IMPACT OF FIRST GENERATION ANTIPSYCHOTICS IN THE LONG TERM OUTCOME OF BIPOLAR I DISORDER, A COMMUNITY-BASED NATURALISTIC FOLLOW-UP STUDY, BUTAJIRA, ETHIOPIA

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This is to certify that the thesis prepared by Nigussie Debero, entitled: *Impact of First Generation Antipsychotics in the Long Term Outcome of Bipolar Disorder, A Community-Based Naturalistic Follow-Up Study, Butajira, Ethiopia* and submitted in partial fulfilment of the requirements for the Degree of Master of Science in Pharmacoepidemiology and Social Pharmacy complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Impact of first generation antipsychotics in the long term outcome of bipolar I disorder, a community-based naturalistic follow-up study, Butajira, Ethiopia

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Background: Bipolar disorder is one of the most severe forms of mental disorders, and is clinically characterized by profound mood swings. Bipolar disorder is an episodic condition requiring long-term, often life-long, treatment to control acute symptoms and stabilize mood. Despite recommendations by some treatment guidelines to avoid use of first generation antipsychotics(FGAs) in maintenance treatment of bipolar disorder, their use is highly prevalent especially in resource limited countries like Ethiopia.

Objective: To assess the impact of the long term use of FGAs in the course and outcome of bipolar I disorder.

Methods: The Longitudinal Interval Follow-up Evaluation(LIFE) chart was used to collect detailed psychosocial, psychopathologic and treatment outcome information.

Results: Among the study participants who were at risk for relapse, 86.5% had experienced relapse during their follow-up. Duration on daily FGAs dose ≥ 300mg Chlorpromazine(CPZ) equivalents was significantly associated with relapse rate in bipolar I disorder. While FGAs use did not predict remission and overall functioning improvement, remission was negatively associated with duration of treatment on daily FGAs dose ≥ 300mg CPZ equivalents. Furthermore, duration on FGAs significantly increased the risk for EPS. On the other hand, FGAs use did not predict suicidality in bipolar I patients.

Conclusion: Findings from the current study suggest that benefits of the long term use of FGAs in bipolar disorder are doubtful. Therefore, providing access to effective medications such as mood stabilizers may be relevant next steps to optimize the outcome of bipolar disorder in settings where FGAs are widely used.

Key words: First generation antipsychotics, bipolar disorder, maintenance treatment, prophylaxis, outcome, Ethiopia

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Acronyms

AAU - Addis Ababa University

APA - American Psychiatric Association

BPD - Bipolar Disorder

CI - Confidence Interval

CIDI - Composite International Diagnostic Interview

CPZ - Chlorpromazine

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, fourth edition

EPS - Extra-Pyramidal Side-effects

FGAs - First Generation Antipsychotics

GAF - Global Assessment of Functioning

KIs - Key Informants

LIFE - Longitudinal Intervention Follow-up Evaluation

MDD - Major Depressive Disorder

OR - Odds Ratio

PSR - Psychiatric Status Ratings

PI - Principal Investigator

RRR- Relapse Rate Ratio

SCAN - Schedules for Clinical Assessment in Neuropsychiatry

SCZ - Schizophrenia

SD - Standard Deviation

SGAs - Second Generation Antipsychotics

SMI - Severe Mental Illness

SPSS - Statistical Package for Social Sciences

TD - Tardive Dyskinesia

WFSBP - The World Federation of Societies of Biological Psychiatry

WHO - World Health Organization

1. Introduction

Bipolar disorder, known as manic-depressive illness in the past, is one of the most severe forms of mental disorders and is characterized clinically by profound mood swings. Bipolar I disorder is a relatively common condition affecting 0.4–1.6% of the general population (Kessler et al., 1997). In Butajira district, the Lifetime prevalence of bipolar I disorder was estimated to be 0.6% for males and 0.3% for females (Negash et al., 2005). Because it is an episodic condition, bipolar disorder requires long-term, often life-long, treatment to control acute symptoms and stabilize mood (Smith et al., 2010).

The course of the pharmacological treatment for bipolar disorder is divided in to three phases: the acute phase, the continuation phase and the maintenance phase. During the acute phase, the disease is characterized by manic, depressive or mixed episodes and the goal of treatment in this phase (usually the first 2 months of treatment) is to get the most severe symptoms of mania or depression under control. Once the individual is stable, the continuation phase of treatment is carried on for the next six to twelve months. It is a time for consolidating improvement, to address residual symptoms and functional impairments such as problems in social relationships, work and housing. In this stage the major purpose of treatment is to prevent relapse. The maintenance phase, also named the prophylactic phase of treatment, generally assumes the patient is symptom free. Medications in this stage are used to decrease the likelihood of recurrence, and other treatments, such as psychotherapy, are geared toward maintaining and improving overall functioning and quality of life (Muzina**,** 2004).

The use of FGAs in bipolar disorder as a maintenance treatment is not recommended because of the fear that treatment-emergent depression and movement disorders (both acute and tardive extrapyramidal side-effects) may occur as a result of the long term use of these agents (Grunze et al., 2009; Tohen et al., 2001; Kusumakar, 2002; Zarate and Tohen, 2004). Despite this, the use of FGAs in this phase is highly prevalent especially in resource limited countries like Ethiopia where the well tolerated second generation antipsychotics and other mood stabilizers cannot be used due to unavailability, unaffordability, lack of monitoring resources and/or other drug related risks (Kusumakar, 2002; Tohen et al., 2001; Zarate and Tohen, 2004).

So far, globally, studies are scarce regarding the effectiveness and safety of these agents in the long term treatment of bipolar disorder and no such studies were done in Ethiopia. The major problem is that studies conducted with these agents in bipolar disorder tend to have focused almost exclusively on the short-term treatment of acute mania. As a result, the maintenance phase of bipolar treatment has been one of the areas in which clinical practice has not been underpinned by data from clinical studies.

Given the frequent use of FGAs in bipolar disorder and that bipolar disorder is a chronic disease requiring long-term treatment, it would be of substantial clinical interest to examine the long term impact of these drugs in maintenance phase treatment of bipolar disorder. Therefore, this study based on relatively large and well characterized cohort with detailed psychopathological, psychosocial and treatment information would offer an unparalleled opportunity to assess the impact of using FGAs in maintenance treatment of bipolar disorder.

2. Literature Review

2.1 Background

Bipolar disorder is one of the most serious and disabling mental disorders. It represents a major public health problem and leads to high mortality from suicide, accidental death, and somatic complications. Bipolar disorder is characterized by recurring manic and depressive episodes and as such requires long-term, often life-long, treatment to control acute symptoms and stabilize mood (Vieta, 2004; Smith et al., 2010).

Mania is the core feature of bipolar disorder, which is characterized by elated or irritable mood lasting for at least a week. Associated behavioural and cognitive symptoms include increased energy and hyperactivity ranging from semi-purposeful engagements to disruptive restless behavior. Increased sexual energy, excessive socializing behavior and over talkativeness, indiscrete and inappropriate behavior, overspending and engagement in unproductive business ventures are additional behavioral symptoms. Patients are optimistic and confident, this generally giving way to grandiosity and grandiose delusions (Fekadu et al, 2011).

The depressive symptoms of bipolar disorder include: a depressed or low mood, loss of interest and possibly loss of energy for at least two weeks. These core symptoms are associated with various biological symptoms such as change of appetite and weight, sleep disturbance, reduced libido, disturbance of menstruation, constipation, and psychomotor retardation or agitation. Cognitive problems may be reflected in slow thinking, reduced speed and latency of speech, reduced volume of speech, subjective impairment in concentration, registration and recall, associated with

objective impairment in psychometric testing. Memory disturbance may be severe and resemble dementia (depressive pseudodementia). The so called negative or depressive cognitions include negative views of self, the world, and the future (pessimism). Vague pessimistic outlook and a tendency to worry unnecessarily in mild depression develop in to hopelessness, worthlessness and excessive guilt when the depression becomes moderately severe. Patients may be unable to distract themselves from these repetitive thoughts (depressive ruminations). Suicidal thoughts or behavior may follow (Fekadu et al, 2011).

2.1.1. Classification of Bipolar Disorder

Based on the symptoms the person displays, bipolar disorder is classified in to three major types: bipolar I, bipolar II and cyclothymic disorder. People who have one or more manic or mixed episodes and usually one or more major depressive episodes are classified under bipolar I disorder. Bipolar I disorder is often considered the most severe form of bipolar disorder because the extreme mood elevation can include psychotic symptoms and frequent risk-taking behavior such as drug use and unprotected sex. People experiencing a manic episode may suddenly have an inflated self-esteem, a decreased need for sleep, an increase in goal-directed activities and excessive involvement in pleasurable but potentially dangerous activities. Manic symptoms can be contrasted with a mixed episode in a manic episode's lack of major depressive symptoms. People having a mixed episode are often agitated, having suicidal thoughts, insomnia and an irregular appetite, among other depression symptoms. Both manic and mixed episodes significantly affect social and occupational functioning and may require hospitalization. A major depressive episode

may include recurrent thoughts of death, a depressed mood and little interest in pleasurable activities (APA, 1994*)*.

Bipolar II disorder is the second type of bipolar disorder and people with this disorder experience a milder form of mania called hypomania. Though a hypomanic episode has the same symptoms as a manic episode, symptoms are not severe enough to impair social and occupation activities or warrant hospitalization. People with bipolar II have also had one or more periods of major depression (APA, 1994*)*.

