A RETROSPECTIVE STUDY ON PREVALENCE OF PRIOR DEPRESSIVE EPISODES IN NEWLY DIAGNOSED BIPOLAR DISORDER

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DEPARTMENT OF PSYCHIATRY,

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CERTIFICATE

This is to certify that this dissertation titled **"A RETROSPECTIVE STUDY ON PREVALENCE OF PRIOR DEPRESSIVE EPISODES IN NEWLY DIAGNOSED BIPOLAR DISORDER"** submitted by **Dr.K.Kiruthiga,** appearing for **M.D (Psychiatry)** degree examination in April 2018 is a original bonafide record of work done from July 2016 to June 2017 by her under my guidance and supervision in partial fulfillment of requirements of the TamilNadu Dr.M.G.R. Medical University, Chennai. I forward this to the TamilNadu Dr.M.G.R. Medical University, Chennai, TamilNadu, India.

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This is to certify that the dissertation entitled **"A RETROSPECTIVE STUDY ON PREVALENCE OF PRIOR DEPRESSIVE EPISODES IN NEWLY DIAGNOSED BIPOLAR DISORDER"** is a bonafide and genuine research work carried out by **Dr.K.Kiruthiga** under the guidance of **Dr.G.Ramanujam, M.D.,** Associate Professor & HOD, Department of Psychiatry, Tirunelveli Medical College, Tirunelveli.

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DECLARATION

I, Dr.K.Kiruthiga, solemnly declare that this dissertation **"A RETROSPECTIVE STUDY ON PREVALENCE OF PRIOR DEPRESSIVE EPISODES IN NEWLY DIAGNOSED BIPOLAR DISORDER"** was done by me at the Department of Psychiatry, Tirunelveli Medical College, Tirunelveli under the guidance and supervision of the Professor of Psychiatry, Tirunelveli Medical college, Tirunelveli between July 2016 and June2017.

The dissertation is submitted to the TamilNadu Dr.M.G.R. Medical University, Chennai-32 in partial fulfillment of the University requirements for the award of the degree of M.D, Psychiatry.

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2.	Study Protocol	☐
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4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
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CERTIFICATE - II

This is certify that this dissertation work title **A RETROSPECTIVE STUDY ON PREVALENCE OF PRIOR DEPRESSIVE EPISODES IN NEWLY DIAGNOSED BIPOLAR DISORDER** of the candidate **Dr.K.KIRUTHIGA,** with registration Number **201528201** for the award of **M.D.** in the branch of **PSYCHIATRY**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **1 percentage** of plagiarism in the dissertation.

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INTRODUCTION

Mood disorders include a large group of psychiatric disorders in where the clinical picture is dominated by pathological moods and related psychomotor and vegetative disturbances. It encompasses the major depressive disorder/ unipolar depression and the bipolar disorder. **Kettler** gave the term **Cade's disease** for the classical bipolar I disorder which was more lithium responsive, to honour John Cade who discovered lithium. The three additional categories are hypomania, cyclothymia and dysthymia.

Mania and depression are classically defined as being 'poles' apart. Thus the term 'unipolar' describes those experiencing only the downward or depressed pole. The term 'bipolar' describes those experiencing either upward (mania) or downward pole (depression) at different times. Both poles can occur simultaneously and is called the 'mixed' state [1].

The cardinal symptoms of mania include an increase in goal directed activities, thoughtless increase in pleasurable activities or risk-taking behavior, increased talkativeness or pressured speech, grandiosity, flight of ideas, distractibility and a decreased need for sleep. Mania is diagnosed when euphoric mood is present for 1 week with 3 of the above symptoms or irritable mood with 4 of the above symptoms are present. If functioning is unimpaired and manic symptoms last atleast 4 days, hypomania is diagnosed. If symptoms last less than 4 days, bipolar disorder not otherwise specified is diagnosed.

Presence of psychotic symptoms or need for hospitalization implies mania even if the duration of 1 week is not met. Cyclothymia and dysthymia are less severe forms of bipolar disorder and major depression respectively [2].

Ghaemi *et al*[3] (2000) stated that bipolar illness is a lifelong disorder with majority of the time spent in depression. But a history of mania or hypomania is essential for the diagnosis of bipolar depression. When adequate past history is not available or if the patient develops depressive episodes prior to manic episodes, bipolar depression presents a diagnostic problem. When a clinician is faced with a depressed patient, it becomes extremely difficult to determine whether it is unipolar or bipolar depression.

Bipolar disorder patients tend to be underdiagnosed and misdiagnosed. This problem may be due to the fact that,

- ❖ Depressive episodes occur more frequently than mania episodes with 50% of lifetime spent in depression and 11% in mania.

- ❖ Bipolar disorder patients may spend long periods in depression before the onset of manic symptoms. Goodwin and Jamison [4] (2007) stated that the most common first mood episode in bipolar disorder appears to be a depression and not mania.

- ❖ Lack of insight is more prominent in mania than depression as stated by Ghaemi *et al* [5, 3] (1995,2000)

- ❖ Difficulty in establishing past history of hypomania especially in currently depressed patients.

- ❖ Absence of reliable external source to report past manic or hypomanic symptoms. Keitner *et al* [6] (1996) reported that relatives report manic symptoms twice more frequently than patients.

- ❖ Failure to recognize less severe forms of mania and uncertain duration threshold for hypomania. Ghaemi *et al* [3] (2000) stated that the DSM focuses more on defining episode characteristics and less on the disorder as a whole.

- ❖ Uncertain status of mixed episodes and antidepressant induced mania.

- ❖ Lack of agreement about the definition of bipolar spectrum disorder.

There is evidence that many patients currently diagnosed as unipolar depression will later develop episodes of hypomania or mania and they were called "the false unipolars". Angst *et al* [7] (2005) reported that of 406 unipolar patients from 1959 to 1985, half of them converted to bipolar disorder. In the NIMH collaborative depressive study, Fiedorowicz *et al* [8] (2011) concluded that ,10% of unipolar patients converted to bipolar in a 10 year follow up and 26% had converted to bipolarity in a 20 year follow up.

On an average only after 8 years a correct diagnosis of bipolar disorder is made. The National Depressive and Manic Depressive Association reported that 48% had been diagnosed as bipolar disorder only after 3 or more consultations.

Berk *et al* [9] (2007) observed that early age of onset is associated with longer delays and misdiagnosis seems inevitable in the earlier stages of disease. However there are some features which can predict bipolarity. The main difficulty in the clinical management of bipolar disorders is accurate diagnosis.

Hirschfeld *et al* [10] (1994) noted that despite the increase in research and education, the misdiagnosis rate had showed no improvement in the past decade.

Bipolar disorder being more severe than MDD in terms of morbidity and mortality, a correct diagnosis is essential for giving the appropriate treatment.. Underdiagnosis of bipolar disorder may lead to overprescription of antidepressants and worsening of course of bipolar disorder. A large proportion of the bipolar patients incorrectly classified as unipolar poses a serious issue both for treatment and research purposes.

RATIONALE OF THE STUDY

Misdiagnosis is not a problem in bipolar patients presenting initially as mania. But bipolar patients presenting initially as depressive episodes are

frequently misdiagnosed as unipolar depression and treated with antidepressants. If the characteristics of bipolar depression could be identified, misdiagnosis could be minimized. A majority of previous studies were prospective studies, including patients with major depressive disorder who were followed up for several years to watch for conversion to bipolarity and the depressive characteristics of both groups and was analysed. Such studies are minimal as several decades of follow up is necessary. Due to the limited time period, attempt was made to analyse this topic retrospectively. Newly diagnosed bipolar patients were enquired about the past depressive episodes, nature of depressive episodes, misdiagnosis in past, usage of antidepressants and switch to mania/hypomania with antidepressants.

REVIEW OF LITERATURE

EPIDEMIOLOGY

Table 1: Rates of Bipolar I disorder in Epidemiological studies	
Study	**Prevalence%**
Epidemiologic Catchment Area study,1980	0.9
National Comorbidity Survey,1990	1.7
National Comorbidity Survey-Revised,2005	1.0
Cross National Collaborative Group,1996	0.5-1.5

The NCS-R reported the lifetime prevalence of bipolar spectrum disorder to be about 4.5%. The World Mental Health Survey [11] had also reported similar rates with the ECA study and the European studies reporting higher rates of about 6%. Thus Katzow *et al* (2003) [12] stated that one cannot assume as previously that bipolar depression is uncommon when compared to unipolar depression.

The lifetime prevalence of Bipolar disorder is one fourth of the prevalence of MDD. This ratio is currently doubted. The ratio of unipolar to bipolar disorder as reported by Goodwin *et al* [4] (2007) is 2:1 and Amesh reported a ratio of 1:1 [12].

The mean age of onset of bipolar I disorder is 18-22 years. Those with bipolar disorder are misdiagnosed for about 7-10 years due to unrecognised hypomania & sub threshold manic symptoms, mania with psychosis wrongly diagnosed as schizophrenia and recurrent depression with ineffective trials of antidepressant. Hence bipolar illness is not recognised until late 20s leading to an impression of a later age of onset.

Men and women are equally likely to develop bipolar disorder but mania is more common in men and depression more common in women. Mania in women is more likely to have a mixed picture [2].

African Americans with bipolar disorder are at higher risk or clinically misdiagnosed as schizophrenia.

HISTORY

In **400 BC, Hippocrates** used the terms melancholia and mania for describing mood disturbances and they were seen as separate ailments.

Aretaues of Cappadocia (150AD) was the first to link mania with melancholia. He had said that mania is actually a worsening of melancholia and not a separate disease.

In 1854, French psychiatrist Jules Falret, integrated the two mood states into a single cycling condition which he called 'la folie circulaire'. Baillarger independently described the same under the name 'la folie a double forme'

In **1882, Karl Kahlbaum** used the term cyclothymia, describing mania and depression as stages of the same illness.

In 1899, Emil Kraepilin advanced this concept and introduced the term manic- depressive insanity (MDI) which was a broad term including what we now call bipolar disorder and major depressive disorder. This was later rephrased as manic-depressive illness (MDI) to include those presenting without psychotic symptoms. Kraeplin's had included patients presenting with only depressive episodes, only manic symptoms ,both depressive and manic episodes & those with mixed episodes. He had defined the condition by its episodes. Kraeplin had stressed the recurrent nature of the MDI, rather than the polarity.

In 1950, Karl Leonhard was the first to make a division of Kraeplin's MDI based on polarity. He coined the terms bipolar (alternating mania and depression) and monopolar (recurrent depression or recurrent mania) [13].

In 1960s major studies were published by **Carlo Perris (1968) & Jules Angst (1966)** and Winokur and Clayton (1967) provided data supporting unipolar-bipolar subdivision. However based on clinical observation they had argued for the inclusion of unipolar mania in the bipolar category. The use of lithium in 1960s &1970s further supported this classification. Also in 1960s and 1970s Leonard's concept of unipolar and bipolar recurrent psychosis was rephrased as unipolar depressive illness and bipolar illness by the American researchers (Washington university, St.Louis) [13].

In 1970, the American revision of Leonard's work became the basis for Research Diagnostic Criteria (RDC) which was later transformed into DSM-III . In **1980, the DSM-III** officially divided the manic-depressive insanity (MDI) concept into major depressive disorder (MDD) and bipolar disorder (BD) [13]. Unipolar depression or major depressive disorder is diagnosed in patients having only depressive episodes. Bipolar disorder is diagnosed in patients presenting with manic episodes only or with both manic and depressive episodes [2].

DSM-III divided Manic Depressive illness into Major Depressive Disorder and Bipolar Disorder based on five fold validators proposed by the Washington University in 1970 [13] . These 5 validators were based on, symptoms, course of illness, treatment response, biological markers and family history.

1) **SYMPTOMS:** Depression is present in both MDD and BD, mania is present only in BD.

2) **COURSE:** Longer, fewer episodes were seen in recurrent depression & shorter , more frequent episodes were seen in recurrent mania plus depression.

Age of onset was around 20 yrs in BD and around 30 yrs in MDD.

3) **TREATMENT RESPONSE:** Patients with recurrent depression responded to Tricyclic antidepressants and those with BD responded to lithium.

4) **BIOLOGICAL MARKERS:** Abnormalities in norepinephrine and serotonin was found in recurrent depression and an abnormality in dopamine was found in recurrent mania.

5) **FAMILY HISTORY:** Mania was present in the family members of manic patients, but mania was not present in the family members of patients presenting with only depression.

With the growing emphasis on mania, the key feature of recurrence was discarded. Zimmermann *et al* [14] (2009) observed that those with subtle manic symptoms tended to be misclassified as unipolar . This situation was addressed by designating patients with depression and less severe manic symptoms as Bipolar II as explained by Endicott *et al* (1985) [15].

In 1990s **Frederick Goodwin**, director of NIMH in the US, and his coauthor **Kay Jamison** [4] noted that Lithium was also effective in pure depression and not just bipolar disorder. With research further insight was gained about neurotransmitters, second messengers and long-term plastic changes in brain were identified. MDD & BD could no longer be differentiated based on biological mechanisms. The simplistic distinction in the treatment response that mood stabilizers & neuroleptics work for BD and that antidepressants work for MDD was greatly weakened [13].

Jules Angst conducted a 10 year prospective study from 1950 to 1960, the Zurich study which had been the central reason for moving away for Kraeplin's concept and for the division of Manic depressive illness into bipolar disorder and major depressive disorder. He continued his Zurich study even after the division and found that many intermediate states existed which had not been described [13].

Further research by **Hagop Akiskal , Athanasios Koukopoulos, Benazzi, Nassir Ghaemi , Smith DJ** and others showed that many patients did not fit both the unipolar and the bipolar category . There was a lack of agreement about the boundaries of bipolar disorder and the term **bipolar spectrum disorder** was proposed to include the less classic varieties. Different types of bipolar spectrum concepts were defined.

There is still no clarity regarding the boundaries of bipolar disorder with the major issues including its overlap schizoaffective, unipolar major depression and cluster B personality disorder. More intensive prospective longitudinal studies are necessary for clarifying these questions. Bipolar spectrum disorder is the focus of current research.

FALSE UNIPOLARS

Ghaemi *et al* [16] (1999), had described the delay in diagnosis of bipolar disorders as follows-

First depression(19.6yrs) →First mania (24.7 yrs) → First professional visit (25.2 yrs)→First antidepressant use (30 yrs) → First mood stabilizer use (33.2 yrs) →First bipolar diagnosis (34.3 yrs).

Patients who were initially classified as unipolar may later develop an episode of mania or hypomania. Early studies suggested that about 5% of those initially presenting with depression would eventually develop hypomania or mania with the exception of 1 study reporting 14%.

It was concluded in the Collaborative Depression Study that about 1 in 4 of unipolar patients were reclassified as having bipolar disorder. Akiskal *et al* [17] (1995) had also reported similar rates.

Higher rates of about 40% were stated by Ghaemi [13] (2013) and Angst [18] (2005), in a study of 406 patients from 1959 to 1985 , had reported even

higher rates, showing that nearly half of the patients diagnosed as major depression converted to bipolar I or bipolar II disorder . Conversion rates were higher in adolescents and children.

Surveys of bipolar patients by Hirschfeld *et al* [10] (2003b) and Lish *et al* [10] (1994) supported a 50% rate of misdiagnosis.

Both surveys and clinical studies indicate that it takes about a decade for the correct diagnosis of bipolar disorder as stated by Ghaemi *et al* [3] (2000). Thus half of the people are misdiagnosed for about a decade.

SOFT SIGNS OF BIPOLARITY

Michael *et al* [19] (2004) compared bipolar & unipolar depression and he described features specific to bipolar depression, which he called the "**bipolar signature**". Akiskal *et al* 20, [21] (1998, 2003) had also discussed the 'Soft signs' of bipolar disorder. Though this difference in phenomenology of bipolar and unipolar depression is of clinical significance, there are only a few rigorous and methodological studies in this area.

Ghaemi et al [22] (2002) had classified the soft signs using 4 diagnostic validators which can be used to differentiate bipolar and unipolar depression when past history of mania or hypomania is not available. The 4 diagnostic validators of bipolar depression are as follows.

- Phenomenology

- Course Of Illness
- Genetics
- Treatment Response

These predictors are still insufficient in terms of their reliability. The presence of the soft signs pose a reason for reassessing a diagnosis of unipolar depression. Katzow *et al* [12] (2003) stated that there is no guideline as to how many of the symptoms need to be present. But more symptoms increase the likelihood of bipolar depression.

Phenomenology as a diagnostic validator of bipolar depression

In bipolar disorder, the phenomenology could be described as 2 fold: Past hypomania/ mania and current depression. The absence of past hypomanic/manic episodes does not rule out bipolar depression adequately.

Many consider the symptoms of bipolar depression to be similar to that of unipolar depression. But various studies have shown specific differences in the phenomenology of both. The following symptoms are more common in bipolar depression as described by Ghaemi *et al* [22] (2002).

- Atypical depression
- Psychotic depression
- Depressive mixed state
- Agitated depression
- Anxious depression
- Irritability/anger attacks (uncertain)
- Melancholic depression (uncertain)

ATYPICAL DEPRESSION

The DSM criteria for atypical features include increased sleep and appetite, rejection sensitivity, mood reactivity and leaden paralysis.

Agosti and Stewart [23] (2001), Benazzi [24, 25] (1999, 2000), Ghaemi *et al* [22] (2002) and Mitchell *et al* [26] (2001) found atypical depressive symptoms to be

more common in bipolar depression than unipolar depression. The NIMH Collaborative depressive study, a 20 year prospective cohort study of depressed patients also found atypical depression to be a predictor of bipolar disorder (Akiskal *et al*. 1995 [17]).

Ghaemi *et al* [27] (2004a) stated that if atypical depression is defined by the presence of any one of the above characteristics fulfilled by 90% of bipolar depressive patients and only 50% of the unipolar depressive patients.

PSYCHOTIC DEPRESSION

Mitchell *et al* [28, 26] (1992, 2001) and Parker *et al* [29] (2000) reported psychotic symptoms to be more common in bipolar depression than unipolar depression. Schatzberg *et al* [30] (1992) found that these patients also had markedly increased guilt, with psychomotor agitation or retardation and they were guarded.

DEPRESSIVE MIXED STATE

These include major depressive episodes with subthreshold manic symptoms. These mixed states were found to less sensitive to lithium than mania & more sensitive to manic switches during antidepressant treatment when compared to 'pure'unipolar depressive episodes. Neuroleptics were found to be effective in the treatment of mixed depression. They were found to reverse even antidepressant induced mixed states.

Ghaemi *et al* [31] (2017) stated that only 20% of the patients had pure mania and only 20% had pure depression and that the remaining 60% had mixed states.

In **DSM-IV ,** a mixed state was diagnosed only when full criteria for both mania and depression are met. In **DSM-5**, mixed states were replaced by mixed specifier for both mania & depression.

Bennazi [32] (2004b) had defined a mixed state as a depressive episode with 3 or more DSM defined manic symptoms for any amount of time [4,13] . His studies showed the prevalence of mixed states to be around 62.2%. Angst et al (2005) found that in a large sample of 5635 patients, 47% met the above criteria for mixed state [31].

Koukopoulos [33] (2007) stated that mania and depression are not two unrelated phenomenon but rather both occur together. Manic symptoms were seen in depressed patients and depressive symptoms seen in manic patients *i.e* mixed states occurred more frequently than pure depression/pure mania. His definition for mixed depression was broader than that given by Benazzi's. As the core symptom of mania is psychomotor activation, depressive disorder with psychomotor excitation (anxiety / agitation / rage /irritability / suicidal impulsivity) was considered as mixed depression [33]. Of 435 patients diagnosed as depressive disorder, 51% met his criteria for mixed depression.

Akiskal 34, 35 (1996, 1999) reported non-euphoric manic symptoms mainly irritability, distractibility and racing thoughts to be frequently present in bipolar depression .Katzow (2003) [12] stated that impulsivity is the characteristic of bipolar disorder. Cassano *et al* [36] (2012) observed that psychomotor activation is the core to manic depressive illness and not mood symptoms. The symptoms such as impulsivity and mood lability are also shared by other disorders such as impulse control disorders and borderline personality disorders [13].

Angst in 1978 [37], described the **proportional mood spectrum** .This extends from depression to mania with mixed states in between.

DEPRESSION (D) ←→ MANIC FEATURES IN DEPRESSION(Dm) ←→ MIXED STATES(MD) ←→ DEPRESSIVE FEATURES IN MANIA(Md)←→ MANIA(M).

Benazzi [38,32] (2004a, 2004b) found depressive mixed states to be more common in bipolar II depression.

