

# Unipolar Mania: A Distinct Entity or Characteristic of Manic Preponderance?



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## SUMMARY

**Objective:** It has been reported that fewer patients with unipolar mania respond to lithium prophylaxis as do those with classical bipolar disorder. This study aimed to determine if the difference to response to lithium is related to unipolar mania or to a high preponderance of mania during the course of bipolarity.

**Materials and Methods:** The study included bipolar-I patients (according to DSM-IV criteria) that had a  $\geq 2$ -year history of either lithium or valproate prophylaxis as monotherapy. The response rate in the patients with unipolar mania and classical bipolar disorder were compared. Then, the response rate to lithium in all the patients with a manic episode rate  $< 50\%$  and  $> 50\%$ , and  $< 80\%$  and  $> 80\%$  during their course were compared. Finally, the above comparisons were repeated, excluding the patients with unipolar mania.

**Results:** The study included 121 bipolar-I patients (34 unipolar mania and 87 classical bipolar disorder). The response rate to lithium prophylaxis was significantly lower in the unipolar mania group than that in the bipolar group, whereas, the response rate to valproate prophylaxis was similar in both groups. Additionally, significantly fewer patients with a manic episode rate  $> 80\%$  during their course responded to lithium, followed by those with a manic episode rate  $> 50\%$ ; however, these differences disappeared when the unipolar mania group was excluded from the comparison.

**Conclusion:** Fewer patients with unipolar mania responded to lithium prophylaxis than those with classical bipolar disorder, which appeared to be related to unipolar mania, rather than to a high manic predominance during the disease course. On the other hand, response to valproate prophylaxis was similar in the unipolar mania and classical bipolar disorder groups.

**Keywords:** Unipolar mania, manic predominance, lithium prophylaxis

## INTRODUCTION

Whether or not unipolar mania is a separate nosological entity has been a contentious issue throughout the history of psychiatry, and the dispute is yet to be settled. According to a comprehensive review from an historical perspective by Angst and Marneros (2001), the milestones can be summarized, as follows. Arateus was the first to report that mania and depression were two different manifestations of the same illness. Then, Falret (1851) described an entity referred to as folie circulaire, which was characterized by a continuous cycle of depression, mania, and free intervals, and as such he was also defining the basics of the modern bipolar disorder concept. Subsequently, Kraepelin (1899) dichotomized endogenous psychoses into manic-depressive insanity and dementia

praecox; however, he was also the first to describe some cases with recurrent manic episodes without depression, which he referred to as periodic mania. In fact, Kraepelin's unification grouped all affective disorders (with a unipolar and bipolar course) under one umbrella. Later, however, Wernicke (1900), persisting with the concept of Falret, claimed that as both mania and depression were mandatory for the diagnosis of manic-depressive insanity, recurrent episodes of singular mania or depression should be distinct disorders. Similarly, Kleist (1911, 1953) and Leonhard (1957) differentiated between unipolar and bipolar disorders. Whereas pure mania and pure melancholia were classified under the rubric of pure phasic psychoses, manic-depressive illness was classified as a polymorphous phasic psychosis (Leonhard 1957). Then, Angst (1966) and Perris (1966) showed that unipolar

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depression was indeed a entity distinct from bipolar disorder, with respect to various aspects, such as gender, genetics, disease course, premorbid personality, and age of onset; however, they concluded that unipolar mania was clinically and genetically strongly related to bipolar disorder and therefore should be regarded as an artifact of it. This conclusion was generally accepted and during the last 50 years only a few studies on unipolar mania have been published.