The third type is cyclothymic disorder which is a milder form of bipolar disorder in which symptoms never reach manic, mixed or major depressive episodes. People with cyclothymic disorder, however, experience periods of hypomania and depression. Like other bipolar disorders, cyclothymia occurs equally in men and women. Cyclothymia often goes untreated or undiagnosed because people often think their symptoms are not severe enough to warrant treatment or it is misdiagnosed. Still others may like their mood elevations as they can be very productive periods (APA, 1994*)*.

2.1.2. Natural history and course of bipolar disorder

Bipolar disorder is generally an episodic, lifelong illness with a variable course. The first episode of bipolar disorder may be manic, hypomanic, mixed, or depressive. Men are more likely than women to be initially manic, but both are more likely to have a first episode of depression. Patients with untreated bipolar disorder may have more than 10 total episodes of mania and depression during their lifetime, with the duration of episodes and inter-episode periods stabilizing after the fourth or fifth episode. Often, four years or more may elapse between the first and second episodes, but the intervals between subsequent episodes usually narrow. However, it must be

emphasized that variability is the hallmark of this illness. Thus, when taking a history, a number of longitudinal issues must be considered, including the number of prior episodes, the average length and severity of episodes, average inter-episode duration, and the interval since the last episode of mania or depression (Swann, et al., 1999).

2.2. Management of Bipolar Disorder

Given the relapsing nature of bipolar disorder, treatment in many cases has to be life-long. The course of the pharmacological treatment for bipolar disorder is divided in to three phases: the acute phase, the continuation phase and the maintenance (prophylactic) phase. In the acute phase of treatment the priority is in controlling acute manic or depressive illness episode. In the acute manic state the aim of treatment is to control the acute excitement and prevent any potential risks from a hazardous manic behavior. The depressive phase is more difficult to treat and the management plan depends on the severity of illness and the history of illness and treatment. If the depressive episode is severe, or history is suggestive of a severe deteriorating course, aggressive intervention will be indicated. Once the individual is stable, the continuation phase of treatment is carried on for the next six to twelve months. It is a time for consolidating improvement, to address residual symptoms and functional impairments such as problems in social relationships, work and housing. In this stage the major purpose of treatment is to prevent relapse. As the name indicates, the aim of the maintenance treatment is to prevent further relapse of acute illness episode. The risk of continuing medication with potentially serious side effects against the risk of a potential relapse has to be balanced in the decision to start maintenance treatment (Fekadu et al**,** 2011).

2.2.1. Acute Phase Treatment

Manic or Mixed Episodes

For patients experiencing a manic or mixed episode, the primary goal of treatment is the control of symptoms to allow a return to normal levels of psychosocial functioning. The rapid control of agitation, aggression, and impulsivity is particularly important to ensure the safety of patients and those around them.

Mood stabilizers which include Lithium and other anticonvulsants such as valproate and carbamazepine have long been used in management of both the manic and mixed episodes**.** First generation antipsychotics such as chlorpromazine, fluphenazine and haloperidol are also used in patients with acute mania, particularly those with psychomotor agitation and psychosis as monotherapy or in combination with mood stabilizers. More recently, the new generation antipsychotics such as clozapine, olanzapine and risperidone are becoming first line choices for mania and some are approved for the management of both manic and mixed episodes because of their generally more favourable short-term adverse effect profile in relation to motor side effects. Short-term adjunctive treatment with a benzodiazepine may also be helpful (Grunze et al., 2009).

Depressive episodes

The primary goal of treatment in bipolar depression, as with non-bipolar depression, is remission of the symptoms of major depression with return to normal levels of psychosocial functioning. An additional focus of treatment is to avoid precipitation of a manic or hypomanic episode.

The first-line pharmacological treatment for bipolar depression is the initiation of either lithium or lamotrigine. While standard antidepressants such as serotonin selective reuptake inhibitors (SSRIs) have shown good efficacy in the treatment of unipolar depression, for bipolar disorder they generally have been studied as add-ons to medications such as lithium because antidepressant monotherapy is not recommended given the risk of precipitating a switch into mania. For severely ill patients, clinicians may initiate treatment with lithium and an antidepressant simultaneously, although there are limited data to support this approach. Tricyclic antidepressants carry a greater risk of precipitating a switch to mania than other antidepressants and are not recommended for bipolar depression (Kusumakar, 2002). Tapered discontinuation of antidepressants shall be considered after full remission of symptoms and continuing on the mood stabilizer. In patients with life-threatening inanition, suicidality, or psychosis, electroconvulsive therapy (ECT) also represents a reasonable alternative. In addition, ECT is a potential treatment for severe depression during pregnancy. Selection of the initial treatment should be guided by clinical factors such as illness severity, by associated features (e.g., rapid cycling, psychosis), and by patient preference, with particular attention to side effect profiles (Goodwin, 2009).

2.2.2. Maintenance Treatment

Primary goals of treatment in this phase include relapse prevention, reduction of sub-threshold symptoms, and reduction of suicide risk. Goals also need to include reduction of cycling frequency and mood instability as well as improvement in overall functioning.

A key challenge faced by clinicians when deciding on the most appropriate long-term management strategy for bipolar patients is the need for mood stabilizing therapy with bimodal efficacy in mania and bipolar depression. The tolerability of the chosen treatment plan is also an important consideration for long-term management, with implications both for patients' quality of life and their willingness to adhere to the prescribed treatment. The high risk of suicide among bipolar patients is of particular clinical concern and is a serious public health issue. An ideal long-term treatment for bipolar disorder should minimize this risk (Vieta, 2004).

Options with the best empirical evidence to support their use as maintenance treatments include lithium or other anticonvulsants such as valproate, carbamazepine and lamotrigine; antipsychotics both FGAs and SGAs, and in some cases antidepressants in combination with mood stabilizers. In general, the long term use of antidepressants especially as monotherapy is not recommended due to the risk of switch to hypomania, mania or cycle acceleration (Vieta, 2004). In general, if one of these medications was used to achieve remission from the most recent depressive or manic episode, it should be continued. Maintenance ECT may also be considered for patients whose acute episode responded to ECT (APA, 2002).

Psychosocial interventions that address illness management (e.g., treatment adherence, lifestyle change, early recognition of prodromal symptoms) and interpersonal difficulties are an important adjunct to pharmacotherapy. These interventions may include psychoeducation; cognitive behavioural or other psychotherapy; group therapy; family therapy; and support groups. Electroconvulsive therapy is an option in life-threatening manic, mixed, or depressive episodes; for treatment-resistant illness; or as an alternative to medication (APA, 2002).

2.3. The use of FGAs for Management of Bipolar Disorder

Antipsychotic drugs have been used in treatment of bipolar patients since the discovery of chlorpromazine in the early 1950s. Thereafter, chlorpromazine and the other classes of first generation antipsychotic drugs (FGAs) were used to control manic excitement, hyperactivity, and aggression in bipolar disorder (Tohen et al., 2001; Yatham, 2003).

The FGAs are effective in patients with acute mania, particularly those with psychomotor agitation and psychosis as monotherapy or in combination with mood stabilizers (Tohen et al., 2001). The dosages used are similar to those effective in schizophrenia. These studies indicate that the rate of control of mania with typical antipsychotics compared to mood stabilizers alone is comparable. The combination of the two classes of agents does provide for more rapid control of excitement, agitation, and psychosis than either mood stabilizer or typical antipsychotics alone (Suppes et al., 2005).

While the SGAs are well recommended because of existence of adequate evidence for their effectiveness, the long term use of FGAs in bipolar disorder treatment is limited by risk of treatment-emergent depression and movement disorders (both acute and tardive extrapyramidal side-effects) (Grunze et al., 2009; Tohen et al., 2001). Some studies have suggested that tardive dyskinesia (TD) resulting from FGAs use was more frequent, severe, or both in patients with bipolar disorder, compared to schizophrenia (Muzina, 2004; Nasrallah et al., 1988; Tohen et al., 2001). Some authorities recommend tapering the doses of FGAs once the manic phase remits and final discontinuation in hope that the mood stabilizer can work alone, but patients

frequently relapse when put on mood stabilizer monotherapy for bipolar maintenance (Perlis, 2007; Sachs and Thase, 2000).

The long term use of FGAs in bipolar disorder remains highly prevalent, especially in resource limited countries where the more effective and well tolerated newer generation antipsychotics and other mood stabilizers (lithium and anticonvulsants) cannot be used due to unavailability, lack of trained staff and monitoring resources and/or other drug related risks, despite the published bipolar practice guidelines discouraging the use of FGAs due to long-term safety concerns (Kusumakar, 2002; Tohen et al., 2001).

Even though the advent of SGAs contributed for the scarcity of research on FGAs, the issues of cost effectiveness, and their propensity to induce weight gain, alter glucose and lipid metabolism has caused doubts on the superiority of the SGAs in the clinical practice. This adds to the need for more researches regarding the long term treatment outcomes of FGAs use in bipolar maintenance (Lieberman, et al., 2005).

3. Objectives

3.1. General Objective:

To assess the impact of the long term use of FGAs in the course and outcome of bipolar I disorder.