AGITATED DEPRESSION

Akiskal *et al* [39] (2005) described agitated depression as a feature of bipolar depression. Benazzi *et al* [32] (2004) found that psychic tension and agitation predicted bipolar II in multivariate regression modeling.

ANXIOUS DEPRESSION

Anxiety may be present in the presence of manic symptoms. But anxiety in the absence of manic symptoms is more common in bipolar than unipolar depression.

Koukopoulos [40] (1999), Perugi *et al* [41] (1999) and Akiskal et al [42] (2002) had suggested a link between anxiety and bipolar depression.

IRRITABILITY/ANGER ATTACKS

Irritability might be present in the presence of manic symptoms. But irritability even in the absence of manic symptoms has been described as a feature of bipolarity by Benazzi and Akiskal [43] (2005b) and had reported a rate of 60% in bipolar and 37% in unipolar depression.

Periis et al [44] (2004) found irritability as a feature in 60% of bipolar depressive atients and 25% of unipolar depressive patients.

MELANCHOLIC DEPRESSION

Also called as anergic depression, it represents marked anhedonia and psychomotor retardation. It can be differentiated from atypical depression by the preserved mood reactivity in atypical depression.

The availability of literature supporting the relation of melancholic depression to bipolar disorder is limited and controversial. The sure link between psychomotor agitation and bipolar depression conflicts the link between psychomotor retardation and bipolar depression (Mitchell *et al*. 1992 [28]).

Overall, atypical depression, psychotic depression and depressive mixed states are well established presentations in bipolar depression. Anxious, agitated, irritable and anergic presentations are found to differ between groups and further research needed to establish associations.

Illness course as a diagnostic validator of bipolar depression

Kraepelins approach argues that cross-sectional symptoms, no matter how well understood, are inadequate for diagnosing an illness. Psychiatric diagnosis is most clearly established by assessing the longitudinal course of illness. Ghaemi [45](2003) had also emphasized that "diagnosis is prognosis".

Ghaemi *et al* [22] (2002) viewed it as the key diagnostic validator and he included the following.

- Early age of onset
- Brief duration of depression
- Recurrence
- Rapid cycling

- Postpartum onset
- Baseline hyperthymic personality

EARLY AGE OF ONSET

Depression with age of onset below 20 or 30 years is associated with bipolarity.

As reported by Hantouche *et al* [46] (1998) in a French Multicentric study early age of onset characterised switch from unipolar to bipolar disorder II.

Goodwin *et al* [4] (2007) showed that new onset depression in a child or young adult has a likelihood of becoming bipolar illness of about 50%.

Geller *et al* [47] (2001) studied a group of unipolar patients who entered the study at a mean age of 12 years and 49% had converted to bipolarity in 10 years. Another study conducted by Goldberg *et al* [48] (2001) with mean age of study population 23 years showed similar results. But a similar study by Akiskal *et al* [17] (1995) with a initial mean age of more than 30 years showed a lower rates of conversion to bipolarity of only 12%.

BRIEF DURATION OF DEPRESSION

Goodwin *et al* [4] (2007) stated that an average untreated bipolar depression lasts 3 to 6 months and an untreated unipolar depression lasts 6 to 12 months. Hantouche *et al* (1998) also stated that bipolar depressive episodes last shorter.

RECURRENT DEPRESSION

Many authors see considerable continuity between recurrent depressive disorder & bipolar disorder [2.] Goodwin & Jamison [4] (2007) suggested that the relationship between bipolarity and recurrent unipolar depression has been obscured by the excessive focus on the distinction between unipolar and bipolar disorders in the recent years. Ghaemi [22] (2002) had described the relation between bipolar and unipolar disorders. He found that the genetic characteristics and treatment response of recurrent depression is similar to that seen in BD.

Dysthymia ←→ Single MDE ←→ Chronic MDD ←→Atypical MDD←→ Psychotic MDD←→ Recurrent MDD←→ Bipolar NOS←→ Hyperthymia←→ Cyclothymia←→ Bipolar II ← → Bipolar I

Aiken *et al* [49] (2015) suggested that recent arguments favour a linear correlation in the illness course between depression and mania. Katzow *et al*[12] (2003) stated that from a clinical standpoint also, the idea of a continuum is useful.

Psychotic depression ←→ Recurrent depression← → Euthymia ←→ Cyclothymia ← → Hypomania ←→ Mania

Athanasios Koukopoulos [33](2007) had argued that the project of trying to separate depression and mania was misguided.

Recurrence of mood episodes was more common in bipolar than unipolar depression

Stephens et al [50] (1991) reported that a quarter of the unipolar patients experienced no further episodes in a 13 year follow up . Judd *et al* [51] (1998) reported that unipolar patients are likely to be symptom free for 12 years after the first episode.

In contrast, Tohen *et al* [52] (1990) found that all bipolar patients developed a recurrent episode in 4 years. Kessing *et al* [53] (1998) reported a rate of one mood episode per year in bipolar depressed patients.

RAPID CYCLING

Studies dating back to Kraeplin emphasizes the importance of cycling .It is defined as 4 or more episodes in a year. Harrow *et al* [54] (1990) stated that it is common in bipolar depression.

Katzow *et al* [12] (2003) stated bipolarity is characterized by cycling which may be the key to the illness and that cycling can be seen at any point in the spectrum, even within the depressive pole.

POSTPARTUM ONSET

Postpartum episodes are more frequent in bipolar depression as reported by Freeman *et al* [55] (2001)

BASELINE HYPERTHYMIC PERSONALITY

Such people have a great deal of energy, need less sleep, have a good libido and more interpersonal conflicts. Diagnosis of bipolar II disorder is difficult to make in hyperthymic personalities when compared to euthymic personalities. Henry *et al* [56] (2001b) stated that hyperthymic personality is a predictor of antidepressant induced mania.

Cassano *et al* [57] (1992) and Perugi *et al* [58] (2001) stated that hyperthymic personality is a feature of bipolarity.

Genetics as diagnostic validator of bipolar depression

Craddock *et al* [59] (1999) had stated that unipolar depression has a heritability of 31-42% and bipolar disorder has a heritability of about 80-90%. Recent studies in bipolar disorder have suggested a heritability of about 85% as reported by Strakowski (2012) [60].

In the CDS follow up study of the 108 who developed bipolar disorder, 19% had a family history of bipolarity.

A greater weightage has been given to family history and antidepressant induced hypomania or mania. Akiskal reported a high specifically for family history of bipolarity (98%).

It has also been suggested to diagnose as bipolar spectrum disorder, patients presenting with only antidepressant induced mania or hypomania. Akiskal reported that many patients with antidepressant induced hypomania/ mania progress to spontaneous hypomania/mania sooner or later [22].

Treatment response as a diagnostic validator of bipolar depression

Ghaemi had reported the following to be more common in bipolar depression than in unipolar depression:

- Antidepressant induced mania
- Antidepressant induced mixed states
- Antidepressant induced suicidality
- Rapid cycling
- Acute nonresponse
- Tolerance (initial response followed by a later relapse despite treatment)

Akiskal [61](2003) reported a high specifically for AD induced hypomania (100%). He stated that many patients with antidepressant induced hypomania/ mania progress to spontaneous hypomania/mania sooner or later [22]. In the CDS follow up study of the 108 who developed bipolar disorder, 11% had developed antidepressant induced mania / hypomania and only 1% had developed subsequent mania / hypomania. Whereas those with spontaneous episodes had a recurrence of 60% . This supports the view that drug induced bipolar disorder is a distinct entity.

Katzow [12] (2003) saw that a significant number of patients not responding to antidepressants were later diagnosed as bipolar disorder. Studies

by Koukopoulos (2007) [33] also showed that many patients with unipolar depression were not responding to antidepressant. In fact they seemed to worsen the outcome of bipolar disorder even when combined with lithium [13, 22].

Goldberg *et al* [62] (2003) stated that antidepressants could induce subthreshold hypomanic states in bipolar patients and El-Mallakh *et al* [63] (2005) said that these subthreshold states might become chronic. Ghaemi *et al* [64] (2004b) stated that antidepressants were associated with rapid cycling in BD which is still controversial.

Ghaemi [45] (2003) stated that treatment nonresponse is a stronger diagnostic validator than treatment response. Antidepressant wear off defined as the experience of acute but not prophylactic response to antidepressants is linked to bipolar disorder. Also lack of response to 3 or more antidepressant trial has been linked to BD [22].

Ghaemi *et al* [64] (2004b) reported the rates of tolerance in bipolar and unipolar depression to be 58% vs 18%.

Athanasios Koukopoulos [33] 2007 was of the notion that mania causes depression. This he called the manic primacy. He stated that treatment of the cause would be more successful than treating the effect. On this notion he

concluded that mood stabilizers would be more effective than antidepressants [31].

Hence an accurate diagnosis of unipolar and bipolar depression is essential & anti-depressants should be used with caution in bipolar patients.

BIPOLAR SPECTRUM DISORDER

The above described ways of differentiating bipolar and unipolar depression is also relevant to the bipolar spectrum concept. This concept originated from the fact that many patients do not meet the classical definitions for unipolar depression or bipolar disorders I and II. These patients either do not have a past history of mania/hypomania or it is not adequately reported, but the depressive episodes exhibit soft signs of bipolarity. Early research suggests it may be useful to identify the bipolar depressive patients who might otherwise be treated as unipolar depression.

Smith *et al* [65] (2005) had reported diagnosing 47% of the unipolar group with this definition and Sharma *et al* [66] (2005) reported 52%.

Ghaemi *et al* [13, 22] (2013) had stated that validating the bipolar spectrum concept would aid in the better diagnosis of bipolar disorder. He had argued that under diagnosis of bipolar disorder and treatment of bipolar depression with antidepressant would cause a greater morbidity and mortality than over

diagnosis. Kendell [67] (1982) also stated that the existing categorical classification tends to hamper both research and clinical practice.

TABLE 2: PROPOSED DEFINITION BY GHAEMI [22] TO IDENTIFY BIPOLAR DEPRESSION

A	At least 1 major depressive episode
B	No manic / hypomanic episode.
C	Bipolar disorder in first degree relative. Antidepressant induced mania / hypomania
D	Age of onset <25 years Hyperthymic personality Recurrent depressive episode (>3) Brief depressive episodes (<3 months) Atypical depression Psychotic depression Postpartum depression Antidepressant wear off Lack of response to >=3 antidepressant trial
❖	If 2 items from criteria "C" then any 1 from criteria "D"
❖	If 1 item from criteria "C" then any 2 from criteria "D"
❖	If no item from criteria "C" then 6 items from criteria "D"

Currently there is an active debate as to whether these subtypes and spectrum exist or not. Clinically there is still a need to make categorical decisions about treatment and to a lesser extent for social and legal purposes. Smith *et al* [68] (2008) stated that the proportion of patients receiving a bipolar

diagnosis would increase Baldessarini 69 (2000) had emphasized that broadening the bipolar criteria would lead to potential pitfalls in understanding & research. Spencer [70] (2011) had been concerned about the over diagnosis of bipolar disorder and iatrogenic harm. He had argued that diagnosis in psychiatry should not be mere intellectual exercises but should have real life validity.

The bipolar spectrum concept can be discredited for its over inclusiveness and overgeneralizations, taking for granted that milder temperamental states are valid elements of bipolar spectrum. However there is increasing evidence that this spectral approach of dimensional nature is an alternative to the traditional categorical approach. Angst [71] (2002) stated that while this hypothesis may be correct, more evidence in the form of long term prospective studies and genetic data is needed to support this concept .

The entire spectrum of bipolar disorder should be addressed. All levels of severity and each level of symptom need to be treated as they are associated with psychosocial impartment of varying significance. Goodwin [4] (2007) suggested that psychotherapeutic interventions may be useful in such cases.

TEMPERAMENT

Temperament is used to describe subclinical symptoms too mild to be included in bipolar disorders.

Temperaments originally described by Kraeplin & Kretschmer**,** include Euthymia, Dysthymia, Cyclothymia, Hyperthymia and Schizothymia. More recently the temperaments were described by Akiskal [72, 73] (1977)**.** In DSM III, cyclothymia and dysthymia was officially included as Axis I disorder. Hyperthymia is not officially considered as a disorder.

In Eysenck questionnaire, temperamental neuroticism is described as being moody, gloomy, worried, dysphoric and hostile *i.e* with low and negative effect. It is a milder form of cyclothymia of 24 hour duration with a tendency of being more introverted in the morning and more extroverted in the evening with no apparent reason for these ups and downs.

Angst *et al* [71] (2002) discussed that 85% of the population report subthreshold states falling within the mood spectrum. These subthreshold symptoms include introversion, extraversion, neuroticism, dysthymia, cyclothymia and hyperthymia. Only 15% of the population had reported no such symptoms over their lifetime that he described as 'supernormal'.

Koukopoulos [33] (2007) reported that about half of the patients diagnosed as unipolar depression have either hyperthymic or cyclothymic temperament.

There are fluctuations in the lifetime of the patient within the spectrum of mood disorders from temperamental neuroticism to minor disorders (hyperthymia/ cyclothymia/dysthymia) to major unipolar or bipolar disorders.

Smillie *et al* [74] (2009) and Jylha *et al* [75] (2010) assessed the personality and found no difference between unipolar and bipolar disorders.

BIPOLAR SUBTYPES

In 1970 Hagop Akiskal [76]**,** began research in the 1st specialized mood disorder clinic in United States and his studies showed that many patients did not fit both the unipolar and bipolar category. Other researchers apart from Akiskal who had suggested bipolar disorder type III to VI were Angst, Baldessarine, Gershan and Klerman [22].

TABLE 3: BIPOLAR SUBTYPES DESCRIBED BY HAGOP AKISKAL [1].

Bipolar ¼	Antidepressant poop out
Bipolar ½	Schizoaffective disorder
Bipolar I	Manic-depressive illness
Bipolar I ½	Depression with protracted hypomania
Bipolar II	Depression with discrete hypomania
Bipolar II ½	Depression with cyclothymic temperament
Bipolar III	Depression with antidepressant induced hypomania
Bipolar III ½	Bipolar disorder associated with substance use
Bipolar IV	Depression with hyperthymic temperament
Bipolar V	Mixed depression & hypomania
Bipolar VI	Bipolar disorder associated with dementia

BIPOLARITY INDEX

Existing rating scales for depression does not capture the phenomenology of bipolar depression adequately. There is a need for sensitive questionnaires for early recognition of bipolar depression like the Bipolarity index by Sachs *et al* [77] (2004) and the Bipolar depression rating scale by Berk *et al* [78] (2004). .

The 5 items included in bipolarity index were age of onset, episode characteristics, illness course, treatment response and family history. Each item is rated from 0 to 20. The total score of bipolarity index is 100. A score of greater than 50 indicates a high probability of bipolar disorder [77].

COURSE OF BIPOLAR DISORDER

Bipolar illness is a lifelong disorder in more than 90% individuals with majority of the time spent in depression. Bipolar disorder begins in adolescence and exhibit increasingly frequent episodes with progressive shortening of euthymic periods. The course is dynamic with a complex combination of symptoms and occurrence of comorbid medical & psychiatric conditions.

In the collaborative depression study, the bipolar patients had been symptomatic for nearly half the follow up period. A dominance of depressive symptoms was seen in bipolar patients with nearly half the time spent in depression. 6.3% of time had been spent in mania /hypomania in bipolar I

patients. In bipolar II, only 0.2% of time was spent in hypomania. Thus bipolar patients experienced 8 times more depression than mania or hypomania in CDS study. The effective management of depressive symptoms is a pressing entity even in bipolar disorders. Hence depressive symptoms need to be given the same priority as mania symptoms.

It was also found in the CDS study that age and duration of episode does not predict repeated episodes. Only family history of bipolarity was significantly associated with the development of subsequent episodes.

Both BP I & BP II do not differ in terms of severity of depressive symptoms but they exhibit less severe manic symptoms. Bipolar II disorder is not less severe as often thought but an equally chronic and highly depressive disorder and needs to be treated with the same priority are bipolar I disorders.

Bipolar II disorder patients are more likely to have less severe but more chronic depressions with shorter interepisode time, a higher suicidal risk and higher prevalence of comorbid anxiety & substance abuse when compared to bipolar I patients. Spence [70] (2011) showed that bipolar II patients are more likely to become rapid cyclers and to develop mixed affective states, particularly agitated depression.

Robinson *et al* [79] (2006) reported that residual cognitive deficits show a severity spectrum with most impairment in bipolar I disorder, intermediate in

bipolar II and least in remitted unipolar depression with deficits proportional to the duration of the illness.

FAMILY HISTORY

Craddock *et al* [59] (1999) had stated that unipolar depression has a heritability of 31-42% and bipolar disorder has a heritability of about 80-90%. Recent studies in bipolar disorder have suggested a heritability of about 85% as reported by Strakowski [60] (2012). He had also stated that, in bipolar families, unipolar depression is more common than bipolar disorder.

However the risk is more in the age group of 15-35years and significantly decreases in middle adulthood. Compared to general population, first degree family members exhibit a 10-fold increased risk in bipolar disorders and a two-fold increased risk in major depressive disorder.. There is evidence that lithium response may be familial and linked to chromosome 15q.

TABLE 4: SHOWING THE HERITABILITY OF BIPOLAR DISORDER

Situation	Relative risk for bipolar disorder
General population	1-2%
Sibling with BD	15-25%
Identical twin with BD	70-80%
Single parent with BD	15-25%
Both parents with BD	50%
2nd degree relative with BD	3-4%

COMORBIDITY

It refers to the occurrence of 2 or more conditions concurrently. Bipolar disorder is often complicated by comorbid medical or psychiatric conditions. Strakowski in his book on bipolar disorders had described the lifetime prevalence of various conditions in bipolar disorder and compared it with the prevalence in general population.

TABLE 5: COMPARING THE COMORBIDITY OF BIPOLAR DISORDER WITH GENERAL POPULATION

CONDITION	LIFETIME PREVALANCE IN BIPOLAR DISORDER	LIFETIME PREVALANCE IN GENERAL POPULATION
Nicotine use disorder	46-80%	21%
Alcohol use disorder	38-48%	14-18%
Drug use disorder	21-41%	6-8%
Anxiety disorder	42-77%	15-25%
Personality disorder	38-48%	9-13%
ADHD	28-90%	5-10%

Comorbid substance use

The terms primary psychiatric disorder and substance induced psychiatric disorder was first introduced by DSM IV. Primary psychiatric disorders have their onset prior to the substance use and persist during periods of extended abstinence. Substance induced disorders have a linear correlation with the substance use and there is a remission within 1 month abstinence.

Substance use disorder and mood disorders are intertwined to a significant extent. Substance use disorders are more common in bipolar I compared to bipolar II disorder. In bipolar individuals binge drinking pattern is common especially during the manic episodes. This may be due to several factors such as impulsivity, an attempt to self medicate anxiety or insomnia. Substance use also clearly worsens the course of bipolar disorder. Clinicians need to be diligent for substance abuse especially if there is a sudden worsening in the course of illness.

Strakowski *et al* [80] (2000) showed that substance use in bipolar disorder patients is 2-4 times higher when compared to the general population .Ghaemi *et al* [12] (2003) reported that substance use increased with antidepressant usage in bipolar disorders.

In the Collaborative Depression Study, alcohol use seen in 23.7% of the sample. Thus a quarter of the patents had presented with co morbid alcohol use and but only 46.5% had received some form of treatment in the study, with a still lower percentage receiving treatment in the general population. Also alcohol use was a strong predictor of relapse in mood disorder. Among those who did not achieve remission 1.67% died within 2 years, half of them committing suicide highlighting the need to address issues of suicide. The factors associated with delayed remission in the CDS study were early morning drinking, binge drinking, longer duration of use and associated psychiatric disorders. The associated risk factors were younger patients, males, unmarried

and low socioeconomic status. A high religious involvement was found to confer a higher protection regardless of the other factors. Nicotine and cannabis use is also common in BD patients. Both substance use and bipolar disorder should be managed aggressively to optimize outcome.

Comorbid anxiety

Compared to general population, anxiety disorder is 3-4 times common in bipolar patients. Prevalence of anxiety is higher in BD compared to MDD. Anxiety worsens the course of bipolar illness .It may resolve with the treatment of bipolar disorder or may need additional treatment. This may be complicated by the fact that antidepressants which are typically used for managing anxiety disorders may worsen the course of bipolar illness.