Even though they are few in number, studies on unipolar mania have raised some doubts about the above conclusion. The following characteristics appeared to be more prevalent in unipolar mania than in classical bipolar disorder: grandiosity (Abrams et al. 1979; Pfohl et al. 1982), psychotic symptoms (Pfohl et al. 1982; Yazıcı et al. 2002), a higher total number of episodes (Khanna et al. 1992), premorbid hyperthymia (Yazıcı et al. 2002), and non-alcohol substance abuse (Pfohl et al. 1982), whereas rapid-cycling and suicidality were less common in unipolar mania (Nurnberger et al. 1979; Yazıcı et al. 2002). Additionally, the age of onset of illness was slightly earlier in unipolar mania (Taylor and Abrams 1973; Shulman and Tohen 1994; Yazıcı et al. 2002) and unipolar mania appeared to be more common in females (Aghanwa 2001; Yazıcı et al. 2002; Solomon et al. 2003).

The primary methodological criticism of these studies was the uncertainty of the diagnostic criteria for unipolar mania, which was mainly related to the insufficient number of manic episodes and duration of follow-up. Indeed, in these earlier studies diagnosis was generally based on rather weak criteria, such as the absence of a depressive episode and the presence of 1-2 manic episodes, whereas in more recent studies diagnosis was based on stronger criteria, such as absence of a depressive episode, presence of at least 3-4 manic episodes, and a minimum of 4 years of follow-up, and internationally accepted diagnostic systems. Still, the stability of the diagnosis remained unclear. Our recent follow-up study showed that 88% of diagnosed cases of unipolar mania based on the stronger criteria remained stable during the following 9 years (Yazıcı et al. 2008).

Perhaps the most crucial finding in support of the view that unipolar mania is a distinct entity from bipolar disorder could be the difference in treatment response characteristics. Although no such difference has been reported with respect to the acute treatment of mania, different response characteristics to prophylactic treatment have been reported. Nurnberger et al. (1979) reported that response to lithium prophylaxis was similar in patients with unipolar mania and bipolar patients that were hospitalized for depression; however, lithium was less effective in bipolar patients that were never hospitalized for depression. That finding might suggest that predominance of depression in bipolar patients may be associated with a better response to lithium maintenance. In such a case the response in unipolar mania could be predicted

to be poorer than that in classical bipolar patients. We also observed that the response to lithium prophylaxis was similar in patients with unipolar mania and bipolar disorder when the response modes were categorized as good, moderate, and poor; however, when we divided the patients into responders and non-responders, combining the good and moderate groups as responders, the unipolar mania group had significantly fewer responders (Yazıcı et al. 2002). That result supports the notion that unipolar mania may be a distinct nosological entity.

On the other hand, Angst et al. (2004) tried to determine whether or not bipolar-I disorder was heterogeneous. In their study bipolar patients were divided into 3 groups:

1. Patients with unipolar mania (M) and bipolar-I patients with a marked preponderance of manic episodes during the disease course (Md) constituted the manic group (M/Md group). This group had been hospitalized only for mania, and depressive episodes (if there were any) were treated without hospitalization.
2. MD group: Nuclear or classical bipolar patients (MD) with a similar number of manic and depressive episodes. This group was hospitalized for both mania and depression.
3. mD group: Bipolar patients with a marked preponderance of depressive episodes (mD). This group was hospitalized only for depression, and manic/hypomanic episodes were treated without hospitalization. Additionally, a group of unipolar depressive patients (D group) that had depression and had only been hospitalized for depressive episodes was included in the study for comparison.

When the above groups were compared two main results emerged: 1. The M/Md group and MD groups had a higher total and more mood-incongruent psychotic symptoms, more patients with manic personality traits, and higher morbidity risk for bipolar spectrum disorders among first-degree relatives; however, fewer of the patients had melancholic personality traits, and the morbidity risk for depressive spectrum disorders among first-degree relatives was lower. On the other hand, opposite trends were observed in the Dm and D groups. These results support the notion that affective disorders are a singular spectrum disorder, which is the result of different mixtures of depressive and manic spectrums. Additionally, the "manic" (M/Md) group appeared to differ from the "classical bipolar" (MD) group in terms of some characteristics: the M/Md group had a lower risk of recurrence, chronicity, and suicide, had better academic achievement, and longer duration of euthymia with or without maintenance treatment. These results indicate that the bipolar-I group was heterogeneous and that manic predominance should be taken into consideration in the future investigations. The researchers concluded that the results provide strong evidence that patients that are predominantly manic should be a diagnostic subgroup distinct from classical bipolar disorder.