3.2. Specific Objectives:

- To assess the role of FGAs in preventing relapse in patients with bipolar I disorder,
- To assess the role of FGAs in improving overall functioning in patients with bipolar I disorder,
- To determine the risk of depression associated with long term use of FGAs in bipolar I patients,
- To determine the risk of extra pyramidal side-effects associated with long term use of FGAs in patients with bipolar I disorder,

4. Methodology

4.1. Description of the Study Area

The Butajira cohort on schizophrenia and bipolar disorders, which the present study was based on, was initiated in 1997 in the district of Butajira (Meskan and Mareko) in the Gurage Zone, Southern Nations, Nationalities and Peoples Regional state of Ethiopia (Figure 1). The Butajira town is situated 132km south of Addis Ababa along the Hossana road. The total population living in the district is estimated to be 290,579 (CSA, 2011). The altitude ranges from 1500 to 3500 meters above sea level. The major ethnic group is Gurage and they speak Guragigna. The official language in the district is Amharic, the national language, used for written communication. The population is predominantly Muslim. They grow cereals, spice (pepper), false banana ('enset') and khat. There are three hospitals (one government general hospital and two charity hospitals), 15 health centers and 75 health posts in the district.

4.2. Study Design

A retrospective cohort study was conducted at the ongoing course and outcome study of schizophrenia and bipolar disorders in Butajira by using the longitudinal interval follow-up evaluation (LIFE), a standard and comprehensive method for assessing the longitudinal course of psychiatric disorders, primarily mood disorders such as bipolar disorder (Keller et al., 1987). The data collection was conducted between October, 2011 and January, 2012.

4.3. Source and Study Population

For the current study, both the source and study population was the cohort of participants with bipolar I disorder in the Butajira Study on Course and Outcome of schizophrenia and Bipolar Disorder.

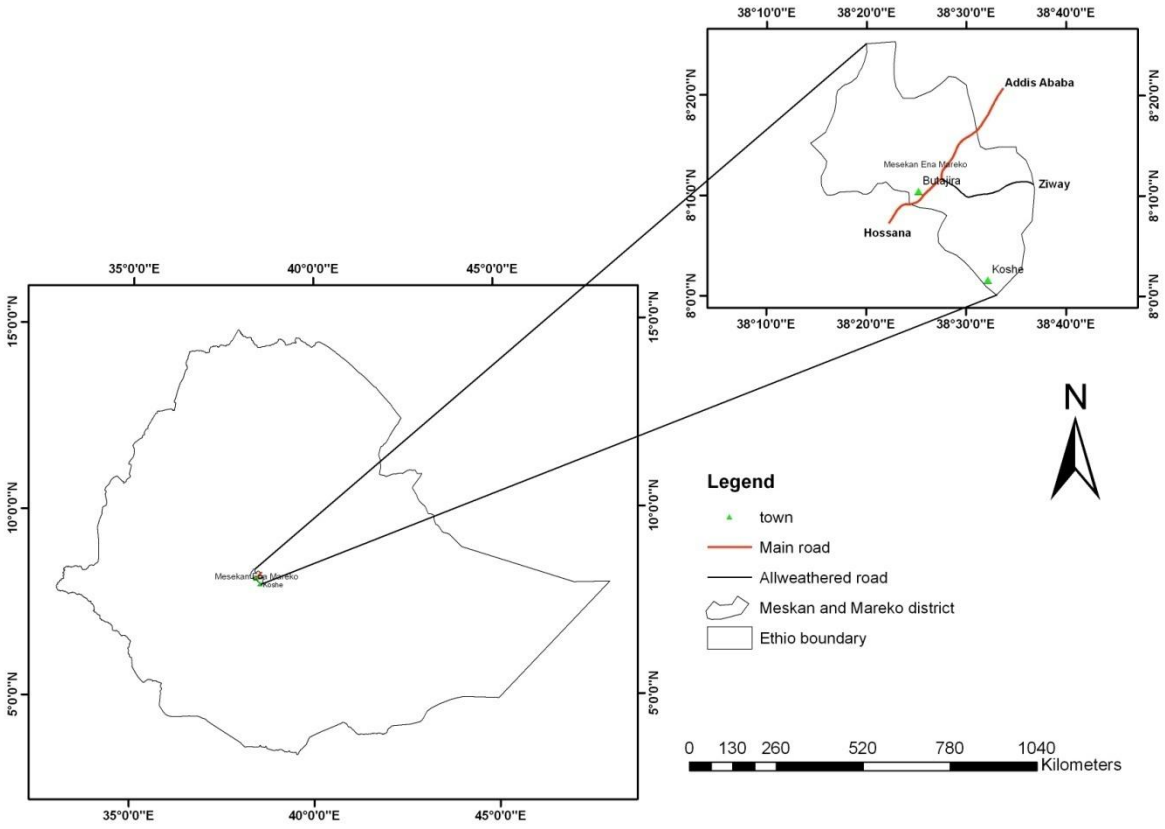

Figure 1: Location map of the study area

4.4. Overview on the Case Identification and Establishment of the Cohort

The cohort was identified through a double-sampling technique. In the first stage, an initial screening was undertaken to identify the potential cases. In the second stage, confirmatory diagnostic assessment was conducted for those identified as potential cases. The initial screening consisted of a supervised, door-to-door survey that targeted the entire adult population (age 15-49) of the District using the Amharic

version (Rashid et al.., 1996) of the affective and psychosis modules of the Composite International Diagnostic Interview, version 2.1 (CIDI 2.1) administered by trained interviewers (WHO, 1997a). Key informants augmented the CIDI interview. Those identified by the CIDI interview and key informants were subject to confirmatory diagnostic assessment using the Schedules for Clinical Assessment in Neuropsychiatry, version 2.1 (SCAN 2.1) (WHO, 1997b). Among the individuals who were SCAN interviewed, 315 were diagnosed as having bipolar I disorder. These SCAN identified cases underwent further assessment to obtain baseline information and were included in the cohort. The procedures followed during establishment of the cohort and the number of potential cases identified by each diagnostic segment is shown in Figure 2. They have been on follow up since the end of the baseline data collection period which lasted from March 1998 to May 2001. Monthly case summaries and annual SCAN interviews were used for recording the patients' clinical status during follow-up. Medications were available to the patients through the study project and were provided routinely depending on the clinical indication. But only FGAs (chlorpromazine, haloperidol, thioridazine and fluphenazine decanoate depot) and tricyclic antidepressants (amitryptyline and imipramine) were available. No other mood stabilizers and second generation antipsychotics were offered because of lack of availability and difficulty with blood monitoring (Fekadu et al., 2006).

The basis for the present study was the cohort of the 315 cases of bipolar I disorder which were identified during the base line assessment (Negash et al., 2005; Fekadu et al., 2006).

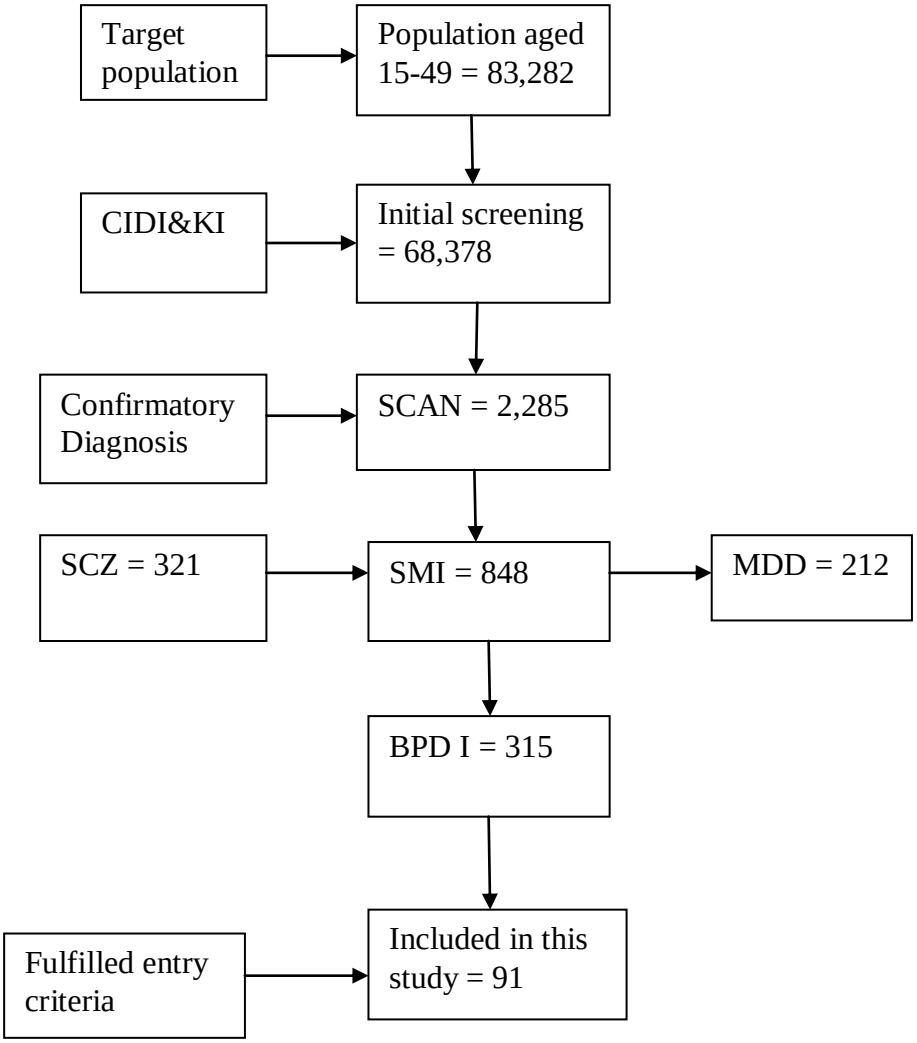

Figure 2: Flow chart showing case identification and establishment of the bipolar I patients' cohort in Butajira, Ethiopia.