TABLE 6 : WHO RATES OF ANXIETY DISORDER IN BIPOLAR DISORDER

CONDITION	BIPOLAR I DISORDER	BIPOLAR II DISORDER
PANIC DISORDER	**18%**	**17%**
OCD	18%	12%
PTSD	**26%**	**25%**
GAD	27%	33%
SOCIAL PHOBIA	**35%**	**36%**

Comorbid risk of suicide

The single and largest risk factor for suicide is the presence of mood disorder. Suicide rates are higher in bipolar illness than unipolar as rapid cycling which occurs exclusively in bipolar patents is a risk for suicide. Ghaemi *et al* [31] (2017) stated that mixed states increased the suicide risk 2.5 times.

Goodwin *et al* [4] (2007) had stated that suicide attempts are seen in about 50% of bipolar patients and completed suicide in about 15%. Substance abuse and certain temperaments were found to be strong predictors of attempted &

completed suicide. History of previous suicide attempts is the strongest predictor of suicide.

Bostwick *et al* [81] (2000) had recommended making suicide risk assessment a routine with ongoing support of protective factors while compensating for risk factors and acute stressors.

Comorbid personality disorders

The dynamic symptoms of bipolar disorder may be difficult to distinguish from cluster B personality disorder. Dunayevich *et al* [82] (2000) had reported high rates of co-occurring personality disorders in bipolar disorders, causing reduced compliance with treatment and higher risk of substance abuse. In addition to treating the bipolar disorder, personality disorders need to be treated with focused psychotherapies long term**.**

Comorbid ADHD

Geller *et al* [83] (2001) suggested that if children are depressed there is a 50% likelihood of bipolar disorder. Wozniak *et al* [84] (1995) reported that 90% of the children who met the criteria for bipolar disorder also met the criteria for ADHD , but only 25% of the children with ADHD met the criteria for bipolar disorder. Thus children are diagnosable with ADHD alone.

Singh *et al* [85] (2006) had also reported high rates of ADHD in bipolar disorder. Dunayevich *et al* [82] (2000) stated that ADHD is more common in

younger individuals with bipolar disorder, affecting 80% of the children with bipolar disorder and one third of the adults with bipolar disorder.

Childhood conduct disorder and ADHD should raise the suspicion of childhood bipolar disorder if it tends to be of episodic nature and is associated with family history of bipolarity. Research in children with follow up into adulthood and increased diligence during treatment is necessary.

Medical comorbidity

Comorbid medical conditions and premature mortality are higher in bipolar disorder than general population as described by Strakowski *et al* [86] (1999) in the following table.

TABLE 7: SHOWING THE MEDICAL COMORBIDITIES IN BPAD & GENERAL POPULATION.

Condition	Bipolar Disorder	General population
Obesity	21-35%	20-36%
Type II DM	8-17%	6-8%
Cardiovascular disease	11-50%	7-20%
Migraine	25-40%	7-16%

Calkin *et al* [87] (2013) and Vancampfort *et al* [88] (2013) studied about the metabolic syndrome in bipolar patients and found that it was more prevalent in bipolar patients than general population with obesity and type II DM leading. This higher risk is often attributed to psychotropic medication but higher rates are also seen in treatment naïve individuals and bipolar patients may have an inherent risk.

Roshanaei *et al* [89] (2009) reported that the leading cause of premature death in bipolar disorder next to suicide is cardiovascular disease

Strakowski *et al* [86] (1999) showed that migraine is seen in nearly half the patients with bipolar disorders and mainly in women. Migraine may vary

with menstrual cycles like mood disorders. Migraine worsens the mood disorder but is often left unaddressed. Hence managing co-occurring medical conditions and integrating clinical practices is a necessity.

AIMS AND OBJECTIVES

AIM

The aim of the study is to determine the prevalence of prior depressive episodes in newly diagnosed bipolar patients, to identify the time taken for correct diagnosis and to look for clinical correlates that could facilitate early diagnosis.

OBJECTIVES

1) To determine the prevalence of undiagnosed and misdiagnosed prior depressive episodes even before the onset of first manic episode.

2) To determine the time interval between the first depressive episode and onset of the first manic episode.

3) To look for the presence of bipolar soft signs in prior depressive episodes.

4) To compare clinical correlates between bipolar patients with mania as initial presentation & bipolar patient with depression as initial presentation.

MATERIALS AND METHODS

This is a cross sectional study done at Department of Psychiatry, Government Medical College Hospital, Tirunelveli. This study was done for a period of one year from July 2016 - June 2017. Ethical approval for the study was obtained from Institutional Ethical Committee, Government medical college hospital, Tirunelveli, prior to the commencement of the study.

INCLUSION CRITERIA

1. Patient fulfilling ICD-10 criteria for diagnosis of bipolar mood disorder.
2. Patients should be diagnosed for the first time as BPAD with current episode mania /hypomania/mixed.
3. Anti-depressant induced mania/hypomania in patients treated as unipolar depression.

EXCLUSION CRITERIA

1. Known bipolar patients on treatment.
2. Patients receiving mood stabilizers for any other reason.
3. Organic affective disorders
4. Schizoaffective disorder
5. Patients not willing to participate in the study.

OPERATIONAL DESIGN

The samples selected in this study were patients attending psychiatry department. Patients diagnosed as bipolar disorder for the first time, currently presenting as mania/ hypomania/mixed episode were selected using ICD- 10 criteria. Patients presenting with antidepressant induced mania or hypomania were also included. Totally 60 newly diagnosed bipolar patients were included in this study consecutively. The purpose of the study and interview were explained and a formal written consent in the mother tongue was obtained. Then these patients were re-interviewed in detain about past depressive symptoms using a semi-structured proforma. Symptoms which were present definitely and clear were only included and marked as either present or absent. Other symptoms which were present questionably were excluded.

TOOLS USED

- Semi – Structured Proforma
- Modified Kuppuswamy Rating Scale
- Young's Mania Rating Scale
- Mood Disorder Questionnaire
- Patient Health Questionnaire-9
- Holmes-Rahe Life Stress Inventory

MODIFIED KUPPUSWAMY RATING SCALE

The modified Kuppuswamy scale [90] (1981) is commonly used to measure socio economic status in urban and peri-urban communities. Mishra revised the Kuppuswamy index in 1998, then Kumar *et al* in 2007 and Singh *et al* in 2017 due to change of price index [91]. The Kuppuswamy scale was devised by **Kuppuswamy** in 1976 and is based on a composite score considering the education and occupation of the head of the family along with monthly income of the family, which yields a score of 3-29. This scale classifies the study populations into high, middle, and low SES.

YOUNG MANIA RATING SCALE (YMRS) [92]

The YMRS developed by Vincent E Ziegler and popularized by Robert Young in 1978, is by far the most commonly used standardized measure of manic symptoms. A modified scale is available for use in pediatric patients. This is an 11-item interviewer rated scale. The items have five defined grades of severity. Four items are double weighted and graded on a 0 to 8 scale (irritability, speech, thought content and disruptive/aggressive behavior) while the remaining seven items are graded on a 0 to 4 scale. The scale is generally rated by a clinician and takes 15–30 minutes to complete.

MOOD DISORDER QUESTIONNAIRE (MDQ) [93]

It is a self-report questionnaire designed by Hirschfeld *et al* in 2000 to help detect bipolar disorder. It is very sensitive and can detect subthreshold manic symptoms. It has 5 main parts with the first part having 13 questions (total of 17 questions). The MDQ was originally tested with adults, but it has also been studied in adolescents and children. It takes approximately 5–10 minutes to complete. In 2006, a parent-report version was created Wagner *et al*. The MDQ is one of the most widely studied and used questionnaires for bipolar disorder, and it has been translated into more than a dozen languages.

PATIENT HEALTH QUESTIONNAIRE

The PHQ-9 is a multiple-choice self-report inventory with a total of 9 questions and it aims to predict the presence of depression. Kroenke, Spitzer, and Williams [94] conducted validity and reliability tests on the PHQ-9 in 2001. It takes less than 3 minutes to complete. PHQ-9 scores of 5, 10, 15, and 20 represents mild, moderate, moderately severe and severe depression. Question 9 screens for the presence of suicide ideation and its duration. . A follow up question is used to assess the patient's level of functioning.

THE HOLMES-RAHE LIFE STRESS INVENTORY [95]

This scale was developed by Thomas Holmes and Richard Rahe in 1967 to determine if stress contributes to illness. Each event, called a Life Change Unit (LCU), had a different "weightage" for stress. More the events, higher the score and higher likelihood for illness. 150 points or less means a relatively low susceptibility to stress-induced health problems. 150-300 points imply 50% chance of a major stress induced health problem in the next 2 years. 300 points or more raises the odds to about 80% according to the Holmes-Rahe prediction model.

STATISTICAL DESIGN

The data collected were analysed with Statistical Package for the Social Sciences 23.0 version and frequencies and percentages were calculated. To find the significance in categorical data, Chi-Square test was used .In the above statistical tools, the probability value <0.05 is considered as significant.

RESULTS

TABLE 8 : SHOWING THE SOCIO–DEMOGRAPHIC PROFILE OF PATIENTS

S.No	Variable		No. of patients(n=60)	Percentage
1	Sex	Male	34	57
		Female	26	43
2	Age	15-19 years	18	30
		20-35 years	28	47
		36-50 years	10	17
		>50 years	4	7
3	Education	Illiterate	3	5
		Primary	17	28
		Middle School	8	13
		High School	20	33
		Diploma	10	17
		Graduate	2	3
5	Occupation	Unemployed	19	33
		Unskilled	22	37
		Semiskilled	5	8
		Skilled	7	12
		Clerk&shop owner	2	3
		Semi profession	5	8

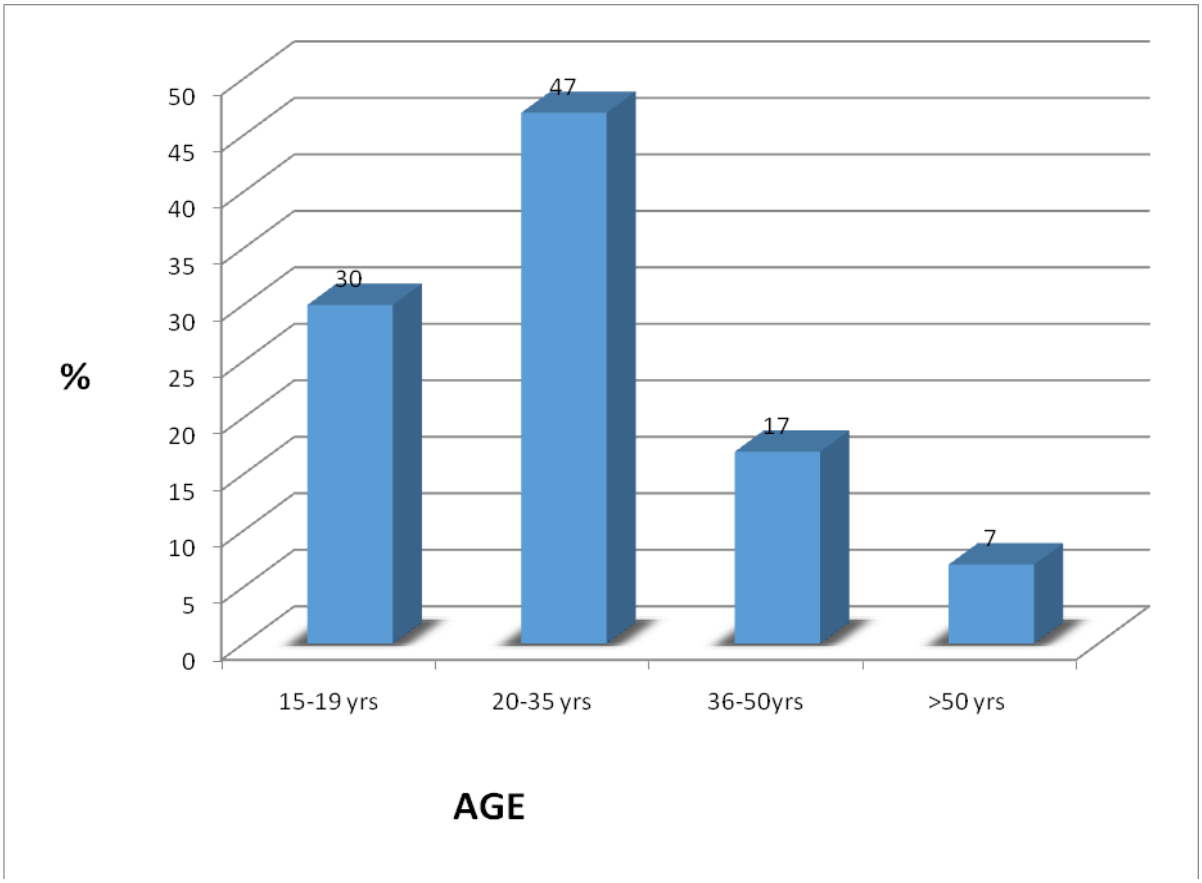
6	Socioeconomic status	Upper lower	20	33
		Lower middle	25	42
		Upper middle	15	25
7	Religion	Hindu	47	78
		Muslim	1	2
		Christian	11	8
		Converted	1	2
8	Marital status	Unmarried	31	52
		Married	26	43
		Separated	3	5

In this study 57% of the newly diagnosed bipolar patients were males and 43% females.

Out of 60 patients, 52% were unmarried, 5% separated and only 43% were married.

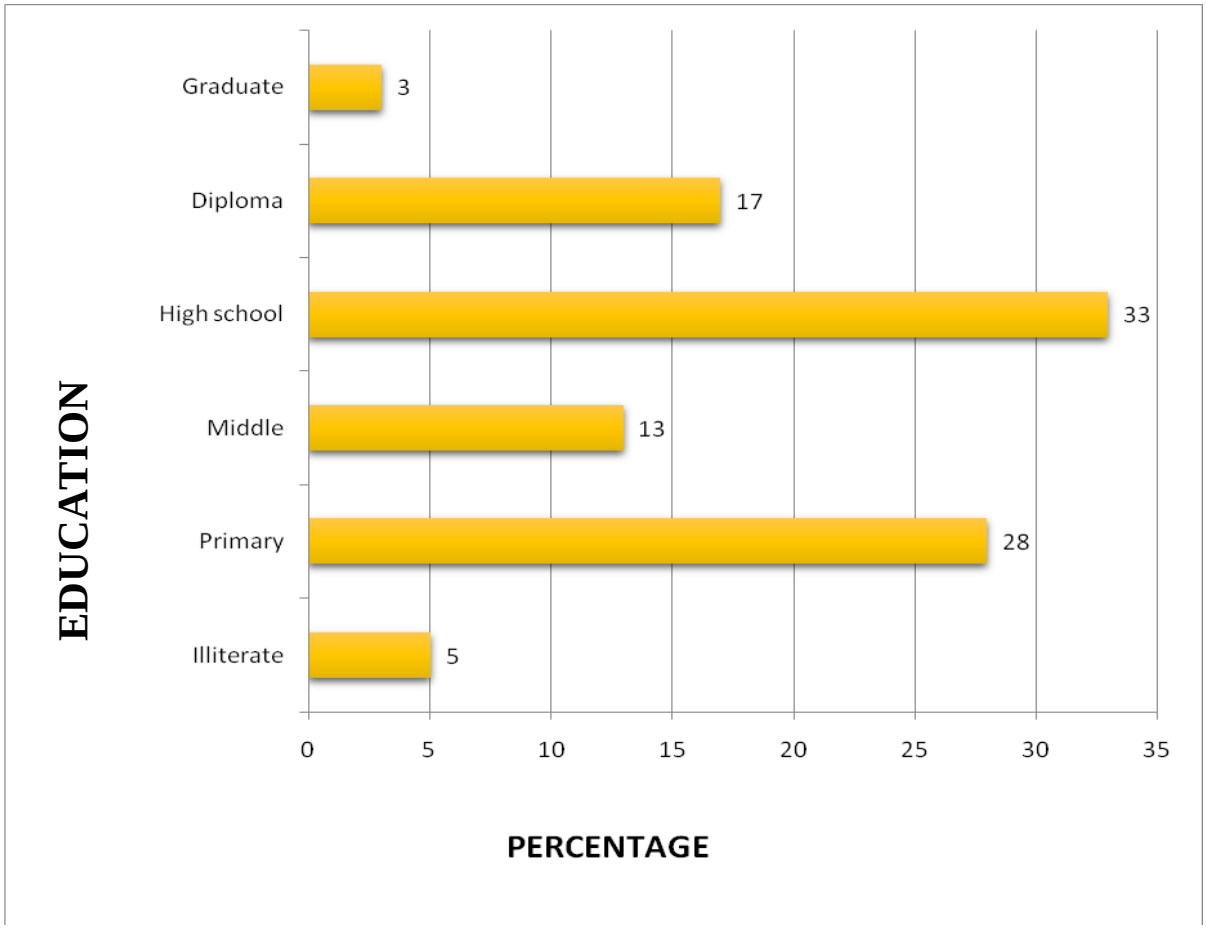
Patients from the Hindu religion are dominating the study population (78%).

PICTURE 1: AGE DISTRIBUTION OF PATIENTS



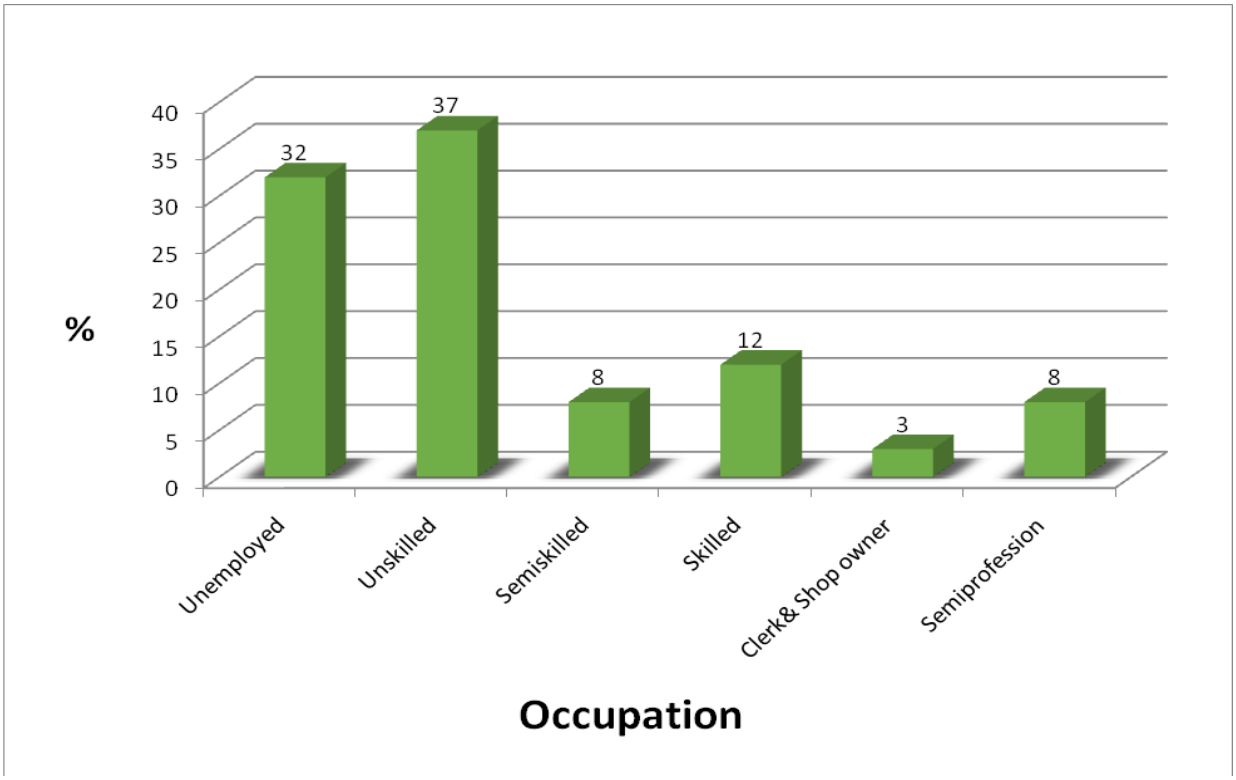
47% of the patients were within the age group of 20-35 years. 77% were lesser than 35 years of age , only 24% were greater than 35 years and only 7% were greater than 50 years.

