or mania with mixed features at Moi Teaching and Referral hospital for 12 months.

The study will be done through history taking and examination of the patients with either bipolar 1 mania or mania with mixed features and a follow up period of 12 months as outpatients. A set of questions will be administered/ to your relative over a period of about one hour(1 hour) to help determine the severity of the illness. You/ your relative will not be exposed to any additional risks than in normal treatment procedures. You will be informed of your/ your relative's examination results. You are free to withdraw yourself/ your relative from the study at any time before or after the procedures.

Your examination/ your relatives result will be kept confidential. Below I have provided the contact mobile telephone number which you or your relative may use in case you need any further clarifications; 0724424708. In case further clarifications or complaints you can contact the institutional research and ethics committee (IREC) Telephone no.2033471/1/2.

I agree to participate in this study/ I agree to my…… (Specify relationship to the patient) to participate in this study.

Patient or guardian/relative's signature …….

Witness signature ……..

APPENDIX II.DATA COLLECTION FORM.

Patient study number……

Date of admission _____

Date of discharge_____

Age _____

Sex : male ☐ female ☐

1. Marital status

1) Married ☐
2) Single. ☐
3) Divorced. ☐
4) Separated. ☐
5) Not specified ☐

2. Education level:

1) None ☐
2) Primary. ☐
3) Secondary. ☐
4) >secondary. ☐

4. Employment.

1) Employed ☐
2) Unemployed ☐

5. Current episode

a) Mania ☐
b) Mixed episode ☐

6. Substance use ☐

Yes

No

1) Alcohol. ☐
2) Bhang. ☐
3) Tobacco. ☐
4) Opiates. ☐
5) Khat (miraa) ☐
6) Inhalants. ☐
7) Hallucinogens ☐
8) Others (specify) _____-

7. Severity of the drug use.

1) No problem; ☐
2) Minor problem; ☐
3) Mild problem; ☐
4) Moderately severe problem; ☐
5) Severe to very severe problem; ☐
6) Not known/Not applicable. ☐

8. Hamilton depression scale score

1) At admission _____
2) Currently _____
3) At discharge _____

8. Young mania rating scale score:

1) At admission _____
2) Currently _____
3) At discharge _____

9. Social and occupational functioning: GAF score:

1) At admission _____

2) Currently _____

3) At discharge _____.

10. Medication history.

1) Antipsychotics ☐

Olanzapine. ☐

Chlorpromazine ☐

Haloperidol. ☐

Others (specify). _____ _____ _____.

2) Mood stabilizers.

Carbamazepine. ☐

Lithium ☐

Sodium valproate. ☐

Others (specify) ☐

3) Benzodiazepines

1) Diazepam ☐

2) Others (specify) ☐

3) Anti-depressants. ☐

TCAs ☐

. SSRIs ☐

Others (specify) ☐

4) Others drugs (specify ☐

11. Non pharmacological treatment.

i. Psychotherapy ☐

ii. Electroconvulsive therapy. ☐

iii. Others (specify) _____

APPENDIX III; GLOBAL ASSESMENT OF FUNCTIONING.

The Global Assessment of Functioning (GAF) assigns a clinical judgment in numerical fashion to the individual's overall functioning level. Impairments in psychological, social and occupational/school functioning are considered, but those related to physical or environmental limitations are not.

The scale ranges from 0 (inadequate information) to 100 (superior functioning). Starting at either the top or the bottom of the scale, go up/down the list until the most accurate description of functioning for the individual is reached. Assess **either** the symptom severity **or** the level of functioning, whichever is the worse of the two. Check the category above and below to ensure the most accurate one has been chosen. Within that category there will be a range of 10. Choose the number that is most descriptive of the overall functioning of the individual.

The recommended methodology for clinicians using the GAF- is as follows:

1. Complete your interview or medication review with the individual.
2. Start at the bottom (most impaired functioning) of the descriptive statements on the GAF.
3. Read the descriptive statements from the bottom toward the top until you find a statement that accurately describes the person you are evaluating and use the number to the left of that statement to produce your GAF- rating. While you may find descriptors above the first item identified that also fit the person being rated, generally the statement that identifies the lowest functional rating is most critical to document the current level of functioning and concomitant intervention needs.

The GAF is a 10 point range. Choose the number that is the most descriptive of the overall functioning of the individual.

Note: Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health illness. Do not include impairment in functioning due to physical (or environmental) limitations.

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GAF Range	Description of Level of Functioning
100-91	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
90-81	Absent minimal symptoms (e.g. mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members)
80-71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentration after family argument); no more than slight impairment in social, occupational, or school functioning(e.g., temporarily falling behind in school work).
70-61	Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.
60-51	Moderate symptoms (e.g., flat and circumstantial speech, occasional panic attacks) OR moderate difficulty in social occupational, or social functioning (e.g., few friends, conflicts with co-workers)
50-41	Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting)OR any serious impairment in social, occupational, or school functioning(e.g., no friends, unable to keep a job).
40-31	Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglect family, and is unable to work, child frequently beats up younger children, is defiant at home, and is failing at school).

30-21	Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day, no job, home or friends).
20-11	Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death, frequently violent, manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears faces) OR gross impairment in communication (e.g., largely incoherent or mute).
10-1	Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.
0	Inadequate Information.

APPENDIX IV: THE YOUNG MANIA RATING SCALE

Which statement best describes the way you have been feeling **for the past week**.