4.5. Entry Criteria

Those patients in the cohort who received a diagnosis of bipolar I disorder, had at least one full year of prospective follow-up completed after entry and who were on medication for at least one year were included in the study. Those patients who died or were lost to follow-up with a medication history of less than one year were excluded from the study to maximise the opportunity of seeing the expected outcome indicators.

4.6. Sampling and Sample Size Determination

The sample size was limited by the number of individuals available for inclusion. Thus only 91 individuals with bipolar I disorder fulfilling the entry criteria were included for the study. However, this sample size would enable detection of a 30% difference in outcomes between groups, for example relapse and side-effect burden at 80% power and 95% confidence interval.

4.7. Study Variables

4.7.1. Dependent variables

- Occurrence of relapse
- Relapse rate
- Suicidal attempt
- Functioning improvement
- Duration in remission
- Occurrence of EPS

4.7.2. Independent variables

Baseline Socio-demographic and clinical variables

- Sex of participant
- Marital status
- Age at onset of illness
- Number of episodes at enrollment
- GAF score at enrollment
- Duration in illness at enrollment
- Clinical state at enrollment

Treatment variables

- Duration on FGAs
- Duration on Fluphenazine decanoate
- Duration on daily FGAs dose ≥ 300mg CPZ equivalents

4.8. Data collection and management

4.8.1. Data Collection Tools

The Longitudinal interval follow-up evaluation (LIFE) chart, a comprehensive method for assessing the longitudinal course of psychiatric disorders (Keller et al., 1987), was used to assess medication use, clinical course and treatment outcome including side effect burden among the participants. The data collectors used LIFE to collect detailed psychosocial, psychopathologic and treatment information for every six-month follow-up interval.

The Psychiatric Status Ratings (PSR), which are the ordinal symptom-based scales with categories defined to match the level of symptoms used in DSM IV diagnostic criteria (APA, 1994), were used to record the course of the disorder in each patient during the follow up period. The assessors used the baseline assessment data, the monthly clinical summary and the annual follow-up SCAN interviews to score the PSRs. An interview guide designed to supplement data extracted from the clinical records was used to obtain additional information from the research nurses, the patient and/or his/her care giver. Global Assessment of functioning (GAF) score measured at baseline and at the end of follow-up was used to assess over all functioning of the patients. The occurrence of extra pyramidal side effect was recorded based on the

participant's overall follow up history. The type, the average daily dosage (in milligram per day) and duration of all psychiatric medications used by the patient throughout the follow-up period were recorded on a monthly basis on a medication grid sheet prepared for this purpose.

4.8.2. Data Collectors

Six data collectors were selected and recruited to extract the data for the study. The data collectors involved were three final year psychiatry residents and three psychiatrists as the task requires good clinical psychiatry background and in some cases clinical judgements. The data collection was started after intensive training on the data collection tools through interactive lectures and diagnostic videos, pilot studies and after a satisfactory inter-rater agreement was achieved.

4.9. Data Entry, Clean up and Analysis

The data were initially scrutinized for accuracy and consistency by the principal investigator and data entry was done using Epi-Data Version 3.1.2. A double data entry scheme was employed to ensure accuracy of data entry. Data checking and cleaning were done using statistical package for social sciences version16 (SPSS ver.16) and the data analysis was then done using SPSS ver.16. Having relapse during follow-up, frequency of relapse, having suicidal attempts during follow-up, improvement in overall functioning, being in complete remission for the median duration of remission and having EPS were included in the logistic model as dependent variables. Various baseline socio-demographic and clinical variables and the follow-up treatment variables were included in as independent variables. The selection of the baseline predictor variables was based on previous reports that

assessed correlates of general outcome (Fekadu, et al, 2006;) and included (1) socio-demographic factors such as Gender, Marital status at enrollment and Age of onset of illness, and (2) Clinical variables including duration of illness, clinical state, GAF score and number of episodes at enrollment. Duration on FGAs, duration on Fluphenazine decanoate and duration on average daily FGAs dose ≥ 300mg chlorpromazine equivalents were the treatment variables selected based on the objective of the current study. Duration in treatment variables was expressed in terms of percent of follow-up duration the participants spent on these treatment exposures. Based on the nature of these variables they were treated either as categorical or continuous. The dose of all other FGAs was converted in to and expressed in term of chlorpromazine (a standard first generation antipsychotic drug) equivalent doses by using their respective chlorpromazine equivalences (Atkins et al., 1997). The linear and logistic regression models were employed to identify the associations between the dependent and the independent variables. The forced entry selection procedure was used throughout the analysis.

4.10. Operational Definitions

Chlorpromazine equivalent: the doses of FGAs were calculated by comparing their relative affinity to dopamine receptors and expressed in terms of chlorpromazine doses. Daily doses of haloperidol 2 mg, trifluoperazine 5 mg and thioridazine 100 mg, and fluphenazine decanoate 5 mg four weekly were equivalent to chlorpromazine 100 mg per day.

PSR Scores: are the ordinal symptom-based severity scores derived from the LIFE chart with categories defined to match the level of symptoms used in DSM-IV diagnostic criteria. The scores are used to record the course of the disorder in each patient during the follow up period. The scores are between one and six. Score of one and two represents remission; score of three and four corresponds with subthreshold symptomatic state and score of five and six corresponds with full DSM-IV episode of illness.

Tolerability: refers to the propensity of FGAs to cause side effects, including suicidality.

End of follow-up: the point of time signalling the end of the follow-up for a particular patient, either because of the end of the study or because the patient has died, is lost to follow-up or is no longer in the cohort because consent has been withdrawn.

Number of participants at risk of relapse: Since a patient can only relapse if they had entered remission, those who never attained remission were excluded; thus the number at risk of relapse refers to the number of participants after excluding those who were persistently ill throughout the follow-up..

Improvement in overall functioning: is the improvement in social, clinical and occupational functioning as expressed in terms of difference in Global Assessment of Functioning (GAF) scores of participants at baseline and at the end of follow-up.

Out of episode: It refers to achieving remission from an episode and is defined as being at PSR 2 or 1 for at least 8 consecutive weeks (2 months).

Relapse from remission: having a PSR score of 5 or 6 after having been out of episode for at least 8 consecutive weeks.

Subsyndromal symptoms: refers to a PSR score of 3 or 4.

5. Ethical Consideration

Approval of the research was obtained from the research and ethics committee of School of Pharmacy, Addis Ababa University. The mother project on which this study is based, the Butajira study on course and outcome of schizophrenia and bipolar disorders, is an approved and ongoing project. Official letter was written to the mother study project and permission was obtained before conducting the data collection. The study participants were informed about the purpose of the study and informed verbal consent was obtained from the participants and/or their family prior to the interview. Participants were assured about confidentiality of the information obtained and were informed that the information used will only be accessible to the research team. In addition, the data assessors were psychiatrists and senior psychiatry residents in order to ascertain the maintenance of confidentiality of the participants' information.

6. Result

6.1. Baseline Socio-demographic and Clinical Characteristics

From the total of 315 bipolar patients recruited in the cohort, 91 fulfilled the inclusion criteria for the current study (Fig. 2). For those who fulfilled the inclusion criteria, data on baseline socio-demographic and clinical characteristics are presented in Table 1. Men were slightly over-represented 58(63.7%) and 50(55%) of the participants were married. More than half of the participants 53(58.2%) were under 25 years of age) at enrolment with a mean age of 24.19 years (SD = 8.48) and median age was 22 years.

At baseline, the participants had illness duration of up to 22 years with a mean duration of 5.2 years (SD 5.77) and median 2.0 years. The number of episodes at enrollment ranged from 1 to 15 and the mean number of episodes was 2.9 (SD = 3.0) with a median of three episodes. While 31(34%) of the participants had a single episode at enrollment, 33 (36%) had three or more episodes. At enrollment, the GAF median score was 55.0. Only 40(44%) of the participants had a global functioning assessment score (GAF) ≥ 65, a score considered to be indicative of minimal level of symptoms.

Treatment variables included in this study were duration on FGAs, duration on Fluphenazine decanoate and duration on daily dose ≥ 300mg Chlorpromazine equivalent. The duration in treatment variables was expressed in terms of percent of follow-up duration the participants spent on these treatment exposures. The mean follow-up duration of the participants was 132.24 months (SD = 26.68), and the median was 139 months. It ranged from 15 to 156 months. The duration on FGAs

ranged from 5% to 99.2% of the follow-up duration. The ranges for duration on Fluphenazine decanoate and duration on daily FGAs dose ≥ 300mg Chlorpromazine equivalent were 0 to 79.1% and 0 to 77.7% of follow-up duration, respectively. The mean and median duration on FGAs were 35.9% and 25.4% respectively. The values of the above measures of central tendency were 5.5 and 0 for Fluphenazine decanoate and 7.0 and 0.6 for duration on daily FGAs dose ≥ 300mg Chlorpromazine equivalent.

Table 1: Baseline Socio-demographic and clinical characteristics of patients with bipolar I disorder, Butajira, Ethiopia, 2012 (n = 91).