PICTURE 2 : EDUCATION OF STUDY POPULATION



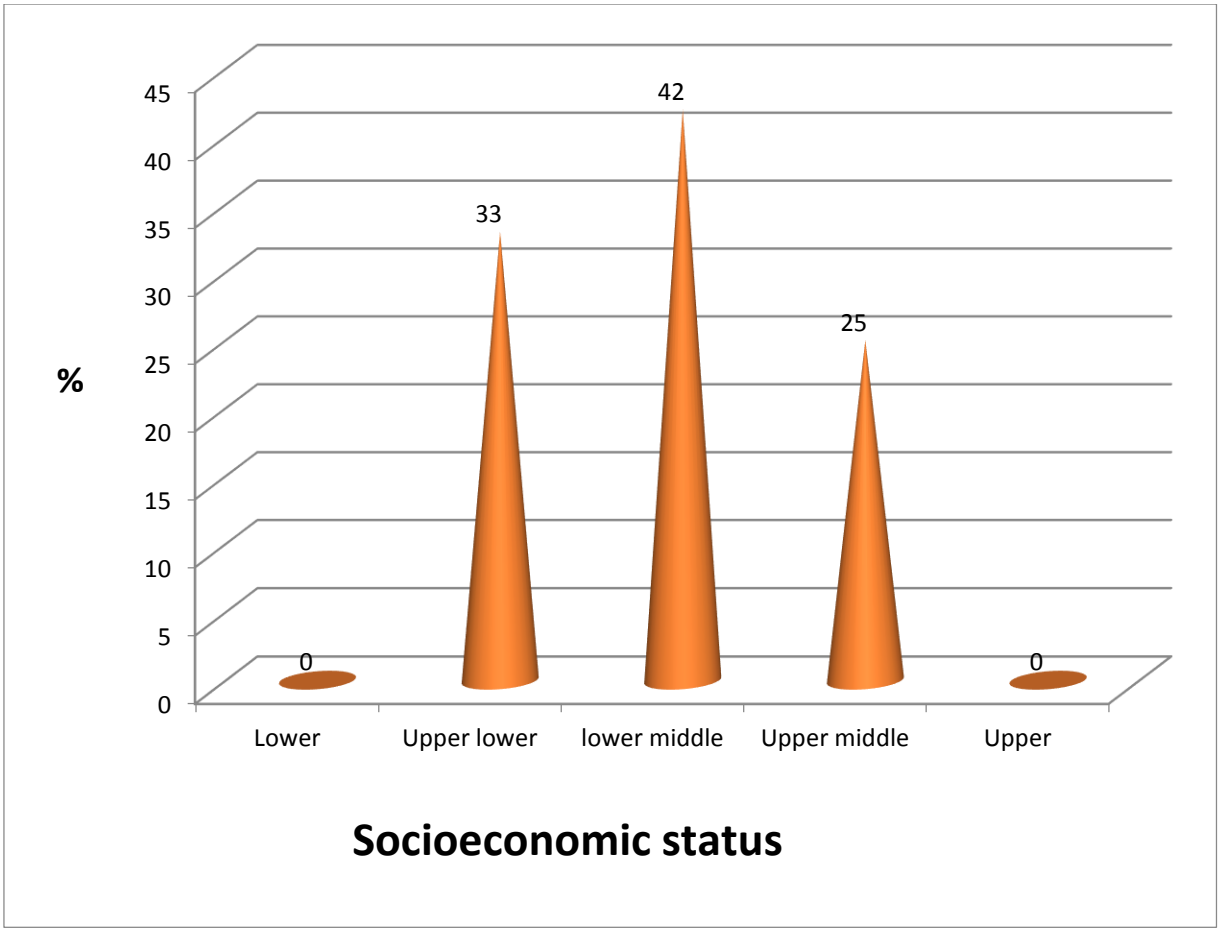
Among the study population only 3% were graduates and there were no post graduates and only 5% were illiterate. 53% had education upto high school or above.

PICTURE 3 : OCCUPATION OF THE STUDY POPULATION



Majority of patients were either unemployed (32%) or unskilled labourers (37%) and only 8% were semi-professionals and there were no professionals.

PICTURE 4 : SOCIO-ECONOMIC STATUS OF THE PATIENTS.



There were no patients from the lower and upper socio economic status. Majority 67% belonged to the middle socioeconomic status.

(lower middle class 42% & upper middle class 25%).

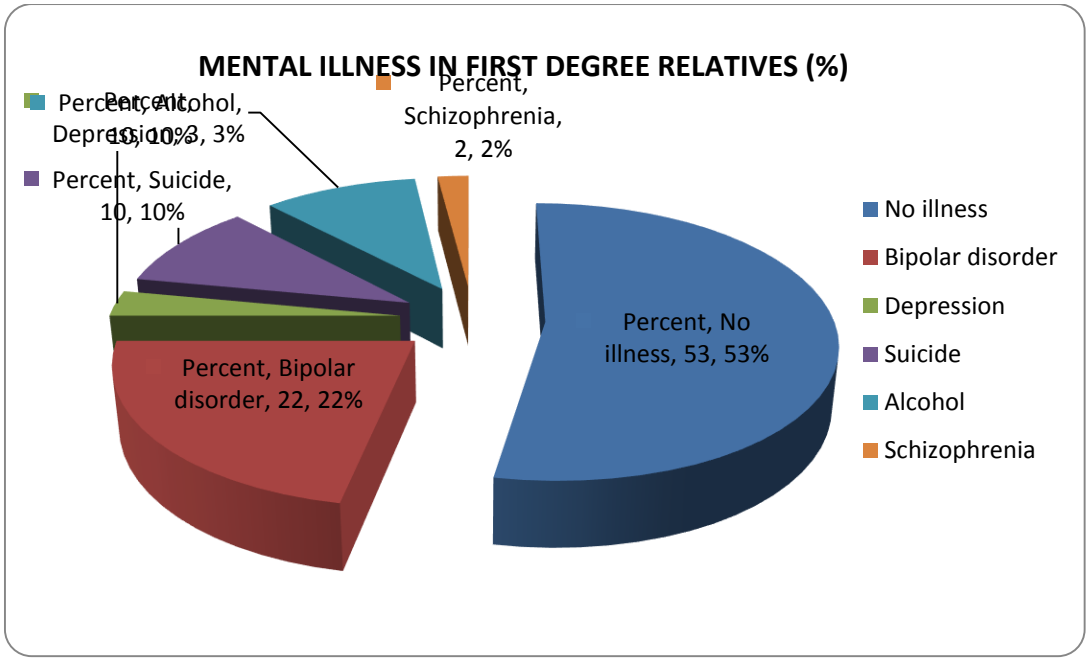
TABLE 9 : SHOWING FAMILY HISTORY OF STUDY POPULATION

Disorder	Relatives

	Frequency	Percent
No illness	23	38
Bipolar disorder	21	35
Depression	3	5
Suicide	9	15
Alcohol	6	10
Schizophrenia	3	5

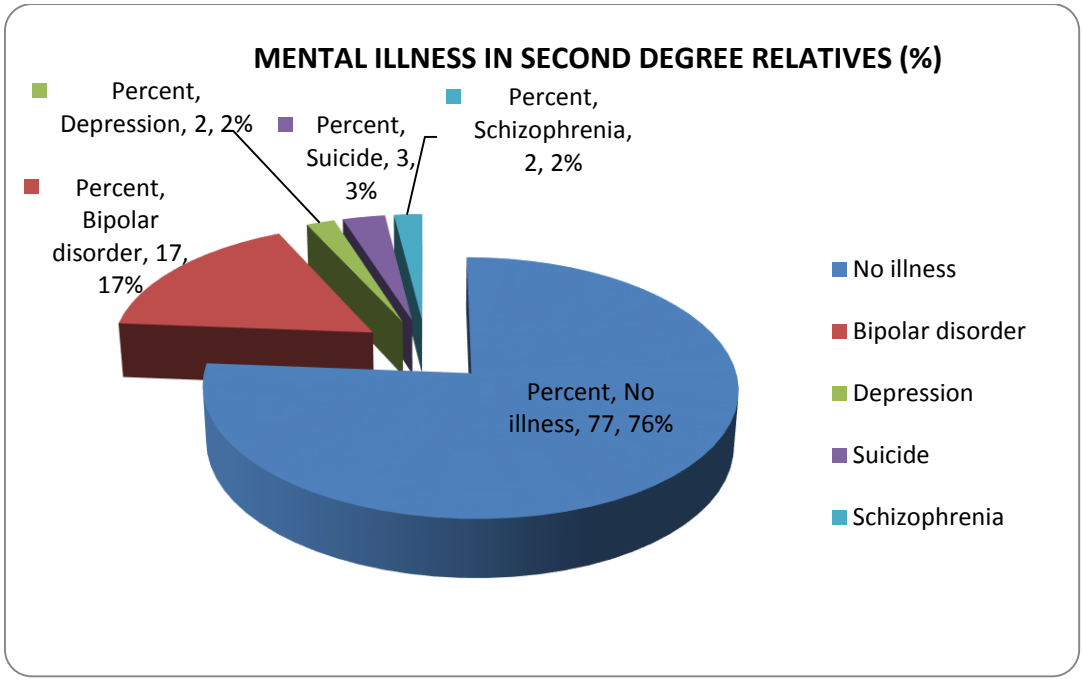
Among the 60 bipolar patients , 38% had no history of mental illness in family , 35% had family history of bipolar disorder , 15% had history of suicidal deaths in family, 10% had relatives who used alcohol and family history of unipolar depression and schizophrenia was each seen only in 5% of patients.

PICTURE 5 : PERCENTAGE OF MENTAL ILLNESS IN FIRST DEGREE RELATIVES OF STUDY POPULATION.



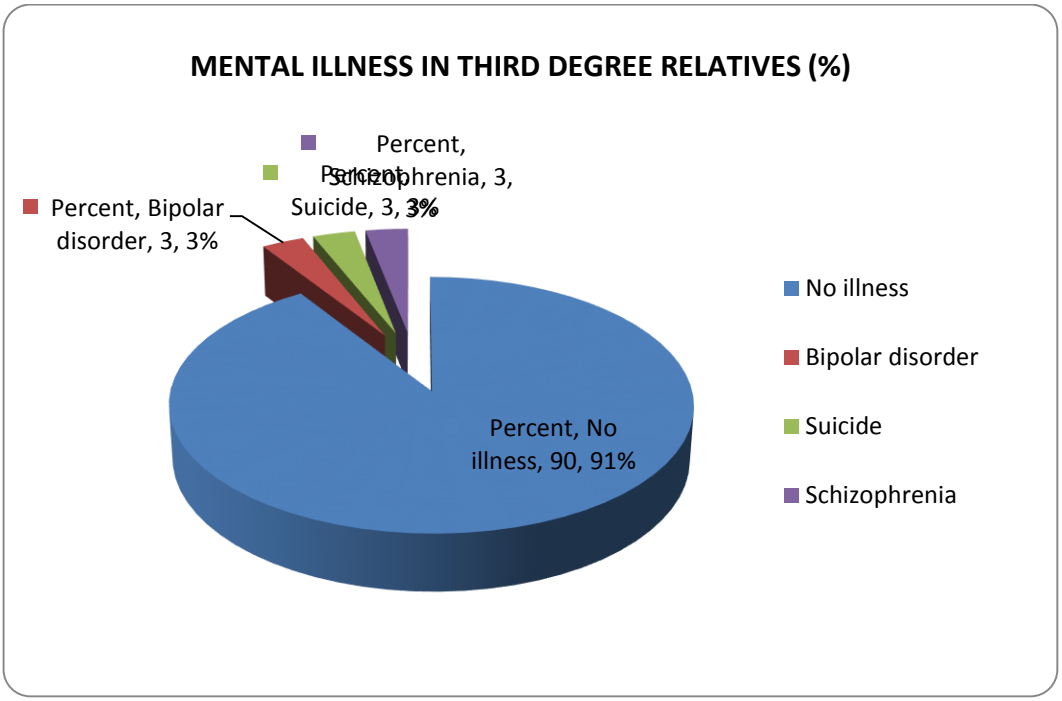
53% of the first degree relatives of the study population had no illness. 22% of first degree relatives had bipolar disorder, 10% used alcohol and 10% had committed suicide. Thus bipolar disorder was present to a greater extent than other psychiatric disorders in 1st degree relatives.

PICTURE 6: PERCENTAGE OF MENTAL ILLNESS IN SECOND DEGREE RELATIVES OF PATIENTS



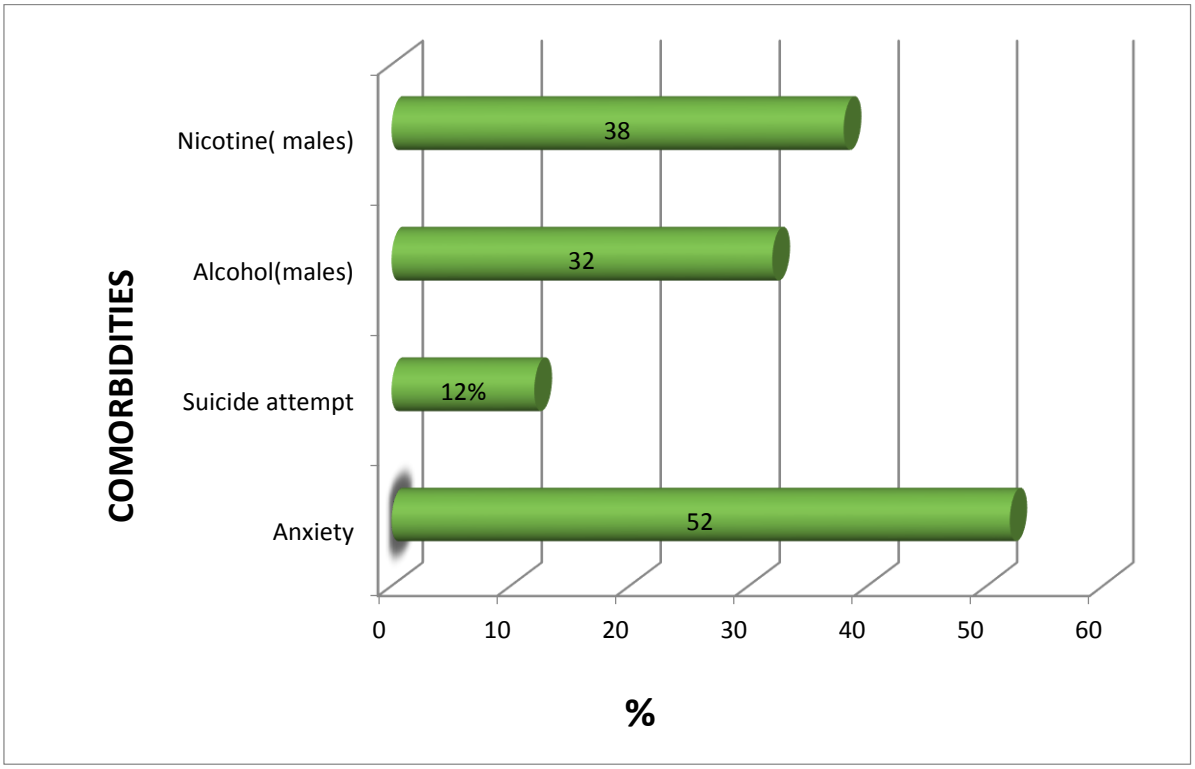
Among the 2nd degree relatives 77% had no illness constituting the majority and 17% had bipolar disorder .Even among the second degree relatives, bipolar disorder was present to a greater extent than other psychiatric disorders.

PICTURE 7: PERCENTAGE OF MENTAL ILLNESS IN THIRD DEGREE RELATIVES OF PATIENTS



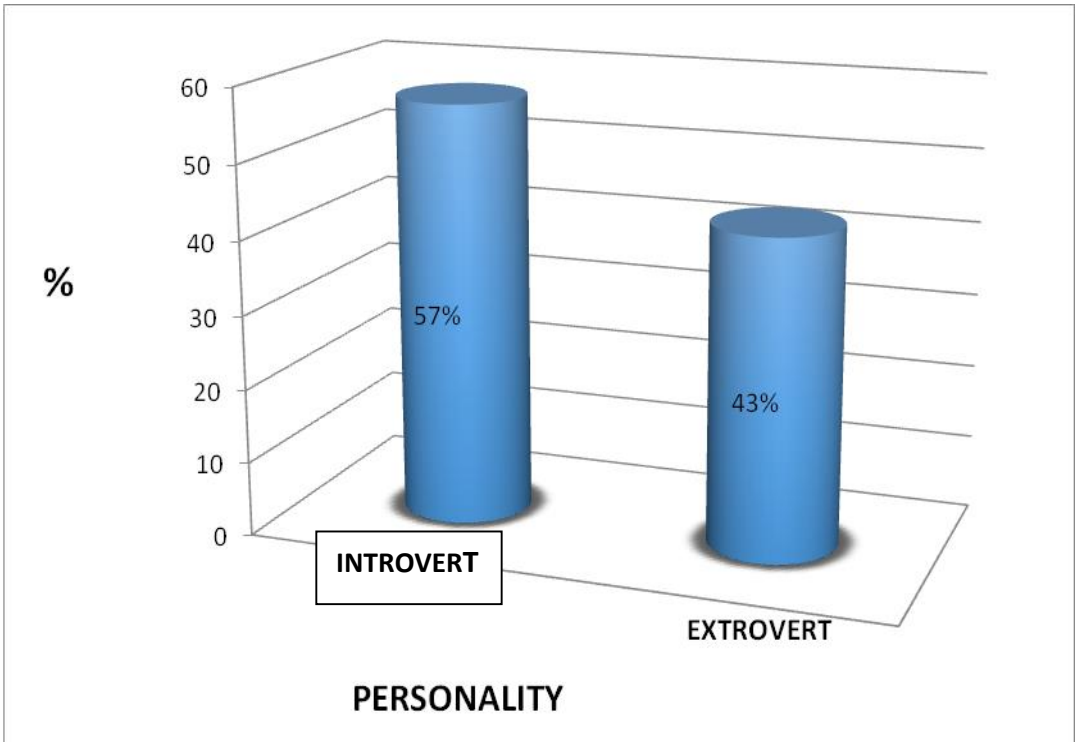
90% of the third degree relatives had no mental illness

PICTURE 8 : PERCENTAGE OF VARIOUS CO-MORBIDITIES IN THE PATIENTS STUDIED



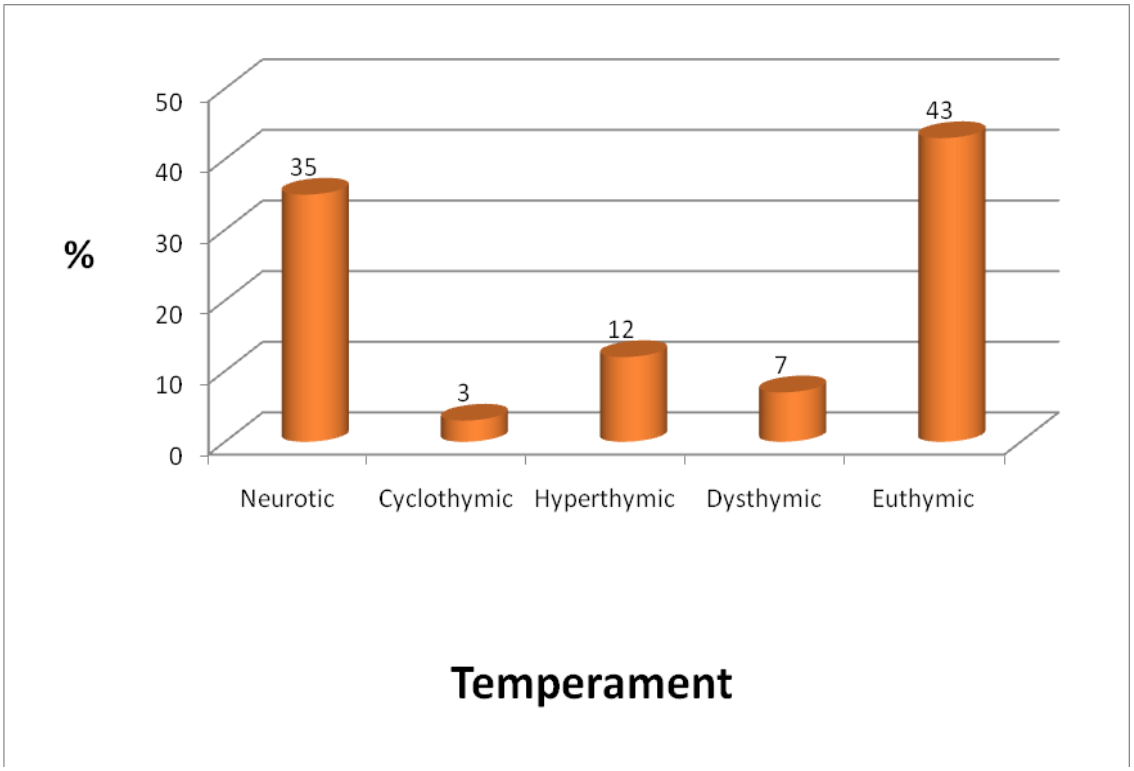
Anxiety was present in 52% of the bipolar patients and suicide attempts were seen only in 12%. There was no substance use among the female patients. Among the 34 male patients, 38% were smokers and 32% were alcoholics.