Based on these data, we wondered if the differences between unipolar mania and classical bipolar emerge because unipolar mania is a distinct entity or because the predominance of mania exceeds a particular rate. The present study aimed to answer this question by investigating the response to prophylactic treatment and determining the following: 1. Are there differences in the response to several prophylactic treatments between patients with unipolar mania and classical bipolar disorder? 2. If there are such differences, are they related to unipolar mania or to the degree of manic preponderance?

## MATERIALS and METHODS

Upon admittance to Istanbul University, School of Medicine, Department of Psychiatry, Mood Disorders Unit, all the patients and their families were administered an 82-item semi-structured interview to collect sociodemographic and clinical data. During this process the life-chart of the illness is drawn by way of re-questioning the clinical symptoms of all episodes and going through the past file records. The patients who are diagnosed as a mood disorder are presented and discussed during the unit's weekly meetings and the chosen long-term treatment modalities and follow-up procedures are initiated.

### Criteria and comparisons

#### A. Inclusion criteria

Patients from the above registry that met the following criteria were included in the study. 1. Diagnosed as bipolar-I disorder, according to DSM-IV. 2. A  $\geq 2$ -year history of prophylactic treatment with lithium, carbamazepine, or valproate monotherapy any time during the course of illness. 3. Convincing response to prophylactic treatment.

#### B. Type of response to prophylaxis

To determine the response to prophylaxis a mirror design was used; the duration of prophylactic treatment was compared to a period of the same duration prior to prophylaxis. Response was categorized as good, moderate, and poor. Good response was considered as no major or minor episodes during the prophylactic treatment. Poor response was considered as no reduction in the frequency, duration, or severity of episodes during prophylactic treatment (episode severity was determined according to DSM-IV episode severity criteria). Cases that were not rated as good or poor response were considered as moderate response. Then, the patients with good and moderate response were combined into the responsive group, which was compared to the patients with poor response (unresponsive group).

#### C. Diagnostic criteria for the unipolar mania and bipolar groups

Patients that met the following criteria were included in the unipolar mania group: 1. Presence of  $\geq 4$  manic or hypomanic ( $\geq 1$  full manic) episodes. 2. Absence of a major depressive or mixed episode as well as absence of a minor depressive episode that necessitated anti-depressive use. Patients that met these criteria, but had duration of illness  $< 4$  years were excluded from the study. The other patients formed the bipolar group.

#### D. Degree of manic preponderance

The percentage of manic episodes during the course of illness was assessed in all patients.

#### E. The role of manic preponderance

The present study made 3 comparisons.

- Manic preponderance: Patients with a manic episode rate  $> 50\%$  (preponderantly manic) and  $< 50\%$  (preponderantly depressive) were compared.
- Marked manic preponderance: Patients with a manic episode rate  $> 80\%$  and  $< 80\%$  were compared.
- Comparison of the two extremes: Patients with a manic episode rate  $> 80\%$  and  $< 50\%$  were compared.

#### F. The role of unipolar mania

In order to determine the possible role of unipolar mania in the above three comparisons they were repeated after excluding the patients with unipolar mania.

### Statistics

Statistical analysis was performed using SPSS v.16 and Pearson's chi-square test, Student's t test, and Fisher's exact test. A P value  $< 0.05$  was considered statistically significant.

## RESULTS

The study included 121 bipolar-I patients (73 [60.3%] female and 48 [39.7%] male). Mean age of the patients was  $44.8 \pm 1.2$  years, mean number of episodes in a year was  $1.2 \pm 0.7$ , mean total number of episodes was  $10.3 \pm 10$ , mean number of hospitalizations was  $2.4 \pm 2.5$ , mean age of onset of illness was  $26.2 \pm 9.4$  years, and mean duration of illness was  $18.2 \pm 10.9$  years. There were 34 patients in the unipolar mania group, and 87 patients in the bipolar group.