Variables	**Category**	**Number**	**%**
Sex	Female	33	36.3
	Male	58	63.7
Marital status	Single*	41	45.1
	Married	50	54.9
Age at onset of illness (yrs)	<25	53	58.2
	≥25	38	41.8
Duration of mental illness at entry (yrs)	<3	43	47.3
	≥3	48	52.7
Number of episodes at enrollment	<3	58	63.7
	≥3	33	36.3
Clinical state at enrollment	in remission	55	60.4
	in episode	36	39.6
GAF at enrollment	< 65	51	56
	≥ 65	40	44

*includes 1 separated, 1 divorced and 3 widowed

6.2. Clinical Outcomes

6.2.1. Relapse

Among the 89 bipolar patients who fulfilled the entry criteria and were at risk for relapse (the remaining two were consistently in episode and were not included in this analysis), 77(86.5%) had experienced relapse at least once during their follow-up. The proportion of participants who relapsed was similar for males and females; 50(87.7%) and 26 (81.2%) respectively, and the difference was not statistically significant. Sixty three (70.8%) of the participants had manic relapse, 37(41.6%) had depressive, and 16(18%) had mixed relapses.

Bivariate analysis using logistic regression showed that being in episode at enrollment was significantly associated with relapse (OR = 9.71; 95%CI = 1.20, 78.50) while other baseline variables and treatment variables had no significant association with relapse. The association did not change much in the final fully adjusted (multivariate) model when both the baseline and the treatment variables were included (OR = 10.44; 95% CI = 1.26, 86.83). Details of the association between baseline clinical characteristics and treatment variables with relapse are shown in Table 2.

6.2.2 Rate of relapse

The minimum and maximum duration of follow-up were 15 and 156 months, respectively. The mean and median duration of follow-up (in months) were 132.24 & 139.0, respectively and the standard deviation was 26.68. Among the 77 participants who experienced relapse during their follow-up, 18 (23.4 %) had a single episode but most had multiple relapses and the number of relapses ranged from one to nine. The mean number of relapses was 2.5 (SD 1.97), the median being 2. The ratio of manic to

depressive episodes/relapses was 1.79(127: 71) and mixed episodes were also recorded in 16 cases (Table 3).

Poisson regression analysis was done to identify the independent predictors of relapse rate. It was found that duration on daily FGAs dose ≥ 300mg CPZ equivalents had statistically significant positive association with relapse rate (β = 0.04; *RRR* = 1.04; 95%CI = 1.02, 1.06) while all other variables did not show significant association. This shows that a unit increase in duration on daily FGAs dose ≥ 300mg Chlorpromazine equivalents results in a 4% increase in the expected rate of relapse.

The association of duration on FGAs and duration on Fluphenazine decanoate was protective but it was not statistically significant. Details on the association of factors with relapse rate are shown in Table 4.

Table 2: The association of baseline socio-demographic and clinical characteristics, and treatment factors with relapse for patients with bipolar disorder, Butajira, Ethiopia, 2012 (n= 89).

Variables	Category	Cases (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Sex of the patient	Female	26(81.2)	1.00	1.00
	Male	50(87.7)	1.65(0.50,5.41)	1.72(0.47, 6.34)
Marital status at baseline	Single*	33(80.5)	0.48(0.14, 0.60)	0.56(0.14,2.27)
	Married	43(89.6)	1.00	1.00
Age at onset of illness	< 25	43(81.1)	0.39(0.10,1.54)	0.54(0.12,2.49)
	≥ 25	33(91.7)	1.00	1.00
Duration of mental illness at enrollment	<3	36(83.7)	1.00	1.00
	≥3	40(87)	1.30(0.40,4.22)	1.41(0.313,6.37)
Number of episodes at enrollment	<3	48(84.2)	1.00	1.00
	≥3	28(87.5)	1.31(0.37,4.66)	1.02(0.22,4.71)
Clinical state at enrollment	in remission	42(77.8)	1.00	1.00
	in episode	34(97.1)	9.71(1.20,78.50) **	10.44(1.26,86.83) **
GAF score at enrollment	<65	45(91.8)	3.27(0.92,11.56)	3.18(0.87,11.70)
	≥65	31(77.5)	1.00	1.00
Duration on FGAs			0.99(0.99,1.02)	1.00(0.98,1.02)
Duration on Fluphenazine Decanoate			1.08(0.89,1.32)	1.10(0.87,1.40)
Duration on daily FGAs dose ≥ 300mg CPZ Equivalents			1.14(0.94,1.37)	1.13(0.94,1.36)

*includes 1 separated, 1 divorced and 3 widowed, ***P < 0.05*

Table 3: Patterns of relapses among patients with bipolar disorder, Butajira, Ethiopia, 2012 (n = 89).

Type of Relapse	**Mean(SD)**	**Median**	**Number**	**% cases**
Relapse(all type)	2.52(1.87)	2	77	86.5
Manic	1.43(1.37)	1	63	70.8
Depressive	0.80(1.28)	0	37	41.6
Mixed	0.28(0.72)	0	16	18.0

Table 4: The association of baseline variables and treatment factors with relapse rate for patients with bipolar disorder, Butajira, Ethiopia, 2012 (n = 89).

Variables	Category	Regression Coefficient (β)	Relapse rate ratio (RRR)	95% CI
Sex of the patient	Female	0.03	1.03	0.77, 1.37
	Male		1.00	
Marital status	Single*	0.07	1.07	0.79, 1.45
	Married		1.00	
Age of onset of illness (in yrs)	< 25	-0.14	0.87	0.64, 1.17
	≥ 25		1.00	
Duration of mental illness at enrollment (in yrs)	<3	0.04	1.05	0.76, 1.44
	≥3		1.00	
Number of episodes at enrollment	<3	-0.20	0.82	0.60, 1.13
	≥3		1.00	
Clinical state at enrollment	in remission	-0.23	0.79	0.51, 1.23
	in episode		1.00	
GAF score at enrollment	<65	-0.03	0.98	0.63, 1.51
	≥65		1:00	
Duration on FGAs		-0.01	0.99	0.98, 1.00
Duration on Fluphenazine decanoate		-0.02	0.99	0.97, 1.00
Duration on daily dose ≥ 300mg CPZ Equivalents		0.04	1.04	1.02, 1.06**

*Single includes 1 separated, 1 divorced and 3 widowed, **$p < 0.05$

6.2.3 Overall Functioning

Global Assessment of Functioning (GAF**)** score is used as a measure of the overall functioning of the individual participant. The GAF score of participants at enrollment ranged from 9 to 83 with mean score 51.79 and median 55. At the end of the follow-up, the minimum and maximum scores were 10 and 94 respectively. The mean and the median scores at the end of follow-up were 65.38 and 70.00 respectively. When GAF score value of 65 (a GAF score at which the patient is believed to function well and no need for treatment unless to prevent relapse of a severe condition) was used as a cut off point (APA, 2000), the proportion of participants who had a better functioning at baseline was 40(44%) while it was raised to 58 (63.7%) at the end of the follow-up (Figure 2).

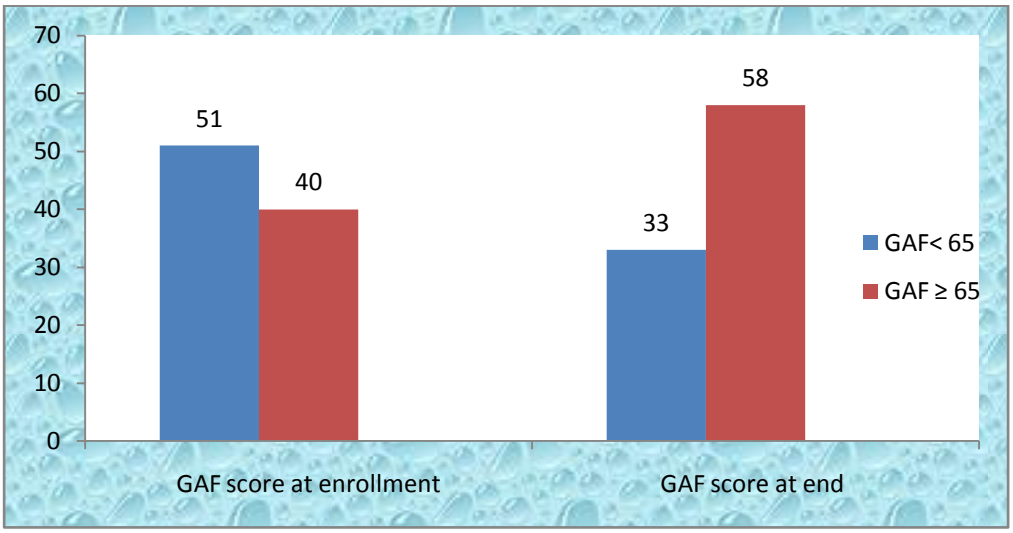

Figure 3: Bar chart showing the number of participants with GAF scores < 65 and ≥ 65 at enrollment and at the end of the follow-up, Butajira, Ethiopia, 2012.

The improvement in overall functioning was expressed as the difference in GAF scores of the participants between the end of follow-up and at enrollment. The

Wilcoxon's signed ranks test indicated that the overall improvement in functioning was statistically significant at p <0.0001.