PICTURE 9: SHOWING THE PERSONALITY OF STUDY POPULATION



Out of the 60 bipolar patients, majority (57%) were introverts

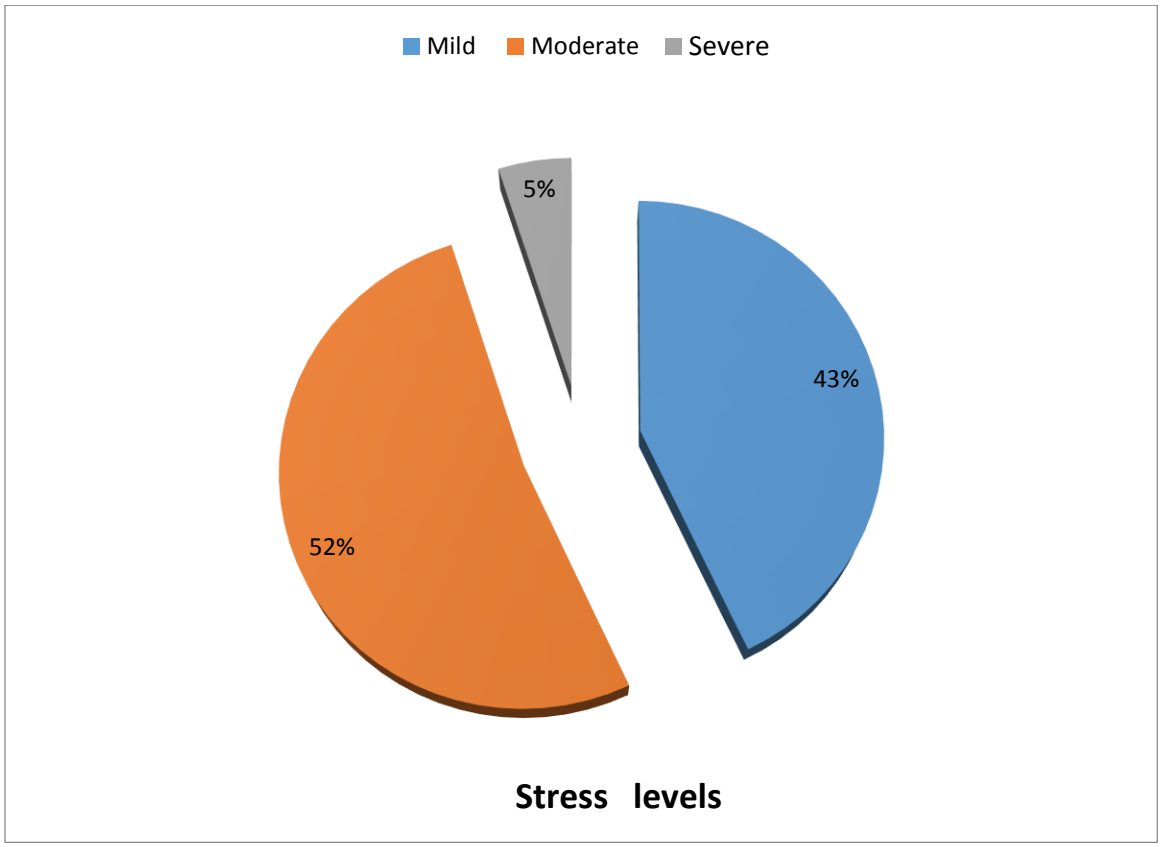
PICTURE 10 : SHOWING THE TEMPERAMENT OF PATIENTS



Among the bipolar patients who were studied, 57% some form of temperament instability with neurotic temperament constituting the majority (35%). Neurotic

temperament as defined above is a milder form of cyclothymia of 24 hour duration.

PICTURE 11: STRESS LEVELS OF PATIENTS AS MEASURED BY THE HOLMES-RAHE STRESS INVENTORY



42% of the patients had mild stress and low susceptibility to health problems. 52% of the patients had moderate stress implying 50% chance of stress induced health problems in next 2 years and only 5% of patients had severe stress raising the odds to about 80%, according to the Holmes-Rahe prediction model.

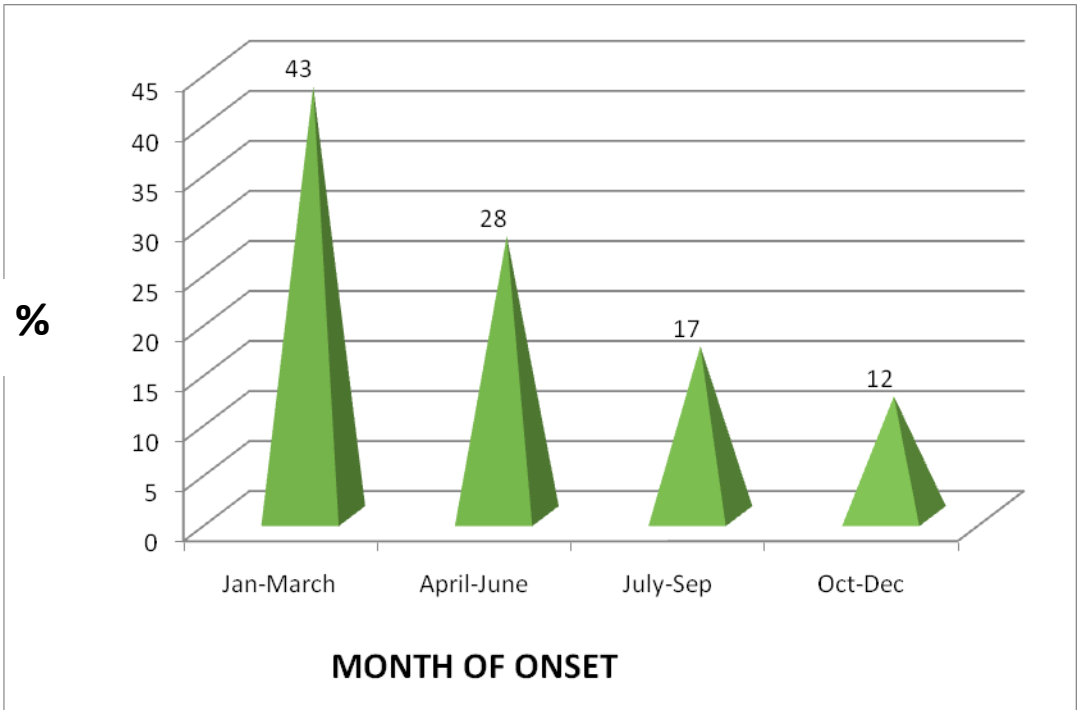
TABLE 10 : SHOWING THE CURRENT EPISODE OF BIPOLAR PATIENTS.

Current Episode	Frequency	Percent
Mania	51	85
Mixed	5	8
Hypomania	4	7
Total	60	100

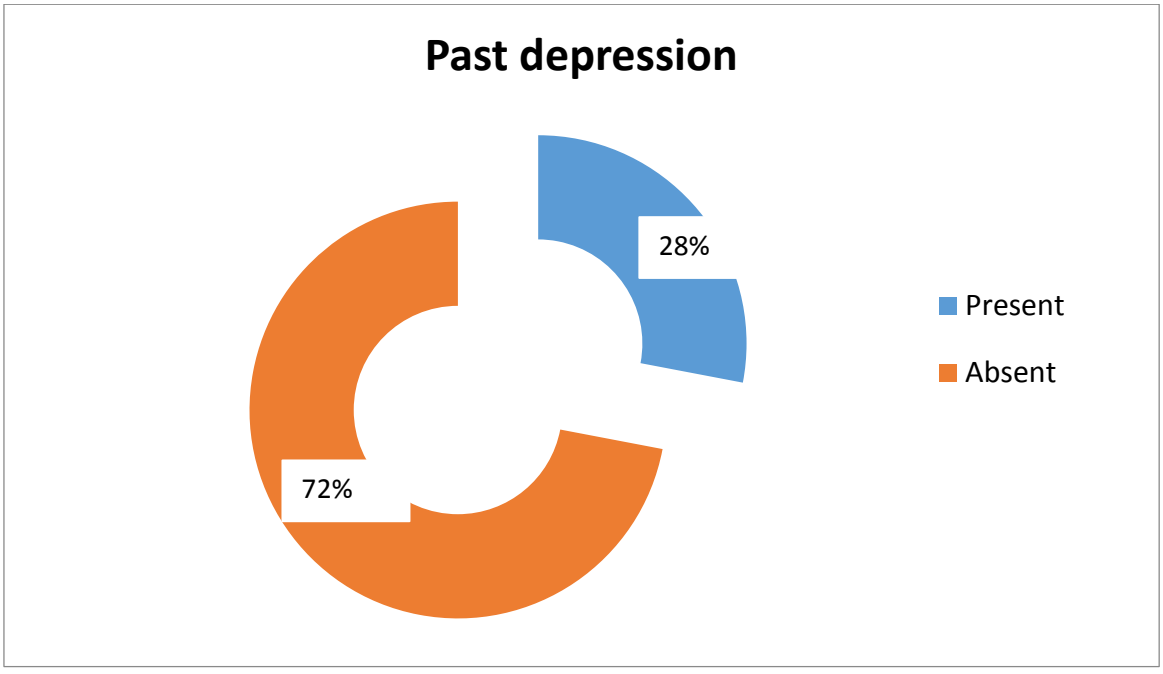
Among the 60 newly diagnosed bipolar patients, 85% had current episode mania, 7% had current episode hypomania and 8% had presented with mixed episode.

43% of patients had developed the current episode during the month of January to March, 28% during the month of April to June, 17% during the month of July to September and 12% during the month of October to December.

PICTURE 12: MONTH OF ONSET OF CURRENT EPISODE



PICTURE 13: PERCENTAGE OF PRIOR DEPRESSIVE EPISODES



In the group of 60 newly diagnosed bipolar patients, 17 patients (28%) had past history of depression. None of the patients had any prior manic

episodes. Hence 28% of bipolar patients had presented with depressive episode prior to the onset of first manic episode. All these patients had reported only one depressive episode in the past.

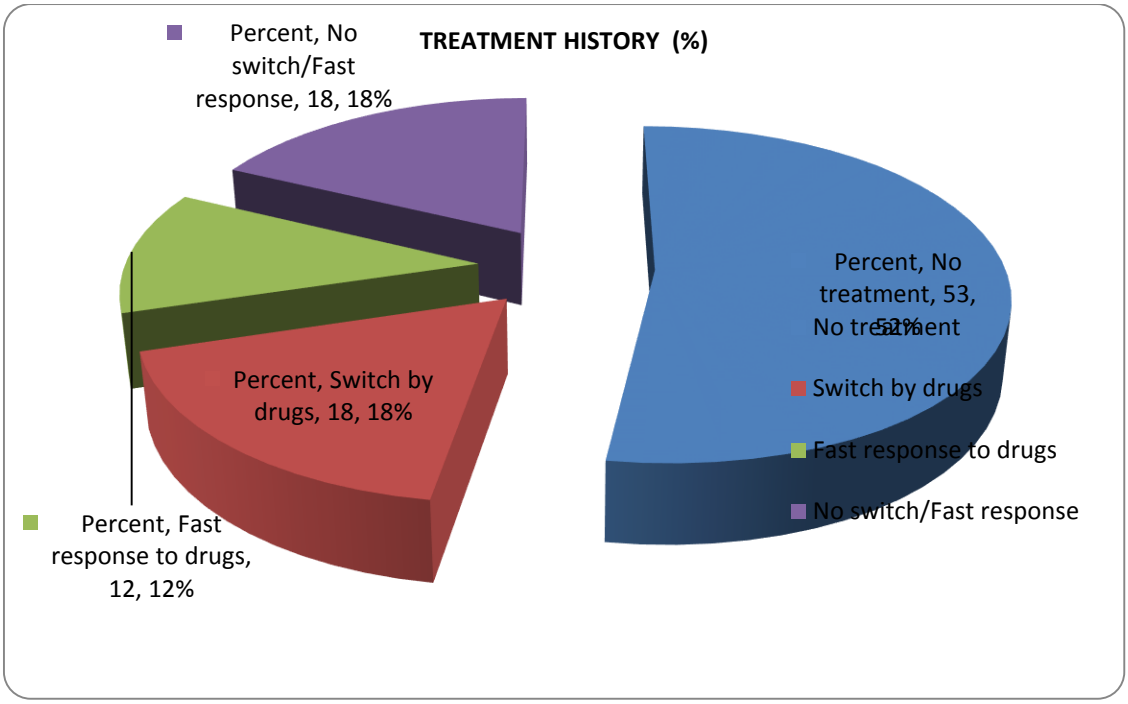
The age of onset of the initial depressive episode was 14 years to 34 years (mean age of onset was 24 years with a standard deviation of 10 years)

Out of the remaining 43 patients who had no prior depressive episodes, 63% had initial manic presentation, 7% had initially presented as mixed episode and 2% as hypomania. Thus the most common initial presentation was mania.

TABLE 11 : SHOWING POLARITY OF THE FIRST EPISODE IN THE STUDY POPULATION

Polarity of initial episode	Frequency	Percentage
Mania	38	63
Depression	17	28
Mixed episode	4	7
Hypomania	1	2
Total	60	100

PICTURE 14: TREATMENT HISTORY FOR THE PAST DEPRESSIVE EPISODE.



Among the 17 patients who had prior depressive episodes, nearly half the patients (53%) had not taken any treatment for depression . Majority of the patients did not have past records and majority had poor treatment compliance.

TABLE 12 : PRIOR DEPRESSION TREATED WITH ANTIDEPRESSANTS.

Antidepressant Treatment	Frequency	Percent
Switch to hypomania	3	37.5%
Fast response	2	25%

The remaining 47% (8 patients) who had been treated were diagnosed as unipolar depression and were prescribed antidepressants. Among them 37.5%

had switched to hypomania within 2 weeks and 25% had shown an immediate response to antidepressant.

TABLE 13: TIME SINCE ONSET OF INITIAL DEPRESSIVE EPISODE TO CORRECT DIAGNOSIS OF BIPOLARITY

Years to diagnose bipolarity	Number of Patients	Percentage
<1	5	29.41
1 to 3	9	52.94
>3	3	17.65

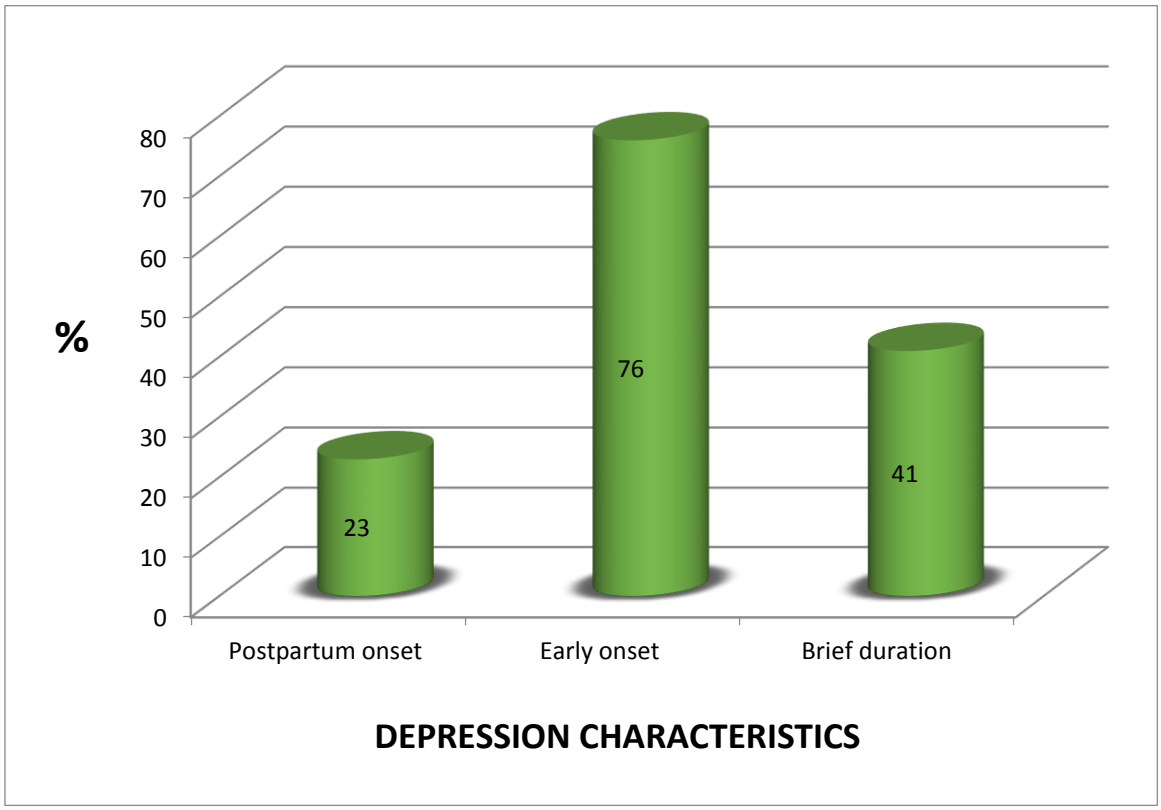
Of the 17 bipolar patients who reported past history of depression , 2 patients had been diagnosed as bipolar 3 months after the depressive episode , 3 patients were diagnosed 6 months after the depressive episode , 4 patients after 1 year, 4 patients after 2 years, 1 patient after 3 years , 2 patients after 15 years and 1 patient after 30 years.

Thus 82% of the patients had received a correct diagnosis within 3 years.

In this study, **the mean years taken for diagnosing bipolar disorder was 4.53 years with a standard deviation of 8.03**. There is a greater sample

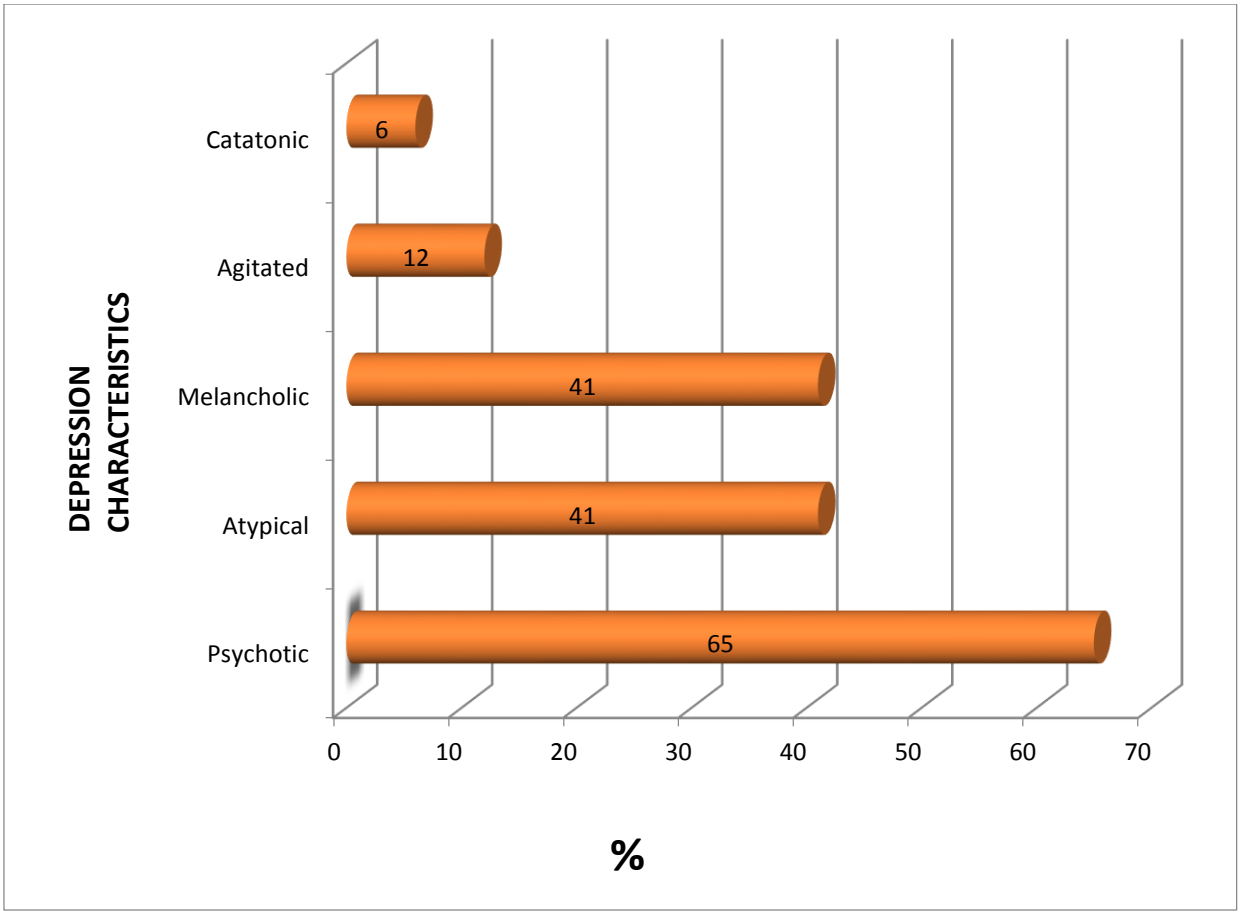
variation for this variable and hence mean could not be relied upon. But the **95% confidence interval was from 0.4019 to 8.656.** That is the years taken for correctly diagnosing bipolar disorder will fall between 0.4 years to 8.7 years for 95% of the population.