1. Elevated Mood

    - Absent
    - Mildly or possibly increased
    - Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
    - Elevated, inappropriate to content; humorous
    - Euphoric, inappropriate laughter, singing

2. Increased Motor Activity or Energy

    - Absent
    - Subjectively increased
    - Animated; gestures increased
    - Excessive energy; hyperactive at times; restless (can be calmed)
    - Motor excitement; continuous hyperactivity (cannot be calmed)

3. Sexual Interest
    - Normal; not increased
    - Mildly or possibly increased
    - Definite subjective increase
    - Spontaneous sexual content; elaborates on sexual matters; hypersexual
    - Overt sexual acts

4. Sleep
    - No decrease in sleep
    - Sleeping less than normal amount by up to one hour
    - Sleeping less than normal by more than one hour
    - Decreased need for sleep
    - No need for sleep at all

5. Irritability

    - Absent
    - Subjectively increased
    - Irritable at times; recent episodes of anger or annoyance
    - Frequently irritable; short, curt
    - Hostile, uncooperative

6. Speech: Rate & Amount

    - No increase
    - Feel talkative
    - Increased rate or amount at times, verbose at times
    - Push; consistently increased rate and amount;
    - Pressured; uninterruptedly, continuous speech

7. Language: Thought Disorder

    - Absent
    - Circumstantial; mild distractibility; quick thoughts
    - Distractible; loses goal of thought; change topics frequently; racing thoughts
    - Flight of ideas; tangentially; difficult to follow; rhyming, echolalia
    - Incoherent; communication impossible

8. Content

    - Normal
    - Questionable plans, new interests
    - Special project(s); hyper religious
    - Grandiose or paranoid ideas; ideas of reference
    - Delusions; hallucinations

9. Disruptive or Aggressive Behavior

- Absent
- Sarcastic; loud at times, guarded
- Demanding; threats
- Threats, shouting
- Assaultive; destructive

10. Appearance

- Appropriate dress and grooming
- Minimally unkempt
- Poorly groomed; moderately disheveled; overdressed
- Disheveled; partly clothed; garish make-up
- Completely unkempt; decorated; bizarre garb

11. Insight

- Present; admits illness; agrees with need for treatment
- Possibly ill
- Admits behavior change, but denies illness
- Admits possible change in behavior, but denies illness
- Denies any behavior change

APPENDIX V: HAMILTON DEPRESSION RATING SCALE.

For each item check the description that best characterizes the patient during the past week.(to be administered by clinician).

1. DEPRESSED MOOD

(Sadness, hopeless, helpless, worthless)

- Absent
- These feelings are indicated only on questioning
- These feelings are spontaneously reported verbally
- Communicates feelings non-verbally i.e., through facial expression, posture, voice, and tendency to weep
- Patient reports VIRTUALLY ONLY these feelings in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT

- Absent
- Self-reproach, feels he has let people down
- Ideas of guilt or rumination over past errors or sinful deed
- Present illness is a punishment. Delusions of guilt
- Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

- Absent
- Feels life is not worth living
- Wishes he were dead or any thoughts of possible death to self
- Suicide ideas or gesture
- Attempts at suicide (any serious attempt rates)

4. INSOMNIA EARLY

- No difficulty falling asleep
- Complains of occasional difficulty falling asleep - more than 1/2 hour
- Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE

- No difficulty
- Patient complains of being restless and disturbed during the night
- Waking during the night - any getting out of bed (except for purposes of voiding)

6. INSOMNIA LATE

- No difficulty
- Waking in early hours of the morning but goes back to sleep
- Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES

- No difficulty
- Thoughts and feelings of incapacity, fatigue or weakness related to activities (work or hobbies)
- Loss of interest in activities (hobbies or work) - either directly reported by patient, or indirectly in listlessness, indecision and vacillation (feels he has to push himself to work or do activities)
- Decrease in actual time spent in activities or decrease in productivity. In hospital, if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
- Stopped working because of present illness. In hospital, if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted

8. RETARDATION: PSYCHOMOTOR

(Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

- Normal speech and thought
- Slight retardation at interview
- Obvious retardation at interview
- Interview difficult
- Complete stupor

9. AGITATION

- None
- Fidgetiness
- Playing with hands, hair,etc
- Moving about, can't sit still
- Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY: PSYCHIC

- No difficulty
- Subjective tension and irritability
- Worrying about minor matters
- Apprehensive attitude apparent in face or speech
- Fears expressed without questioning

11. ANXIETY: SOMATIC

(Physiological concomitants of anxiety, such as - Gastro-intestinal: dry mouth, wind, indigestion, diarrhea, cramps, belching. - Cardio-vascular : palpitations, headaches. - Respiratory: hyperventilation, sighing. - Urinary frequency - Sweating)

- Absent
- Mild
- Moderate
- Severe

- Incapacitating

12. SOMATIC SYMPTOMS: GASTROINTESTINAL

- None
- Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen
- Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms

13. SOMATIC SYMPTOMS: GENERAL

- None
- Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
- Any clear-cut symptom

14. GENITAL SYMPTOMS

(Loss of libido, menstrual disturbances)

- Absent
- Mild
- Severe

15. HYPOCHONDRIASIS

- Not present
- Self-absorption (bodily)
- Preoccupation with health
- Frequent complaints, requests for help, etc. ...
- Hypochondriacal delusions

16. LOSS OF WEIGHT

- No weight loss
- Probable weight loss associated with present illness (>500g/week)
- Definite weight loss(>1kg/week)

17. INSIGHT

- Not depressed (based on above items) OR Acknowledges being depressed and ill

- Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- Denies being ill at all

Study budget.

	ITEM	**UNIT**	**TOTAL**
1.	Research computer	**1**	**40,000**
2.	Printer	**1**	**10,000**
3.	Stationary and printing costs	**-**	**20,000**
4.	miscellaneous	**-**	**10,000**
5.	Research assistance costs	**2**	**20,000**