Bivariate analysis using linear regression showed that functioning improvement is significantly associated with being in episode at enrollment (β = 23.74; t = 5.41; 95% CI = 15.03, 32.46) and having a GAF score at enrollment of < 65(β = 24.03; t = 5.61; 95% CI = 15.52, 32.54) at p < 0.001 while other variables were not significantly associated with functioning improvement.

Multiple linear regression was conducted to identify the independent predictors of functioning. In this regard, being in episode at enrollment and having a GAF score of < 65 at enrollment had statistically significant positive association with functioning improvement, (β = 24.13; t = 5.47; 95% CI = 15.35,32.90) and β = 23.56; t = 5.42; 95% CI = 14.92,32.21) at p < 0.001.

On the other hand, number of episodes at enrollment being ≥ 3 had statistically significant negative association (β = -9.94; t = -2.02; 95% CI =-19.70,-0.17) with functioning at p < 0.05. For those who had experienced ≥ 3 episodes at enrolment, the functioning improvement falls by a factor of 10 when compared to those who experienced 2 or less episodes. Other variables including the treatment factors did not predict functioning improvement. Details on the association of factors with functioning improvement are shown in Table 5.

Table 5: The association of factors with improvement in overall functioning for patients with bipolar disorder, Butajira, Ethiopia, 2012 (n =91).

Variables	Regression coefficient(β)	t-statistic	95% CI
Female, reference Male	-5.43	-1.21	-14.34,3.47
Single*, reference married	5.96	1.23	-3.70,15.63
Age at onset <25yrs, reference ≥ 25yrs	-2.45	-0.51	-12.10,7.20
Clinical state at enrollment in episode, reference in remission	24.13	5.47	15.35,32.90**
Number of episodes at enrollment ≥3, reference <3	-9.94	-2.02	-19.70,-0.17**
Duration of mental illness at enrollment ≥3, reference <3	7.01	1.44	-2.67,16.69
GAF at enrolment < 65, reference ≥65	23.56	5.42	14.92,32.21**
Duration on FGAs	0.01	0.101	-0.15,0.16
Duration on Fluphenazine decanoate	0.05	0.38	-0.23,0.33
Duration on daily FGAs dose ≥ 300mg CPZ equivalents	-0.14	-0.92	-0.43,0.16

* Single includes 1 separated, 1 divorced and 3 widowed, ** p<0.05

6.2.4 Duration in Remission

Duration in remission was computed in terms of percent of follow-up duration (in months) the participants remained in full remission. The median percentage of follow-up duration patients spent in full remission was 88.6, and 89.0 % of patients were in remission for at least 50% of the follow-up duration. While 3.3% of the patients were in remission for the entire follow-up period, only 2.2% were continuously ill, either being in a manic or depressive episode.

The crude analysis using binary logistic regression showed that association of being in full remission for a period longer than the median duration of remission was

statistically significant with clinical status at enrollment being in remission, GAF score at enrollment being ≥ 65 and duration on daily FGAs dose ≥ 300mg CPZ equivalents. According to this bivariate analysis, the odds of being in remission was about 4 times higher for those in remission at enrollment when compared to those in episode (OR = 3.98; 95% CI = 1.62, 9.75; p = 0.003); and it was 3.5 times higher for those with GAF score ≥ 65 when compared to those with GAF score at enrollment <65, (OR = 3.50; 95% CI = 1.46, 8.36; p = 0.005). On the other hand, the participants on daily FGAs dose ≥ 300mg CPZ equivalents were less likely to be in remission as compared to those on lower dose(OR = 0.90; 95% CI = 0.83,0.97; p = 0.007).

Multivariate analysis was done using logistic regression to identify the independent predictors of remission and it was found that clinical status at enrollment being in remission, GAF at enrollment being ≥ 65 and duration on daily FGAs dose ≥ 300mg CPZ equivalents were the significantly associated factors with remission. Participants who were in remission at enrollment were more likely to be in remission as compared to those who were in episode (OR = 3.72; 95% CI = 1.48, 9.32; p = 0.005). Similarly, those with GAF score at enrolment ≥ 65 were more likely to be in remission as compared to those whose GAF score was below 65 (OR = 3.66; 95% CI = 1.47,9.12; p = 0.005). On the other hand, as duration on daily FGAs dose ≥ 300mg CPZ equivalents increases, the odds of being in remission decreases significantly (OR = 0.90; 95% CI = 0.83,0.98; p = 0.013). Details on association of factors with duration in remission are shown in Table 6.

6.2.5 Risk for Suicide

Suicidal attempts and/or gestures are considered as one of the major manifestations of depression and are used in the current study as indicators of depression. Among the participants, 24 (26.4%) had attempted suicide during the follow-up period. The number of suicidal attempts ranged from 1 to 4. Among the participants who attempted suicide, 18 (75%) had a single attempt.

Bivariate analysis on logistic regression showed that number of episodes at enrollment was significantly associated with suicidal attempts (OR = 3.54; 95% CI = 1.34, 9.33; $p = 0.011$).

Multivariate analysis using logistic regression was done to identify factors which independently predict suicidal attempts. Being married, age at onset of illness being below 25 years and number of episodes at enrollment being three or higher were significantly associated with experiencing suicidal attempts. The odds of suicidal attempts was 6 times higher for participants who were married at enrollment as compared to their single counterparts (OR = 6.01; 95% CI = 1.68,21.44). For participants with age at enrollment of < 25 years, the odds of attempting suicide was 3.7 times higher as compared to those with age at enrollment ≥ 25 years (OR = 3.70; 95% CI = 1.01,13.53). The odds of attempting suicide for participants with number of episodes at enrollment ≥ 3 was about 5 times higher as compared to those with lower episodes (OR = 4.71; 95% CI = 1.32, 16.77). All other variables did not significantly predict the risk for suicidal attempts. The association of factors with experiencing suicidal attempts are shown in Table 7.

6.2.6. Risk for Extra-Pyramidal Side-Effects

No extra-pyramidal side-effects (EPS) were documented for 66(72.5%) of the participants throughout their follow-up period. Among the 25 participants who experienced EPS, about 18 (70%) had encountered only mild symptoms. According to the documents reviewed, severe EPS and Tardive Dyskinesia (TD) were found to be experienced by only one participant each during their follow-up period.

Bivariate analysis showed that all the treatment variables were statistically significant predictors of EPS (at least for mild to moderate EPS). Other factors being constant, the use of all the treatment factors (FGAs, Flupenazine decanoate and daily FGAs dose $\geq$ 300mg CPZ equivalents) increases the risk for EPS. These associations were maintained even after adjusting for age at enrollment and sex of the participant. The association of treatment variables with EPS during follow-up are shown in Table-8.

Table 6: Association of factors with complete remission using median duration of remission as a cut off for patients with bipolar disorder, Butajira, Ethiopia , 2012(n = 91).

Variables	Category	Cases (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Sex of the patient	Female	17(51.5)	1.06(0.45,2.50)	1.15(0.45,2.91)
	Male	29(50.0)	1.00	1.00
Marital status	Single*	20(48.8)	1.00	1.00
	Married	26(52.0)	1.14(0.50,2.60)	1.22(0.44,3.36)
Age of onset of illness (in yrs)	< 25	29(54.7)	1.00	1.00
	≥ 25	17(44.7)	0.67(0.29,1.55)	0.77(0.28,2.12)
Duration of mental illness at enrollment (in yrs)	<3	19(44.2)	0.62(0.27,1.41)	0.60(0.21,1.64)
	≥3	27(56.2)	1.00	1.00
Number of episodes at enrollment	<3	31(53.4)	1.38(0.58,3.25)	1.86(0.65,5.27)
	≥3	15(45.5)	1.00	1.00
Clinical state at enrollment	in remission	35(63.6)	3.98(1.62,9.75) **	3.72(1.48,9.32)**
	in episode	11(30.6)	1.00	1.00
GAF score at enrollment	<65	19(37.3)	1.00	1.00
	≥65	27(67.5)	3.50(1.46,8.36) **	3.66(1.47,9.12)**
Duration on FGAs			1.01(0.98,1.01)	1.00(0.98,1.01)
Duration on Fluphenazine decanoate			0.97(0.93,1.01)	0.96(0.93,1.01)
Duration on daily dose ≥ 300mg CPZ Equivalents			0.90(0.83,0.97)**	0.90 (0.83,0.98)**

*Single includes 1 separated, 1 divorced and 3 widowed, **$p < 0.05$

Table 7: The association of baseline characteristics and treatment variables with suicidal attempts for patients with bipolar disorder, Butajira, Ethiopia, 2012 (n = 91).

Variables	Category	Cases (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Sex of the patient	Female	8(24.2)	0.84(0.31,2.24)	0.61(0.19,1.91)
	Male	16(27.6)	1.00	1.00
Marital status	Single*	7(17.1)	1.00	1.00
	Married	17(34.0)	2.50(0.92,6.82)	4.71(1.32,16.77)**
Age of onset of illness(in yrs)	< 25	15(28.3)	1.27(0.49,3.31)	3.70(1.01,13.53)**
	≥ 25	9(23.7)	1.00	1.00
Duration of mental illness at enrolment (in yrs)	<3	12(27.9)	1.00	1.00
	≥3	12(25)	0.86(0.34,2.19)	0.26(0.07,1.01)
Number of episodes at enrolment	<3	10(17.2)	1.00	1.00
	≥3	14(42.4)	3.54(1.34,9.33)**	6.01(1.68,21.44)**
Clinical state at enrolment	in remission	13(23.6)	1.00	1.00
	in episode	11(30.6)	1.42(0.55,3.65)	1.75(0.58,5.27)
GAF score at enrolment	<65	16(31.4)	1.83(0.69,4.85)	2.84(0.89,9.05)
	≥65	8(20.0)	1.00	1.00
Duration on FGAs			1.01(0.99,1.03)	1.01(0.99,1.03)
Duration on Fluphenazine decanoate			0.99(0.96,1.03)	1.01(0.97, 1.04)
Duration on daily dose ≥ 300mg CPZ equivalents			0.99(0.95,1.03)	0.99(0.95,1.04)

*Single includes 1 separated, 1 divorced and 3 widowed, ***p < 0.05*

Table 8: The association of treatment variables with EPS during follow-up for patients with bipolar disorder, Butajira, Ethiopia, 2012 (n = 91).