Picture 15: Characteristics of prior depressive episode in study population



In the prior depressive episode, majority **(76 %) had an early age of onset (< 25 years),** in 41% of the patients the depressive episode lasted less than 3 months , and among the female patients 23% had postpartum onset of depression.

PICTURE 16 : CHARACTERISTICS OF PRIOR DEPRESSIVE EPISODES IN STUDY POPULATION



Among the 17 patients who had past depressive episodes , **65% had depression with psychotic features** which constituted the majority, 41% had atypical depression, 41% had melancholic depression, 12% had agitated depression , 52% had co-morbid anxiety associated with depression as discussed previously and one patient had catatonic features associated with depression.

TABLE 14 : TOTAL NUMBER OF BIPOLAR SOFT SIGNS PRESENT DURING THE PAST DEPRESSIVE EPISODE.

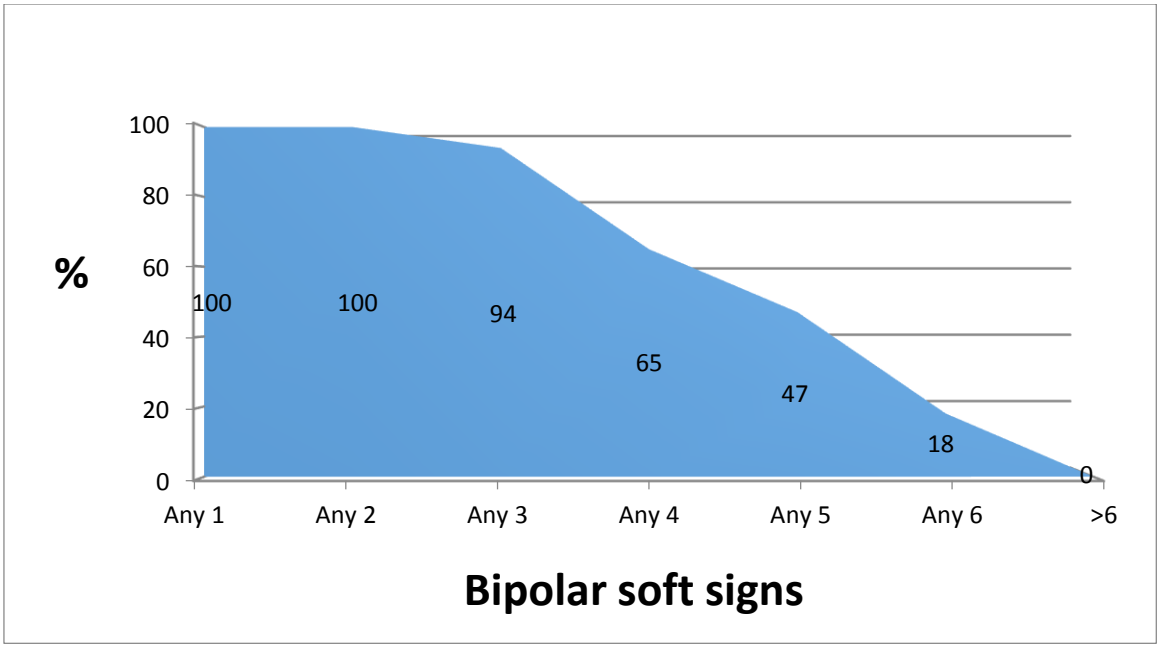
Bipolar soft signs	Number	Percent
Any 1	17	100
Any 2	17	100
Any 3	16	94
Any 4	11	65
Ant 5	8	47
Any 6	3	18
>6	0	0

Out of the bipolar soft signs as described by Ghaemi *et al* [22] (2002) , 11 signs had been described in this study which included age of onset less than 25 years , less than 3 months duration of depression , postpartum onset, psychotic depression, atypical depression, melancholic depression, agitated depression, anxious depression, hyperthymic temperament, family history of bipolarity and switch with antidepressants.

Among the 11 characteristics of bipolar depression that had been defined, 6 characteristics were present in 18% of patients, 5 characteristics in

47%, any 4 characteristics in 65% of patients, any 3 in 94% and any 2 in all the patients.

PICTURE 17: TOTAL NUMBER OF BIPOLAR SOFT SIGNS PRESENT DURING THE PAST DEPRESSIVE EPISODE.



The bipolar soft signs had been described in majority of the past depressive episodes. They could be used as a diagnostic tool for identifying bipolar depression.

The 60 newly diagnosed bipolar patients were divided into two groups for analysis. The 1st group included the 17 patients who had past history of depression. Group 2 included the remaining 43 patients who had no past history of depression.

GROUP 1- Bipolar patients with depression as initial presentation

GROUP 2- Bipolar patients with mania as initial presentation

TABLE 15 : COMPARING THE SEX DISTRIBUTION BETWEEN BOTH GROUPS.

Group	Male		Female		Staistical results
	Number	Percent	Number	Percent	
Group 1	4	24	13	76	χ^2 =10.608 P=0.001 N=60
Group 2	30	70	13	30	

76% were females and 24% were males in the patients initially presenting as bipolar patients. 70% were males and 30% were females in patients initially presenting as mania. **The p value was 0.001 which was statistically significant.**

Among the bipolar patients, females are more likely to present initially as bipolar depression and males are more likely to present initially as mania. Thus females are more likely to be misdiagnosed as unipolar depression.

PICTURE 18 : COMPARING THE SEX DISTRIBUTION BETWEEN BOTH GROUPS

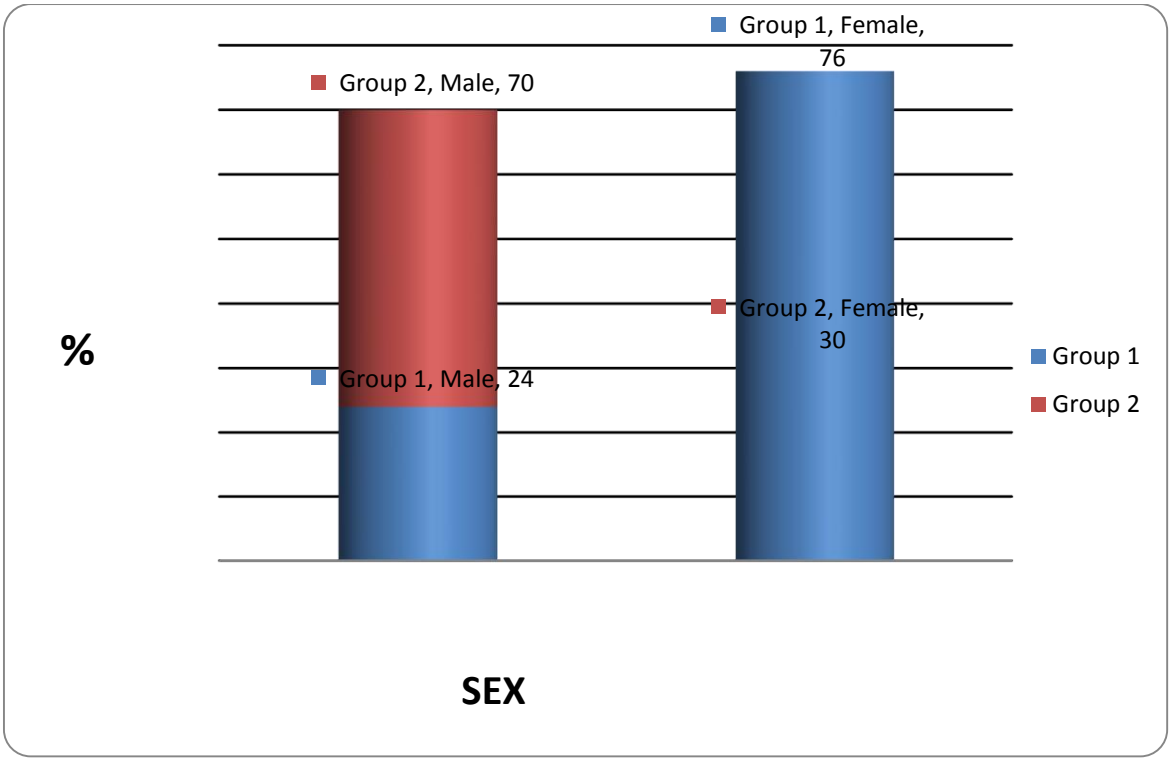


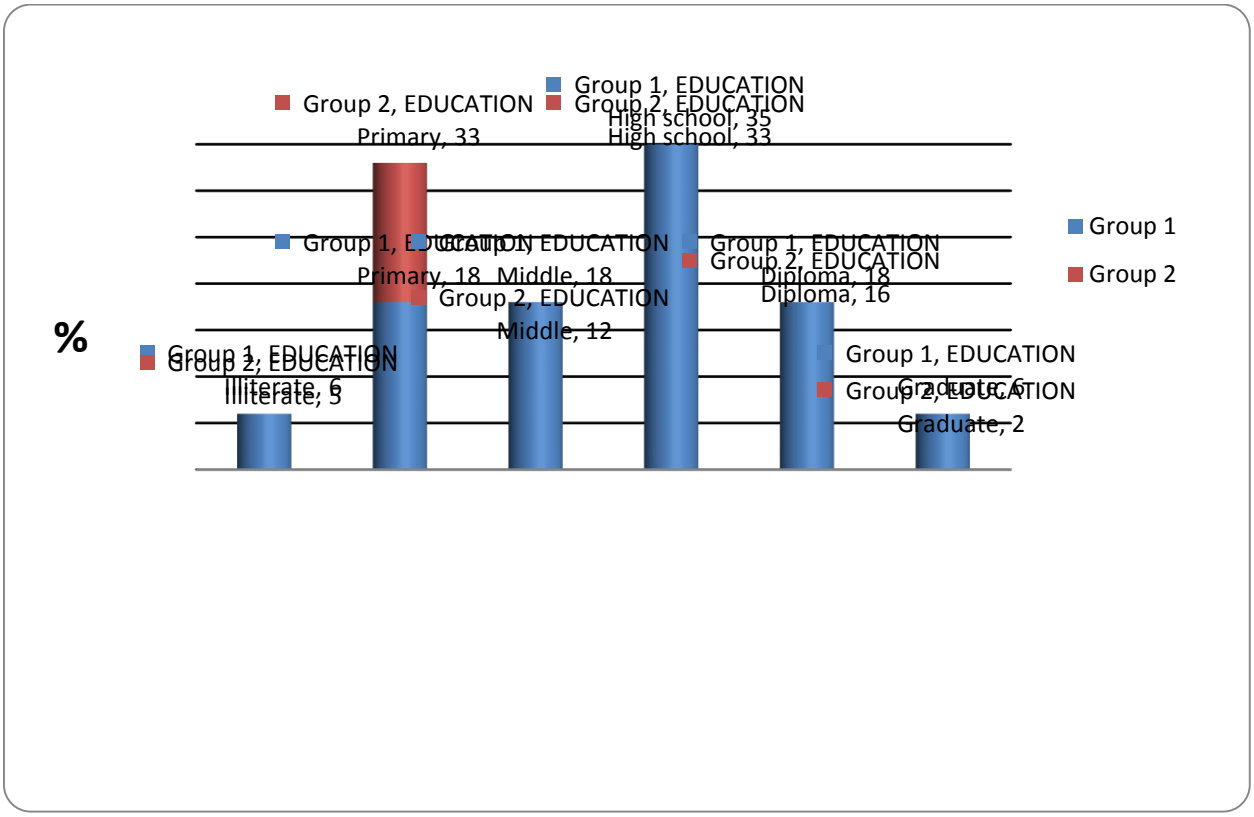
TABLE 16: COMPARING THE MARITAL STATUS OF BOTH GROUPS

Group	Unmarried		Married		Separated	
	Number	Percent	Number	Percent	Number	Percent
Group 1	9	53	8	47	0	0
Group 2	22	51	18	42	3	7

There was no significant difference in the marital status between those initially presenting as bipolar depression and those with mania as initial presentation.

The χ^2 =1.827 and p value was 0.53 which was statistically insignificant.

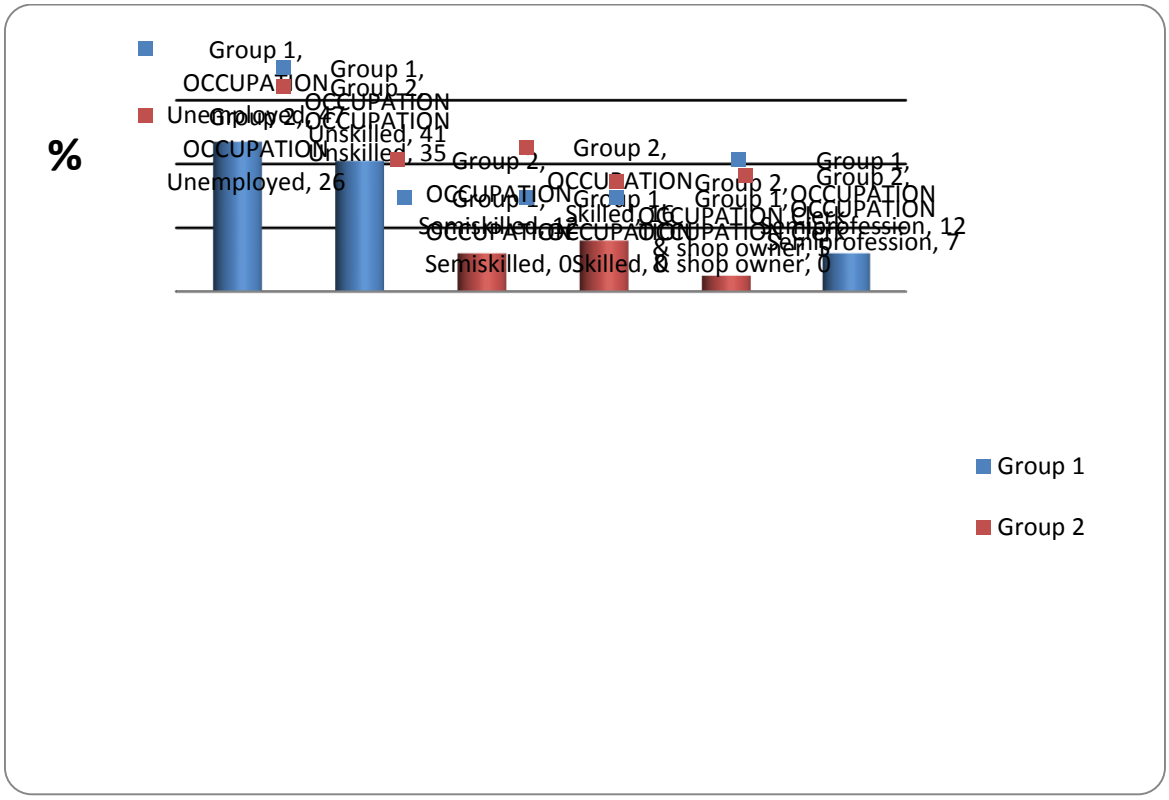
PICTURE 19 : COMPARING THE EDUCATIONAL STATUS OF BOTH GROUPS.



The educational status between both groups did not show any major difference.

The p value was 0.872 which was statistically insignificant

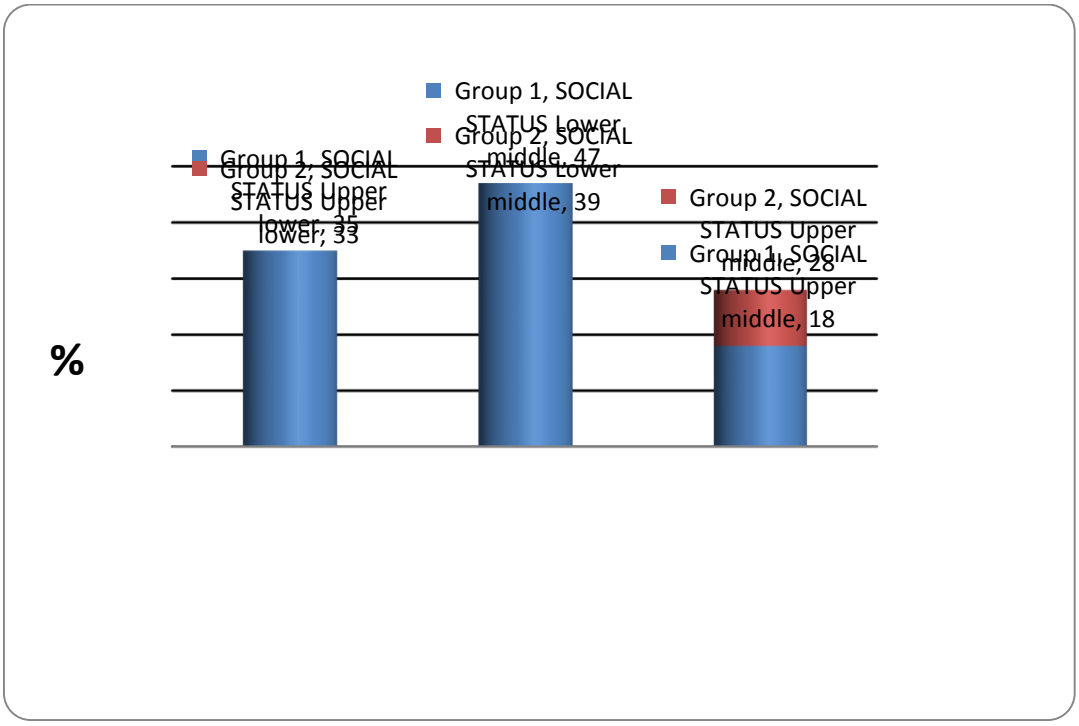
PICTURE 20: COMPARING THE OCCUPATIONAL STATUS OF BOTH GROUPS



Unemployed and unskilled laborers were more in the bipolar patients first presenting as depression (88%) as opposed to 60% in the patients with first manic presentation. Whereas patients exhibiting more skill in work were seen in those with initial manic presentation (40%) as opposed to 12% in patients initially presenting as bipolar depression.

The χ^2 =7.776 and p value was 0.19 which was statistically insignificant.