Variables	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Duration on FGAs	1.03(1.01,1.04)*	1.03(1.01,1.04)*
Duration on Fluphenazine decanoate	1.06(1.01,1.11)*	1.06(1.01,1.12)*
Duration on FGAs Dose ≥ 300mg CPZ Equivalents	1.05(1.01,1.09)*	1.05(1.01, 1.09)*

*$p < 0.05$

7. Discussion

The current study, which was done based on the largest community-based cohort on bipolar disorder in Sub-Saharan Africa, is believed to have produced adequate and reliable information on the impact of FGAs in long term treatment of bipolar-disorder.

Report by a previous follow-up study done in similar setting in Ethiopia with patients on medication for 1–5 years duration have reported a relapse rate of 65.9% (Fekadu et al., 2006). Our report of relapse rate of 86.5% is comparable to the previous finding considering the longer follow-up duration of our sample and the recurrent nature of bipolar disorder.

In the current study, the effect of FGAs for preventing relapse was found to be insignificant. The recurrent nature of bipolar disorder and our inclusion criteria might have contributed to this finding. That means since the duration our participants spent taking FGAs could be even a single year according to our inclusion criteria and the medication use pattern may not be uniform so that relapse might have happened at any time the participants were not on FGAs. Furthermore, non adherence to FGAs due to the long term adverse effects of these drugs might also have contributed for the finding.

The ratio of manic to depressive relapses was almost double (1.79). This could be because of over-representation of male over female in our sample as the rate of manic relapses are higher in men when compared to women (Zarate and Tohen, 2004). Another possible explanation for this could be the frequent relapses of manic episodes as a result of poor adherence or medication discontinuation because of adverse effects.

According to our result, as the duration on FGAs with average daily dose ≥ 300mg Chlorpromazine equivalents increases, the rate of relapse also increases. A probable reason for such association could be drug discontinuation or poor adherence due to adverse effects such as movement disorders including EPS which occur as a result of long term use of such higher doses of FGAs. Although we could not present the adherence data because there was no systematic record of medication adherence of the cohort, it was evident in the current study that duration on FGAs with average daily dose ≥ 300mg Chlorpromazine equivalents had significant association with EPS which is reported as a major contributor to antipsychotics non-adherence (Hamer and Haddad, 2007). Therefore, this implies that the association between relapse rate and average daily FGAs dose ≥ 300 chlorpromazine equivalents could also be due to medication non-adherence at such higher doses. Another possible explanation could be the fact that higher doses of FGAs are usually prescribed for severe and frequently cycling conditions, and if such conditions do not respond to the medication, it is obvious to see higher relapse rate.

According to the current study, being in episode at enrollment and having a GAF score at enrollment of < 65 were significant predictors of functioning improvement. This finding is obvious that the participants who were in episode and those who had lower GAF scores at enrollment have a lower level of functioning and when they are subject to any intervention meant for increasing their functioning including psychotherapy and pharmacotherapy, their overall functioning improvement will be significantly higher as compared to those who were in remission and had higher GAF scores, respectively. First generation antipsychotics including their depot formulation (Fluphenazine decanoate) did not predict functioning improvement. Furthermore,

duration on daily FGAs dose ≥ 300mg CPZ equivalents was negatively associated with functioning. This may either be because of poor compliance to medication due to side effects including EPS at such higher doses. The result supports the finding from a randomized clinical trial which reported the increased risk for depression, treatment discontinuation and emergence of EPS as result of continued use of FGAs in remitted manic patients (Zarate and Tohen, 2004).

According to the current study, being in remission at enrollment and having a GAF score of ≥65 at enrollment were independent predictors of remission for at least the median duration of remission. This may be because of the fact that the chance of being in remission is higher for those patients with no or limited clinical symptoms and for those who are functioning well at enrollment.

The use of FGAs including Fluphenazine decanoate did not predict being in remission. The reason for this may be patients' poor compliance to medication due to the severe long term adverse effects of this class of drugs including EPS. These findings support reports from other studies that showed the long term use of FGAs is associated with precipitation of depressive relapses and EPS (Zarate and Tohen, 20004). Previous studies have also reported ineffectiveness of FGAs for long term management of bipolar disorder. A study by Lieberman et al., (2005) reported that FGAs were not effective in preventing relapse and recurrence in maintenance phase treatment of bipolar disorder. This is also in line with the report from Ciudad et al.,(2005) which stated in a comparative naturalistic study with inpatients that for patients in Olanzepine group, the probability of obtaining a clinical response is 1.5 times higher but the probability of developing EPS is 5 times higher in patients on FGAs as compared with those on Olanzepine. But this finding is in contrary with

report by Lieberman et al., 2005 which claimed that depot FGAs are effective in maintaining remission in bipolar maintenance.

In the current study, early age of onset and higher number of relapses at enrollment significantly predicted risk for suicidal attempts. This may be due to the severity of course of illness which resulted from early onset of the illness and recurrences of the disorder which could increase the risk for suicidality. The other factor which was found to be significant predictor of suicide was being married at enrollment. This association was possibly because of the socioeconomic burden for the married participants as compared to their single counterparts. In the current study, none of the treatment factors predicted suicidal risk. This shows that FGAs use may not be associated with precipitation of depressive relapses. This finding is inconsistent with reports from other studies (Zarate and Tohen, 2004).

According to our finding, all the treatment factors were found to be strongly associated with development of EPS. This could be the reason for the patients´ non adherence and as a result failure of FGAs to independently predict remission in long term treatment of bipolar disorder. Our finding is in line with the reports from other studies (Ciudad et al., 2005; WFSBP, 2004; Janno et al., 2004; Zarate and Tohen, 20004).

8. Strengths and Limitations of the Study

8.1. Strengths of the study

The study was based on large community based cohort with systematic and long term data on baseline clinical information, follow-up psychosocial, psychopathologic and medication use information.

The data collection was done by psychiatrists and final year psychiatry residents so that the quality of the data collected could be ascertained.

The study was done using a standard tool so that the validity and reliability of the results can be assured.

The follow-up duration of the cohort was quite long with an average follow-up duration of 11 years so that long term effects of FGAs including rare adverse effects associated with their long term use can also be traced.

8.2. Limitations of the study

The fact that effects of other concomitantly used medications such as anticholinergic agents and antidepressants was not studied

The fact that there were no systematic records of adverse effects of FGAs including EPS in the cohort

The fact that there were no systematic records of medication adherence information.

The first limitation refers to the concomitant use of other medications. In the study setting, the concomitant use of tricyclic antidepressants and anticholinergic agents is not uncommon. Their purpose in such cases is to prevent and/or control depressive symptoms and EPS, respectively. Therefore, the concomitant use of antidepressants

might have masked the effect of FGAs to precipitate depression and/or exacerbate depressive symptoms. Likewise, the concomitant use of anticholinergic agents may prevent the development of EPS.

Regarding the second limitation, due to the lack of a mechanism designed to systematically record adverse effects of the drugs such as weight gain, drowsiness, and cardiovascular side effects, the study could not fully assess overall tolerability of FGAs in long term treatment of bipolar I disorder. As a result, we used the EPS records which were so done during the routine clinical practice to predict the effect of FGAs on developing these adverse effects. Hence, this might have affected our result.
In case of the third limitation, we could not be certain whether the participants were taking their medications according to the way agreed with their providers. That was because there were no systematic records on the adherence to medication. Therefore, these might have also affected the results of our study.

The fact that no formal inter-rater reliability was done could be another possible limitation. However, the data collection and assessment was conducted after intensive training, pilot studies and after a satisfactory inter-rater agreement was achieved between the raters. Therefore, we believe that the absence of a formal inter-rater reliability assessment would not bias our findings in a significant way. The above limitations should, therefore, be considered during interpreting the results of this study.

9. Conclusion and Recommendations

9.1. Conclusion

The long term use of FGAs did not result in significant improvement in functioning; could not significantly prevent relapses and had no significant association with remission for patients with bipolar I disorder. Furthermore, their long term use by patients with bipolar I disorder was associated with EPS. These findings suggest that benefits of the long term use of FGAs in bipolar disorder are doubtful.

9.2. Recommendations

- The health care providers should counsel their patients on the common adverse effects of these drugs and their management so as to improve treatment outcome.
- Mood stabilisers should be made widely available given the doubtful nature of the benefit of FGAs for management of bipolar disorder.
- Well designed Randomized controlled trials and/or naturalistic studies aimed to assess the effectiveness and tolerability of FGAs are warranted before we have confidence in the benefit of FGAs in maintenance treatment of bipolar disorder.

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Annexes

Annex I: **Data Collection Tools**

Annex IA**: LIFE Chart Clinical Data Extraction form**

Narrative: please include treatment, course ratings & current status

Additional Instruction

Below is a chart for summarizing the detailed clinical information to be gathered from research and clinical notes as well as field workers, patient, family members and nursing staff. Use all available information. List only pertinent symptoms that help with diagnosis and making decision on PSR severity rating. The focus should be on change of symptoms and medications.

Date	Symptomatic state	Medications used	PSR estimate

***Section IB*: Baseline socio demographic and clinical characteristics**

Name of Rater_____ Patient name_____ SCAN No. _____

Sex _____Current Age _____ Diagnosis at enrollment _____

Diagnosis at follow-up _____ Marital status at enrollment _____

Age at onset of illness_____ Number of episodes at enrollment_____

Duration in illness before enrollment (in yrs) ____ Clinical state at enrollment _____

***Section IC*: Medication Grid Sheet**

(developed on publisher and attached on separate folder)

Annex ID: **Psychiatric Status Rating (PSR) Sheet**

SCAN: [ ][ ][ ] [ ] Rater ID: [ ][ ] Date: [ ][ ]/[ ][ ]/[ ][ ] [ ][]

Code	Month																										
	Day																										
	Year																										
	Month #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
1	Major Depressive Episode																										
2	Manic Episode																										
Code	Month																										
	Day																										
	Year																										
	Month #	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
1	Major Depressive Episode																										
2	Manic Episode																										
Code	Month																										
	Day																										
	Year																										
	Month #	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78
1	Major Depressive Episode																										
2	Manic Episode																										
Code	Month																										
	Day																										
	Year																										
	Month #	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104
1	Major Depressive Episode																										
2	Manic Episode																										

SCAN: [ ][ ][ ] [ ] Rater ID: [ ][ ] Date: [ ][ ]/[ ][ ]/[ ][ ] [ ][]

Code	Month																										
	Day																										
	Year																										
	Month #	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130
1	Major Depressive Episode																										
2	Manic Episode																										
Code	Month																										
	Day																										
	Year																										
	Month #	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156
1	Major Depressive Episode																										
2	Manic Episode																										

PSR Reliability: _____

1 = very good 3 = fair
2 = good 4 = poor
5 = very poor

EPS Level: ____

1 = no EPS 3 = moderate
2 = mild EPS 4 = severe
5 = TD

Suicidal Attempts: _____

1 = no attempt 2 = yes

***Section IE*: Global Assessment of functioning (GAF Score)**

Point of time	GAF Score
At enrollment	
At end of follow-up	

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***AnnexII* : Data Collection Guides**

***AnnexIIA:* Psychotropic Medication List**

(LIFE DSM-IV medication codes)

Code number = Generic name

01 = Imipramine	14 = Thioridazine
02 = Amitriptyline	19 = Diazepam
09 = Chlorpromazine	21 = Haloperidol
13 = Fluphenazine decanoate	25 = Trihexiphenidyl (benzhexol**)**

Annex IIB: **Patient/Care giver Interview Guide**

This interview guide is designed to help the interviewer fill any gaps or difficulties which he/she encountered when extracting data from the research and clinical records about the course of the patient so that the PSR scores can consistently be recorded.

Prior to conducting the interview, the interviewer should review and extract all the available clinical follow up data from the records. In conducting the interview, the interviewer may use clinical judgement as to the best way to elicit information regarding the course. The following guidelines are offered to assist in this process.

1. The interviewer should begin the interview by obtaining an overview of what has happened to the subject since the time of the last interview. This overview serves as a time to reacquaint (or acquaint) both the subject and interviewer while providing information on whether the subject has recovered, relapsed and/or developed new conditions.
2. The interviewer should then return to questions about the missing information regarding the change points or duration of conditions in the clinical course during extracting the data.
3. To help the subject/care giver date the change points or duration of conditions required, the interviewer should keep on probing until reasonable recall is obtained. The interviewer can ask such questions as “was that in November?” “did that happen before or after Christmas?”, etc.

***Annex IIC*: Guide for use of conventional six-point PSR scales**

The psychiatric Status Rating (PSR) was developed to generate analyzable data on the course of the patient's psychopathology. The PSRs are numeric values which have been operationally linked to the DSM-IV criteria. DSM-IV criteria information is gathered in the interview, and then translated in to ratings for each month of the follow-up. The ratings are crucial in the follow-up because they indicate the severity level of an episode as well as whether the patient has recovered or relapsed. Two separate rating scales are used for the PSRs: a 3-point and a 6-point scale.

3 point scale

The 3 point scale has three positions: PSR3, full criteria: PSR1 asymptomatic and PSR2 somewhere in between. The top and bottom represent relatively small part of the scale since the thresholds are so strict.

The patient must meet all the DSM-IV criteria to be onset for any disorder. Generally a PSR of 2 may not be used to start a new episode of whatever diagnosis is being considered. Once in an episode, PSRs may fluctuate freely among 3, 2 and 1 to reflect fluctuations among the states of being full criteria, residually symptomatic and asymptomatic. The patient is considered to be "out of episode" if s/he remains symptomatic PSR 1 for at least 8 weeks. Once a diagnosis is officially "out of episode", less than full criteria symptoms may continue to be recorded on the grid.

6 point scale

The 6 point scale is basically a 3 point scale that breaks the three scores in to two component parts. What was a 3 has been converted to either a 5 or a 6; a 2 has been

converted to a 3 or a 4; and a 1 has been converted to a 1 or a 2. As with the 3 point scale, the top and bottom are relatively small.

Simple meeting full criteria warrants a PSR 5. If the patient goes so far beyond simply meeting full criteria to the point of being extremely impaired or displaying prominent psychotic symptoms, they warrant a PSR 6. It is crucial that everyone agrees on and understands the criteria for PSRs.

A PSR of 3 or 4 is used for any level of symptomatology that lies between full criteria (5/6) and a level that does not warrant keeping the subject in episode (2/1). 3 and 4 are distinguished from each other by the number and intensity of symptoms that the subject continues to report for an ongoing episode. A level 4 is commonly used when the patient is missing only one requirement for full criteria and level 3 is used frequently as a catchall for most other in episode symptomatology.

On the 6 point scale a patient is considered to be "out of episode" if at PSR 2 or 1 for at least 8 consecutive weeks. The PSR 2 differs from the PSR 1 only in so far as it represents some level of residual symptomatology, but not enough to warrant keeping the subject in episode. On both scales, PSR 1 represents an asymptomatic state for the diagnosis in question.

Once a subject is "out of episode" for a particular diagnosis, symptoms that are less than full criteria may continue to be coded on the grid. Note: less than full criteria symptoms for a major affective or anxiety disorder may be coded on the grid line for the particular disorder as long as it has been 1 year or less since the episode completely offset (at least 8 weeks at a PSR 1 or 2). If the episode has been offset for longer than one year, you may assess the particular symptoms to determine if they

more accurately reflect a minor or not otherwise specified diagnosis prior to coding them as subsyndromal symptoms of major affective or anxiety disorder.

	Code	Term
	6	Severe
Onset	5	Full Criteria
	4	Marked
	3	Partial Remission
Offset	2	Residual
	1	None

***Annex IID*: DSM IV Criteria for Major Depressive Disorder and Mania**

i: Diagnostic criteria for Major Depressive Disorder

A. At least five of the following symptoms have been present during the same two weeks period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day (as indicated by subjective account or observation made by others)

(3) Significant weight loss when not dieting or weight gain (e.g. more than 5% of body weight in a month) or decrease in appetite nearly every day

(4) Insomnia or hypersomnia nearly every day

(5) Psychomotor agitation or retardation nearly every day(observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) Fatigue or loss of energy nearly every day

(7) Feelings of worthlessness or excessive or inappropriate guilt(which may delusiona) nearly every day(not merely self reproach or guilt about being sick)

(8) Diminished ability to think or concentrate or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) Recurrent thoughts of death (not just fears of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairement in social, occupational or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g. drugs of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

ii: Diagnostic criteria for Mania

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity

(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

(3) more talkative than usual or pressure to keep talking

(4) flight of ideas or subjective experience that thoughts are racing

(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant

external stimuli)

(6) increase in goal-directed activity (at work, at school, or sexually) or psychomotor agitation

(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a Mixed Episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment) or a general medical condition (e.g., hyperthyroidism).

***Annex IIE*: Global Assessment of Functioning (GAF) Score**

In this section, you are expected to judge the individual's overall level of functioning by using the GAF Scale. 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. Give the patient a GAF rating based on the worst level that the patient remained at for at least one week.

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 warmth and integrity. No symptoms.

90-81 Absent or 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 concentrating after family argument); no more than slight impairment in social, occupational, or school functioning (e.g., temporarily falling behind in schoolwork).

70-61 Some mild symptoms (e.g., depressive 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 affect and circumstantial speech, occasional panic attacks) **OR** moderate difficulty in social, or school functioning (e.g., few friends, conflicts with peers, or co-workers).

50-41 Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) **OR** any serious impairment in social, 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, irrelevant) **OR** major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work, child frequently beats up younger children, is defiant at home, and is failing at school).

30-21 Behaviour 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 faeces) **OR** gross impairment in communication (e.g., largely incoherent or mute).

10-1 Persistent danger of hunting 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.