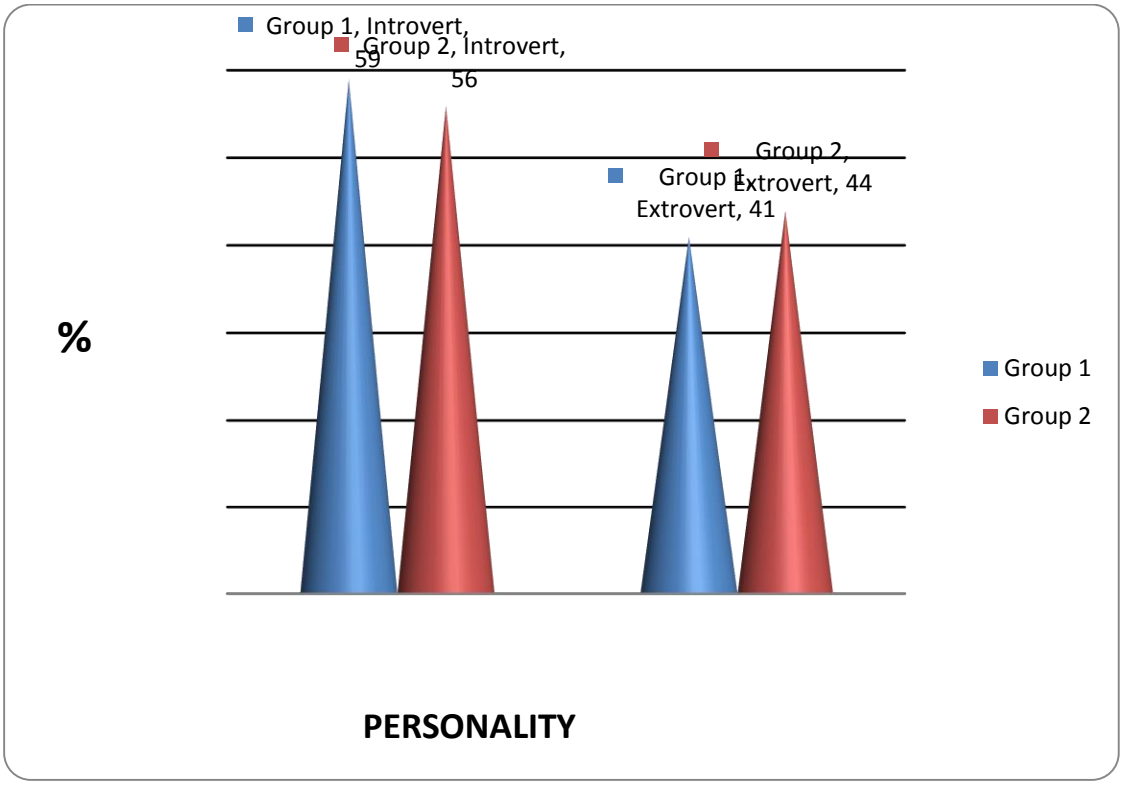
PICTURE 21 : COMPARING THE SOCIOECONOMIC STATUS OF BOTH GROUPS.



There was no major difference in the socioeconomic status between both groups with 65% of the patients in both groups belonging to the middle class.

The χ^2 =0.706 and p value is 0.703 which is statistically insignificant.

PICTURE 22 : COMPARING THE PERSONALITY IN BOTH GROUPS

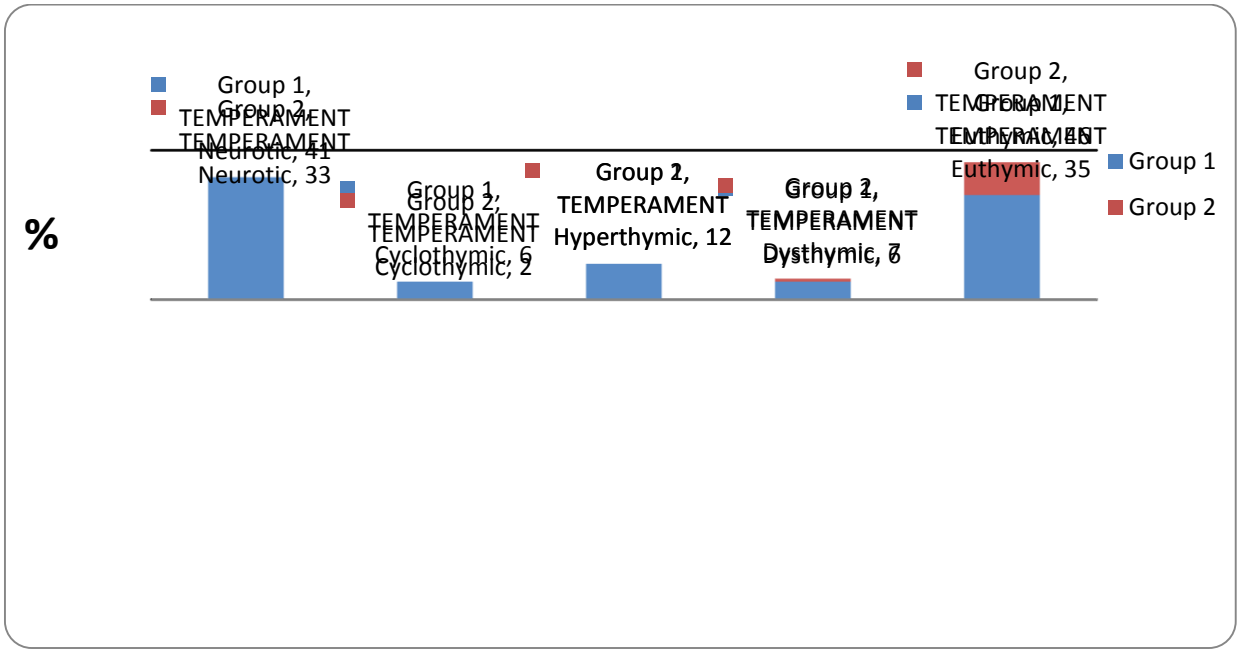


77A majority of patients in both groups were of introvert personality.

The p value was 0.832 which was statistically insignificant.

Euthymic temperament and neurotic temperament constituted the majority in both groups. But neurotic temperament was slightly more in patients presenting initially with depression and euthymic temperament was slightly more in patients initially presenting as mania. Neurotic temperament has been defined as a milder form of cyclothymia. The χ^2 =1.097 and p value was 0.895 which was statistically insignificant.

PICTURE23: COMPARING THE TEMPERAMENT OF BOTH GROUPS



PICTURE 24: COMPARING THE CO-MORBIDITIES IN BOTH GROUPS

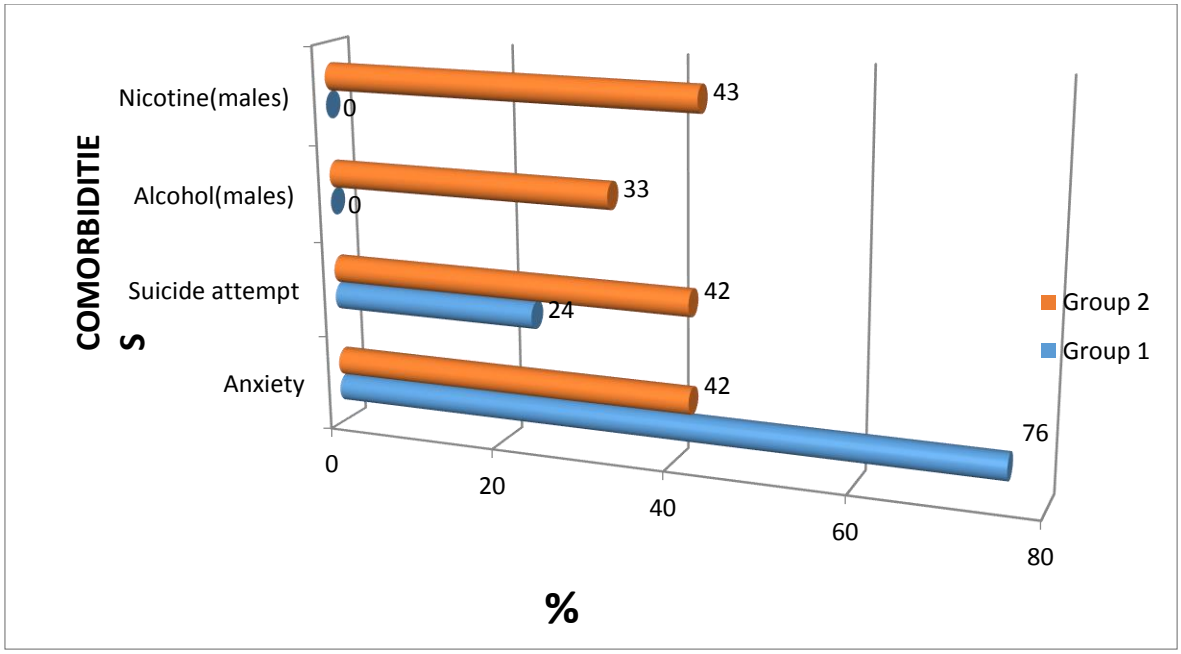


TABLE 17 : SHOWING COMPARISON OF ANXIETY AND SUICIDE ATTEMPTS IN BOTH GROUPS

Group	Anxiety			Suicide attempt		
	Number	Percent	Statistical results	Number	Percent	Statistical results
Group 1	13	76	χ^2 =5.844 P=0.016 N=60	3	24	χ^2 =0.823 P=0.364 N=60
Group 2	18	42		4	42	

Anxiety was more in bipolar patients having initial depressive episodes (76%).

The χ^2 =5.844 and 0.823 and p values for anxiety and suicide attempt was 0.016 and 0.364 respectively. p value for anxiety was statistically significant.

Among the BPAD patients first presenting as mania suicide attempts were higher (42%), when compared with those first presenting as depression (24%). The p value was 0.364 which was statistically insignificant.

Alcohol and nicotine usage in bipolar males was present only in the group where mania was the initial presentation and absent when depression was the initial presentation.

The p value for alcohol and nicotine usage was 0.169 and 0.094 respectively. Both values were statistically insignificant.

TABLE 18 : DIFFERENCE IN ALCOHOL AND NICOTINE USE AMONG MALES OF BOTH GROUPS

Group	Alcohol use			Nicotine use		
	Number	Percent	Statistical results	Number	Percent	Statistical results
Group 1	0	0	χ^2 =1.889 P=0.169 N=34	0	0	χ^2 =2.806 P=0.094 N=34
Group 2	10	33		13	43	

DISCUSSION

This study conducted among newly diagnosed bipolar patients, included 60 patients with current episode mania/hypomania/mixed features. Out of these 60 patients, 57% were males, 77% were lesser than 35 years of age and only 7% were greater than 50 years of age, only 43% were married , 78% were Hindus, 69% were unemployed/ unskilled labourers, 53% had education upto high school or above but only 3% were graduates and majority (67%) belonged to the middle socioeconomic status.

57% had temperamental instability in our study with neurotic temperament constituting the majority (35%) .This was lower than what was already observed. Angst et al [71] (2002) discussed that 85% of the population report subthreshold states falling within the mood spectrum. The remaining 15% he described as 'supernormal'. Koukopoulos [33] (2007) also reported that about half of the patients diagnosed as unipolar depression have either hyperthymic or cyclothymic temperament.

Alcohol use was seen in 32 % of males and nicotine use was seen in 38% of males included in our study This is slightly lower than what was described by Strakowski *et al* [80] (2000) who found alcohol use in 38-48% of patients and nicotine use in 46-80% of patients. In the Collaborative Depression Study, alcohol use was lower than that found in our sample (23.7%).

In our study, suicide attempts were found in 12%. Goodwin *et al* [4] (2007) had stated that suicide attempts are seen in about 50% of bipolar patients and

completed suicide in about 15% which is greater than what was observed in our study.

Among the 60 newly diagnosed bipolar patients included in our study, the prevalence of past depressive episodes was 28% (nearly ¼) . Thus in our study 28% of the bipolar patients had been considered as unipolar patients in the past (including both treated and untreated). This is in concordance with the NIMH collaborative depressive study where 1 in 4 of unipolar patients was reclassified as having bipolar disorder. Akiskal *et al* [17] (1995) had also reported similar rates. Higher rates of about 40% were stated by Ghaemi [13] (2013) and Angst [18] (2005) had reported even higher rates, showing that nearly half of the patients diagnosed as major depression converted to bipolar I or bipolar II disorder . Surveys of bipolar patients by Hirschfeld *et al* [10] (2003b) and Lish *et al* [10] (1994) supported a 50% rate of misdiagnosis with the very early studies showing low rates of about 5% to 10%.

In our study, after the initial depressive episode, 82% had converted to bipolarity within 3 years and the remaining 18% only after 15 years. Thus it could be concluded that, if a patient diagnosed as MDD were to develop a manic or hypomanic episode, it is more likely to happen in the initial few years. Higher conversion rates were reported in the initial few years of misdiagnosis in several other studies. In the CDS study, the diagnostic conversion from unipolar depression to bipolar disorder was 2.5% per year for the first 5 years

and 0.5% per year thereafter as reported by Aiken *et al* [49] (2015) . Angst *et al* [7] (2005) also reported higher rate of conversion to bipolarity in the first 4 years.

The common initial presentation in bipolar patients in our study was mania. Goodwin and Jamison [4] (2007) stated that the most common first mood episode in bipolar disorder appears to be a depression and not mania and the findings of the present study contradicted this.

In our study, the mean years taken for correctly diagnosing bipolar disorder is 4 ½ years (SD-8.03) .Thus the time taken for 95% of the population to receive a correct diagnosis is 5 months to 8.7 years (95% confidence interval is 0.4 to 8.7). As per literature, on an average only after 8 years a correct diagnosis of bipolar disorder is made. Ghaemi *et al* [3] (2000) had described the delay in diagnosis in two studies, one study showing a delay of 7.5years (SD-9.8) and another study showing a delay 7 years for bipolar I & 12 years bipolar II disorder.

The age of onset of past depression in our study was from 14 years to 34 years (mean was 24 years with standard deviation of 10 years). Age of onset was less than 25 years in 76% of those who had presented with initial depression in our study. Studies by Goodwin *et al* [4] (2007) and Geller *et al* [47] (2001) studied unipolar patients with mean age at onset of study 12 years and 23 years respectively showed50% converting to bipolarity. But a similar study by Akiskal *et al* [17] (1995) with a initial mean age of more than 30 years showed

a lower rates of conversion to bipolarity of only 12%. Hantouche *et al* [46] (1998) in a French Multicentric study also showed that early age of onset characterised switch from unipolar to bipolar disorder II.

Goodwin *et al* [4] (2007) stated that an average untreated bipolar depression lasts 3 to 6 months and an untreated unipolar depression lasts 6 to 12 months. Hantouche *et al* (1998) also stated that bipolar depressive episodes last shorter and this finding was found in 41% of our patients who had past depressive episode.

Among the 60 bipolar patients included in our study, 38% had no history of mental illness in family, 35% had family history of bipolar disorder. In the CDS follow up study of the 108 who developed bipolar disorder, 19% had a family history of bipolarity. Craddock *et al* [59] (1999) had stated that bipolar disorder has a heritability of about 80-90%. Recent studies in bipolar disorder have suggested a heritability of about 85% as reported by Strakowski [60] (2012). Akiskal reported a high specifically for family history of bipolarity (98%).

Strakowski [60] (2012) had also stated that, in bipolar families, unipolar depression is more common than bipolar disorder but only 5% had family history unipolar depression in our study population.

In our study 37.5% of patients who were treated with antidepressants in their prior depressive episode had switched to hypomania within 2 weeks. Goldberg *et al* [62] (2003) stated that antidepressants could induce subthreshold hypomanic

states in bipolar patients and El-Mallakh *et al* [63] (2005) said that these subthreshold states might become chronic. Akiskal [61](2003) reported a high specifically for AD induced hypomania (100%). He stated that many patients with antidepressant induced hypomania/ mania progress to spontaneous hypomania/mania sooner or later [22] In the CDS follow up study of the 108 who developed bipolar disorder, 11% had developed antidepressant induced mania / hypomania which was less than what was observed in our study. Among the 17 patients who had past depressive episodes, 65% had depression with psychotic features. Mitchell *et al* [28, 26] (1992, 2001), Schatzberg *et al* [30] (1992) and Parker *et al* [29] (2000) had reported psychotic symptoms to be more common in bipolar depression than unipolar depression.

In our study 41% had atypical depression. Agosti and Stewart [23] (2001) , Benazzi [24,25] (1999 , 2000) , Akiskal *et al* [17](1995) , Ghaemi *et al* [22] (2002) and Mitchell *et al* [26] (2001) found atypical depressive symptoms to be more common in bipolar depression than unipolar depression.

Akiskal *et al* [39] (2005) and Benazzi *et al* [32] (2004) described agitated depression as a feature of bipolar depression which had been observed only in 12% of our patients who had past depressive episode.

Anxiety was seen in 52% of patients included in our study. Strakowski *et al* [80] (2000) had reported a similar rate for anxiety of about 42-77%. Koukopoulos

[40] (1999), Perugi *et al* [41] (1999) and Akiskal *et al* [42] (2002) had suggested a link between anxiety and bipolar depression.

In our study melancholic depression was found to a significant extent (41%). The availability of literature supporting the relation of melancholic depression to bipolar disorder is limited and controversial. The sure link between psychomotor agitation and bipolar depression conflicts the link between psychomotor retardation and bipolar depression (Mitchell *et al*. 1992 [28]). Among the female patients in our study, 23% had postpartum onset of depression. Postpartum episodes are more frequent in bipolar depression as reported by Freeman et al [55] (2001).

In our study hyperthymic temperament was found only in 12% of patients who presented with past depression. Koukopoulos [33] (2007) reported that about half of the patients diagnosed as unipolar depression have either hyperthymic or cyclothymic temperament. Henry *et al* [56] (2001b), Cassano *et al* [57] (1992) and Perugi *et al* [58] (2001) stated that hyperthymic personality is a feature of bipolarity.

Stephens *et al* [50] (1991) and Judd *et al* [51] (1998) reported that unipolar patients are likely to be symptom free for about a decade. Tohen *et al* [52] (1990) and Kessing *et al* [53] (1998) reported recurrent depressive episodes in bipolar disorder. But this finding was not replicated in our study.

Females (76%) more likely to present initially as bipolar depression and males (70%) more likely to present initially as mania (The p value was 0.001 which is statistically significant) . In our study anxiety was more in patients initially presenting as bipolar depression (The p value was 0.016 which is statistically significant). Thus Female bipolar patients are more likely to have depression as the initial presentation and hence more likely to be misdiagnosed and also patients with comorbid anxiety are more likely to have depression as the initial presentation.

The presence of the soft signs poses a reason for reassessing a diagnosis of unipolar depression. Katzow *et al* (2003) stated that there is no guideline as to how many of the symptoms need to be present. But more symptoms increase the likelihood of bipolarity. Out of the bipolar soft signs as described by Ghaemi *et al* [22] (2002) , 11 signs had been described in our study which included age of onset less than 25 years , less than 3 months duration of depression , postpartum onset, psychotic depression, atypical depression, melancholic depression, agitated depression, anxious depression, hyperthymic temperament, family history of bipolarity and switch with antidepressants and among them 6 characteristics were present in 18% of patients, 5 characteristics in 47% , any 4 characteristics in 65% of patients, any 3 in 94% and any 2 in all the patients. The bipolar soft signs had been described in majority of the past

depressive episodes. They could be used as a diagnostic tool for identifying bipolar depression.

Overall in studies till date, atypical depression and psychotic depression and are well established presentations in bipolar depression. Anxious, agitated and melancholic presentations are found to differ between groups and further research needed to establish associations. But in this study all the above features were found to a significant extent.

CONCLUSION

Based on the above findings and statistical analysis the following conclusions are made:

- Nearly one fourth of the bipolar patients had experienced prior depressive episodes before the onset of first manic episode.
- The common initial presentation in bipolar disorder is mania (63%)
- 82% of the bipolar patients with depression as initial presentation had developed manic episodes within 3 years.
- The time taken for 95% of the population to receive a correct diagnosis of bipolarity is 5 months to 8.7 years. **(**95% confidence interval was from 0.4019 to 8.656)
- Female bipolar patients are more likely to have depression as the initial presentation and hence more likely to be misdiagnosed. Patients with

comorbid anxiety are also more likely to have depression as the initial presentation.

- The soft signs of bipolarity such as family history of bipolarity, switch with antidepressants, early age of onset, brief duration of depression, anxious depression, psychotic, melancholic and atypical depression was present to a significant extent in the initial depressive episode. Also postpartum onset, agitated depression & hyperthymic temperament was present to lesser extent but recurrent depressive episodes were not found in any patient in our study. Hence validating the bipolar spectrum concept would aid in the better diagnosis of bipolar disorder.

LIMITATIONS

- These findings were obtained from a tertiary care government setting and may differ from those obtained at a primary care setting or a private sector.
- The sample size is small as only newly diagnosed patients could be included in the study.
- Since our study was done retrospectively, it is subject to recall bias and the description of past depressive episode lacks the expertise of a trained clinician.
- Majority of the studies available were prospective studies leading to difficulty in comparison.
- Since our sample had included only bipolar patients, comparison between the phenomenology of bipolar and unipolar depression could not be done.
- Since the temporal correlation of prior substance abuse could not be clearly established due to recall bias, it was considered as a comorbidity.

FUTURE DIRECTIONS

- More rigorous and methodological studies are necessary for clarifying the difference between bipolar and unipolar depression.

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SEMISTRUCTURED PROFORMA

AGE: < 20yr / 21-30 yr / 31-40 yr / > 40yr SEX: Male / Female
RURAL / URBAN
EDUCATION: Illiterate/ Primary / Higher secondary / Graduate /Postgraduate
Discontinued: yes/no
OCCUPATION : Unemployed / Unskilled/ Semiskilled/ Skilled
MARTIAL STATUS : Married / Unmarried / Widow or Separated CHILDREN : Yes / No
SOCIAL STATUS: Lower / Middle / Upper RELIGION: Hindu /Muslim /Christian/ Change

MONTH OF INTAKE EPISODE ONSET: jan- march/ april-june/ july- sep / oct- dec
POLARITY OF INTAKE EPISODE :Mania / Hypomania / Mixed
: with/without psychotic symptoms
: Antidepressant induced mania/hypomania
Prior undiagnosed manic/hypomanic episode: yes/no
Prior depressive episode : yes/no
No of depressive episodes :
Duration of depressive episode
Treatment with ECT : yes/no
Treatment with antipsychotics : yes/no
Treatment with antidepressants : yes/no
Inpatient management : yes/no
Duration of treatment :
Antidepressant wear off : yes/no
Lack of response to >3 antidepressants: yes/no
Years for mania conversion :
DEPRESSIVE EPISODE CHARACTERISTICS
Duration :
Early onset : yes/ no
Brief episode (<3months) : yes/no
Psychotic depression : yes/ no
Postpartum depression : yes/no
Atypical / melancholic /catatonic
Anxiety symptoms : yes/no
Suicide attempt : yes /no

COMOBIDITY
Anxiety disorder : yes/no
Substance abuse : yes / no
alcohol / cigarette/cannabis /others
Sucideattempt : yes / no
no of attempts :
FAMILY HISTORY :
Bipolar / Depression/ Suicide / Anxiety / Schizophrenia / Substance / Postpartum Psychosis
MENSTRUAL HISTORY : Regular cycles / irregular cycles / menopause
EXTROVERT / INTROVERT
NEUROTICISM : yes/no
TEMPERAMENT : Depressive / Hyperthymic / Cyclothymic / Neurotic/ Euthymic

Modified Kuppuswamy rating scale (proposed updating for January 2017)

Education of head of family				**Score**
Profession or honours				7
Graduate or postgraduate				6
Intermediate or post high school diploma				5
High school certificate				4
Middle school certificate				3
Primary school certificate				2
Literate				1
Occupation of head of family				
Profession				10
Semi-profession				6
Clerical, Shop-owner				5
Skilled worker				4
Semi-skilled worker				3
Unskilled worker				2
Unemployed				1
Monthly income of family				
In 1976	In 1998	In 2007	In 2017 (January 2017 CPI)	
>=2000	13408	>41430	19844	12
1000-1999	6704-13407	9922-19843	20715-41429	10
750-999	5028-6703	7441-9921	15536-20714	6
500-749	3352-5027	4961-7440	10357-15535	4
300-499	2011-3351	2976-4960	6214-10356	3
101-299	677-2010	1002-2975	2092-6213	2
<=100	<676	<1001	<2091	1
Socioeconomic class				**Total score**
I	Upper			26-29
II	Upper middle			16-25
III	Lower middle			11-15
IV	Upper lower			5-10
V	Lower			<5

Young Mania Rating Scale (YMRS)

1. Elevated Mood
   0 Absent
   1 Mildly or possibly increased on questioning
   2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
   3 Elevated; inappropriate to content; humorous
   4 Euphoric; inappropriate laughter; singing

2. Increased Motor Activity-Energy 0 Absent
   1 Subjectively increased
   2 Animated; gestures increased
   3 Excessive energy; hyperactive at times; restless (can be calmed)
   4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. Sexual Interest
   0 Normal; not increased
   1 Mildly or possibly increased
   2 Definite subjective increase on questioning
   3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
   4 Overt sexual acts (toward patients, staff, or interviewer)

4. Sleep
   0 Reports no decrease in sleep
   1 Sleeping less than normal amount by up to one hour
   2 Sleeping less than normal by more than one hour
   3 Reports decreased need for sleep
   4 Denies need for sleep

5. Irritability
   0 Absent
   2 Subjectively increased
   4 Irritable at times during interview; recent episodes of anger or annoyance on ward
   6 Frequently irritable during interview; short, curt throughout
   8 Hostile, uncooperative; interview impossible

6. Speech (Rate and Amount)
   0 No increase
   2 Feels talkative
   4 Increased rate or amount at times, verbose at times
   6 Push; consistently increased rate and amount; difficult to interrupt
   8 Pressured; uninterruptible, continuous speech

7. Language-Thought Disorder 0 Absent
   1 Circumstantial; mild distractibility; quick thoughts
   2 Distractible, loses goal of thought; changes topics frequently; racing thoughts
   3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
   4 Incoherent; communication impossible

8. Content
   0 Normal
   2 Questionable plans, new interests
   4 Special project(s); hyper-religious
   6 Grandiose or paranoid ideas; ideas of reference
   8 Delusions; hallucinations

9. Disruptive-Aggressive Behavior
   0 Absent, cooperative
   2 Sarcastic; loud at times, guarded
   4 Demanding; threats on ward
   6 Threatens interviewer; shouting; interview difficult
   8 Assaultive; destructive; interview impossible

10. Appearance
   0 Appropriate dress and grooming
   1 Minimally unkempt
   2 Poorly groomed; moderately disheveled; overdressed
   3 Disheveled; partly clothed; garish make-up
   4 Completely unkempt; decorated; bizarre garb
11. Insight
   0 Present; admits illness; agrees with need for treatment
   1 Possibly ill
   2 Admits behavior change, but denies illness
   3 Admits possible change in behavior, but denies illness
   4 Denies any behavior change

THE MOOD DISORDER QUESTIONNAIRE

Instructions: Please answer each question to the best of your ability.

	YES	NO
1. Has there ever been a period of time when you were not your usual self and...		
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	O	O
...you were so irritable that you shouted at people or started fights or arguments?	O	O
...you felt much more self-confident than usual?	O	O
...you got much less sleep than usual and found you didn't really miss it?	O	O
...you were much more talkative or spoke much faster than usual?	O	O
...thoughts raced through your head or you couldn't slow your mind down?	O	O
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	O	O
...you had much more energy than usual?	O	O
...you were much more active or did many more things than usual?	O	O
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	O	O
...you were much more interested in sex than usual?	O	O
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	O	O
...spending money got you or your family into trouble?	O	O
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	O	O

3. How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights? *Please circle one response only.*

No Problem Minor Problem Moderate Problem Serious Problem

4. Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	O	O
5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?	O	O

The Patient Health Questionnaire (PHQ-9)

Patient Name _____ Date of Visit _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	**Not At all**	**Several Days**	**More than Half the Days**	**Nearly Every Day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Column Totals _____ + _____ + _____

Add Totals Together _____

10. If you checked off any problems, how difficult have those problems made it for you to Do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

The Holmes-Rahe Life Stress Inventory

The Social Readjustment Rating Scale

INSTRUCTIONS: Mark down the point value of each of these life events that has happened to you during the previous year. Total these associated pointed.

Life Event	
1. Death of spouse	100
2. Divorce	73
3. Marital Separation from mate	65
4. Detention in jail or other institution	63
5. Death of a close family member	63
6. Major personal injury or illness	53
7. Marriage	50
8. Being fired at work	47
9. Marital reconciliation with mate	45
10. Retirement from work	45
11. Major change in the health or behavior of a family member	44
12. Pregnancy	40
13. Sexual Difficulties	39
14. Gaining a new family member (i.e. birth, adoption, older adult moving in, etc.)	39
15. Major business adjustment	39
16. Major change in financial state (i.e. a lot worse or better than usual)	38
17. Death of a close friend	37
18. Changing to a different line of work	36
19. Major change in number of arguments with spouse (i.e. a lot more or less)	35
20. Taking on a mortgage (for home, business, etc.)	31
21. Foreclosure on a mortgage or loan	30
22. Major change in responsibilities at work (i.e. promotion, demotion, etc.)	29
23. Son or daughter leaving home (marriage, college, military, etc.)	29
24. In-law troubles	29
25. Outstanding personal achievement	28
26. Spouse beginning or ceasing work outside the home	26
27. Beginning or ceasing formal schooling	26
28. Major change in living condition (i.e. new home, remodeling, deterioration, etc.)	25
29. Revision of personal habits (i.e. dress, associations, quit smoking, etc.)	24
30. Troubles with the boss	23
31. Major changes in working hours or conditions	20
32. Changes in residence	20
33. Changing to a new school	20
34. Major change in usual type and/or amount of recreation	19
35. Major change in church activity (i.e. a lot more or less)	19
36. Major change in social activities (i.e. clubs, movies, visiting, etc.)	18
37. Taking on a loan (i.e. car, tv, freezer, etc.)	17
38. Major change in sleeping habits (i.e. a lot more or less)	16
39. Major change in number of family get-togethers (i.e. a lot more or less)	15
40. Major change in eating habits (i.e. a lot more or less, eating hours, surroundings, etc)	15
41. Vacation	13
42. Major holidays	12
43. Minor violations of the law (i.e. traffic tickets, jaywalking, etc.)	11

Now, add up all the points you have to find your score.

150pts or less means a relatively low amount of life change and a low susceptibility to stress-induce health problems.
150 to 300pts implies about a 50% chance of a major stress-induced health problem in the next 2 years.
300pts or more raises the odds to about 80%, according to the Holmes-Rahe prediction model.

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
(மருத்துவ ஆய்வில் பங்கேற்பதற்கு)

ஆய்வு செய்யப்படும் தலைப்பு:
பங்கு பெறுவரின் பெயர்:
பங்கு பெறுவரின் வயது:

		பங்கு பெறுவர் இதனை ✓ குறிக்கவும்
	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	☐
	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்காள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன் எனக்கு கொடுக்கப்பட்டஅறிவுரைகளின் படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்றேன்.	☐

பங்கேற்பவரின் கையொப்பம் / ..... இடம் .....
கட்டைவிரல் ரேகை
பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....
ஆய்வாளரின் கையொப்பம் /..... இடம் .....
ஆய்வாளரின் பெயர் .....
மையம் .....
கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
சாட்சியின் கையொப்பம் /..... இடம் .....
பெயர் மற்றும் விலாசம் ....

MASTER TABLE

Sl.No.	Age	Sex	Marriage	Education	Occupation	SocialStatus	Religion	Month	1st degree relative	2nd degree relatives	3rd degree relatives	HRSI	Personality	Temperament	ANXIETY	SUICIDE	Alcohol	Nicotine	Episode	Past depression	disorder	Anti depressanttreatment	Postpartum onset	Earlyonset depression	Brief duration	Psychotic	Atypical	Melancholic	Catatonic	Agitated	Criteria
1	1	2	0	**6**	1	3	4	3	0	**3**	0	2	2	5	1	**1**	**0**	**0**	1	**1**	1	**1**	0	**1**	**1**	**1**	**1**	0	0	0	**1**
2	1	2	0	3	1	2	1	2	0	**1**	0	1	1	1	1	0	0	0	1	**1**	1	0	0	**1**	0	**1**	0	**1**	0	0	0
3	3	1	**1**	**5**	**6**	4	1	2	0	0	0	2	1	1	0	0	0	0	1	**1**	2	0	0	0	0	**1**	0	**1**	0	0	0
4	2	1	0	4	2	3	3	2	0	0	0	2	1	1	1	0	0	0	1	**1**	2	0	0	**1**	0	0	**1**	0	0	0	0
5	2	2	**1**	1	2	2	1	1	**1**	**1**	0	2	2	1	1	0	0	0	1	**1**	15	0	**1**	**1**	**1**	0	**1**	0	0	0	**1**
6	1	2	0	**5**	1	4	1	1	0	0	0	1	2	1	1	0	1	0	**3**	**1**	0.25	**1**	0	**1**	**1**	0	0	0	0	**1**	**1**
7	4	2	**1**	2	1	2	1	1	**3**	0	0	2	1	1	1	0	0	0	1	**1**	30	**2**	**1**	**1**	0	**1**	0	**1**	0	0	0
8	3	2	**1**	2	1	2	1	1	0	0	0	3	2	3	1	0	0	0	1	**1**	2	3	0	0	0	**1**	**1**	0	0	**1**	0
9	1	1	0	4	2	3	1	1	0	0	0	2	1	5	0	0	0	0	**3**	**1**	0.5	0	0	**1**	**1**	**1**	0	0	0	0	0
10	1	1	0	3	2	3	1	4	**1**	**5**	**1**	2	1	1	1	0	0	0	1	**1**	3	3	0	**1**	0	**1**	0	0	**1**	0	**1**
11	2	2	**1**	4	2	3	1	3	**1**	0	0	2	2	3	1	0	0	0	1	**1**	1	3	**1**	0	0	**1**	0	**1**	0	0	**1**
12	1	2	0	4	**6**	4	3	1	0	0	0	1	1	5	0	0	0	0	1	**1**	0.5	0	0	**1**	**1**	**1**	0	**1**	0	0	0
13	2	2	0	3	1	2	3	3	0	0	0	1	1	5	0	0	0	0	**3**	**1**	0.25	**1**	0	**1**	**0**	0	**1**	0	0	0	0
14	3	2	**1**	2	2	2	1	4	**3**	0	0	1	2	5	1	0	0	0	1	**1**	15	0	0	0	0	**1**	0	**1**	0	0	0
15	2	2	**1**	4	2	3	1	4	0	0	0	1	2	2	1	**1**	0	0	1	**1**	2	**2**	0	**1**	0	0	**1**	0	0	0	0
16	2	2	**1**	**5**	1	3	1	1	0	**2**	0	2	1	5	1	0	0	0	1	**1**	0.5	0	0	**1**	**1**	0	**1**	0	0	0	0
17	1	2	0	4	1	3	1	1	0	0	0	1	1	4	1	**1**	0	0	**2**	**1**	1	0	0	**1**	**1**	**1**	0	**1**	0	0	0
18	2	2	**1**	2	2	2	1	1	**4**	0	0	2	2	1	1	**1**	0	0	**2**	0											
19	1	1	0	4	**4**	4	1	2	0	0	0	2	1	1	0	0	1	1	1	0											
20	3	1	**1**	2	**4**	4	1	1	**1**	**1**	0	1	1	5	1	0	1	1	1	0											
21	3	1	**1**	2	2	2	1	1	**1**	0	**5**	2	1	1	1	**1**	0	1	1	0											
22	2	2	**1**	2	1	2	3	2	0	0	**5**	1	1	1	1	0	0	0	1	0											

23	2	1	**1**	4	**4**	4	3	2	**1**	0	0	1	1	5	0	0	1	0	1	0													
24	4	1	**1**	4	2	3	1	2	0	**1**	0	1	2	1	1	0	1	1	1	0													
25	3	1	**1**	2	1	2	1	2	**1**	**1**	**3**	2	1	5	1	0	1	1	1	0													
26	1	2	0	4	1	3	1	2	0	0	0	1	2	5	0	0	0	0	1	0													
27	2	1	0	**5**	**4**	4	1	1	**4**	**1**	0	2	2	5	0	0	0	0	1	0													
28	2	1	0	3	2	3	1	2	**1**	0	0	2	2	5	0	0	1	1	1	0													
29	1	1	0	2	1	2	3	2	0	**1**	0	1	2	3	0	0	0	0	1	0													
30	2	1	0	4	2	3	1	1	0	0	0	1	1	5	0	0	1	1	1	0													
31	2	1	**1**	**5**	3	3	1	3	**5**	0	0	2	1	1	1	0	0	0	1	0													
32	4	1	**1**	2	2	2	1	3	0	0	**1**	1	1	5	0	0	0	0	1	0													
33	1	2	0	4	**6**	4	3	1	**3**	0	0	2	2	3	0	**1**	**0**	**0**	1	0													
34	2	2	0	**5**	1	4	1	1	0	0	0	1	2	3	0	0	0	0	1	0													
35	2	2	**1**	4	1	3	1	1	0	0	0	2	2	1	1	0	0	0	**3**	0													
36	2	1	0	4	2	3	1	1	**4**	0	0	3	1	5	0	0	0	0	1	0													
37	2	1	2	2	3	3	2	1	**1**	0	0	2	2	3	1	0	0	0	1	0													
38	3	1	**1**	**5**	3	3	3	2	**1**	0	0	2	1	4	0	0	0	0	1	0													
39	2	1	0	**5**	1	3	1	4	0	**1**	0	2	1	5	0	0	0	0	1	0													
40	1	1	0	**5**	2	3	1	1	**2**	0	0	2	1	5	0	0	0	0	1	0													
41	2	1	**1**	**6**	**6**	4	3	2	0	0	**3**	2	1	4	1	0	0	0	1	0													
42	2	2	2	1	3	2	1	2	0	0	0	2	1	1	1	0	0	0	1	0													
43	2	2	2	3	3	3	1	2	0	0	0	2	1	1	1	0	0	0	1	0													
44	1	1	**1**	4	**4**	4	1	2	**4**	0	0	2	2	1	0	0	0	0	1	0													
45	2	1	0	4	**5**	4	1	2	**4**	0	0	2	2	5	1	0	0	0	1	0													
46	2	1	0	4	2	3	1	3	**4**	0	0	2	1	1	0	0	0	0	1	0													
47	1	1	0	3	**6**	4	3	3	**1**	0	0	1	1	5	0	0	0	0	1	0													
48	3	1	0	1	2	2	1	3	0	0	0	3	2	3	0	0	0	0	1	0													
49	1	1	0	3	2	3	1	3	0	0	0	1	1	5	0	0	1	1	1	0													
50	2	1	0	**5**	**4**	4	1	1	**1**	**1**	0	1	1	1	0	0	0	0	1	0													
51	4	1	**1**	2	**5**	4	1	3	0	0	0	1	1	5	0	**1**	**0**	**1**	**2**	0													
52	2	2	0	3	1	2	3	4	0	0	0	1	2	1	0	0	0	0	1	0													
53	3	1	**1**	2	**4**	3	1	4	**3**	0	0	2	2	5	1	0	1	1	**2**	0													
54	3	2	**1**	4	2	2	1	1	0	0	0	1	2	2	1	0	0	0	1	0													

55	2	1	0	2	2	2	1	1	**3**	0	0	1	1	4	1	0	1	1	1	0												
56	1	1	0	4	1	3	1	1	**2**	**1**	0	1	2	5	0	0	0	1	1	0												
57	2	2	**1**	2	2	2	1	1	**3**	**3**	0	2	2	1	1	0	0	0	1	0												
58	1	2	0	4	1	3	1	1	0	0	0	1	2	5	0	0	0	0	1	0												
59	1	2	0	2	1	2	1	4	**1**	0	0	1	1	5	0	0	0	0	1	0												
60	2	1	**1**	2	2	2	1	1	0	0	0	2	1	5	1	0	0	1	**2**	0												

KEY OF MASTER CHART

Age→ 15 to 19 yrs-1, 20 to 35 yrs- 2, 36 to 50 yrs-3, >50 yrs-4

Sex→Male-1, female 2

Marital status→Married-1, unmarried-0, separated-2

Education→illiterate-1, primary-2, middle-3, high school-4,

post diploma-5, graduate-6,professors-7

Occupation→unemployed-1, unskilled-2, semiskilled-3

Skilled-4, clerk & shop owner-5, semiprofession-6, profession-7

Social status→ lower-1, upper lower-2, lower middle-3, upper middle-4, upper-5

Religion→Hindu-1, muslim-2, Christian-3, converted-4

Family history (1^{st} , 2^{nd} , 3^{rd} degree relatives)→ 0 -no illness, 1-Bipolar disorder, 2-Depression, 3-Suicide, 4-alcohol,5-schizophrenia

HRSI→<150-1 (slight risk), 150 to 299- 2 (moderate), >300-3 (severe risk of disease)

Personality→Introvert-1, extrovert-2

Temperament→ neurotic-1, cyclothymic-2, hyperthymic-3, dysthymic-4, euthymic-5

Month→jan to march-1, april to june-2 ,july to sep-3 , oct to dec-4

Anxiety→yes-1, no-0

Suicide attempt→ yes-1, no-0

Alcohol→yes-1, no-0

Nicotine→yes-1, no-0

Current episode→ mania-1, mixed episode-2, hypomania-3

Past depression→yes-1, no-0

Duration of depression→<1month-1, 1 to 3 months-2, 3 to 6 months-3

Post partum onsetof depression →yes-1, no-0

Antidepressant treatment→No treatment-0 , switch by drugs-1, fast response to drugs-2,

no switch/fast response by drugs -3

Early onset depression → yes-1, no-0

Brief duration depression →yes-1, no-0

Psychotic depression→yes-1, no-0

Atypical depression →yes-1, no-0

Melancholic depression →yes-1, no-0

Catatonic depression →yes-1, no-0

Agitated depression →yes-1, no-0