### Response to prophylactic treatment

The type of response to prophylactic treatment was evaluated only for lithium and valproate, because there were only 10 patients treated with carbamazepine. The response rate to

**Table 1.** Some characteristics and responses to prophylactic treatment in the unipolar mania and bipolar groups.

	UM (n = 34)	BP (n = 87)	P
Female/Male n, (%)	17/17 (50/50)	56/31 (64.4/35.6)	0.6
Family history of BP, n (%)	13 (38.2)	29 (33.3)	0.6
Rapid-cycling, n (%)	1 (2.9)	5 (5.7)	0.5
Premorbid hyperthymia, n (%)	4 (11.8)	11 (12.7)	0.8
Attempted suicide, n (%)	1 (2.9)	18 (20.7)	0.16
Mean episode severity (mild-moderate-severe), n (%)	2-5-27 (5.9-14.7-79.4)	6-35-46 (6.9-35-46)	0.02
Psychotic symptoms n (%)	31/34 (91.2)	58/87 (66.7)	0.006
Response to Li prophylaxis Responders/total group (%)	13/24 (54)	63/76 (83)	0.004
Response to Val prophylaxis responders/total group (%)	19/20 (95)	27/29 (93)	0.06

UM. Unipolar mania; BP: bipolar disorder; Li: lithium; Val: valproate.

lithium prophylaxis was significantly lower in the unipolar mania group than that in the bipolar group (54% versus 83%,  $P = 0.004$ ), whereas the response rate to valproate prophylaxis was similar in both groups (95% in the unipolar mania group and 93% in the bipolar group). There weren't any significant differences in family history of bipolar disorder, rapid cycling, premorbid hyperthymia, or suicidal attempts between the two groups; however, in the unipolar mania group the frequency of psychotic ( $P = 0.006$ ) and severe ( $P = 0.02$ ) episodes was higher (Table 1).

### The role of manic preponderance and unipolar mania

The probable effect of manic preponderance on the response to prophylactic treatment was investigated in terms of three aspects.

The role of the predominance of manic or depressive episodes

Manic episode predominance is defined in two ways as lesser and greater sway, the former as having an episode rate just above 50% and the latter as having an episode rate more than 80%.

The response rate to lithium prophylaxis was 70.1% among the patients with lesser manic sway, versus 87.9% among those with a depressive sway. This difference showed a trend towards significance ( $P = 0.051$ ). When the unipolar mania group was excluded, however, that difference disappeared (79.1% and 87.9%, respectively,  $P = 0.312$ ) (Table 2).

**Table 2.** Response to lithium prophylaxis in the patients with a manic episode rate <50% and >50%.

	M >50%	M <50%	P
Response to Li (UM included) responders/total group (%)	47/67 (70.1)	29/33 (87.9)	0.051
Response to Li (UM excluded) responders/total group (%)	34/43 (79.1)	29/33 (87.9)	0.312

M. Manic episode rate; UM: unipolar mania group; Li: lithium prophylaxis

**Table 3.** Response to lithium prophylaxis in the patients with a manic episode rate <80% and >80%.

	M >80%	M <80%	P
Response to Li (UM included) responders/total group (%)	28/43 (65)	48/57 (84.2)	0.027
Response to Li (UM excluded) responders/total group (%)	15/19 (78.9)	48/57 (84.2)	0.59

M. Manic episode rate; UM: unipolar mania group; Li: lithium prophylaxis

The response rate to lithium prophylaxis was 65% in the patients with a greater manic sway, versus 84.2% in those with a manic episode rate <80% ( $P = 0.027$ ); however, the significance of this difference again disappeared having the unipolar mania group excluded (78.9% and 84.2%, respectively,  $P = 0.59$ ) (Table 3).

**This comparison is repeated once more, this time comparing the extremes.** Among the patients with greater manic sway, the response rate to lithium prophylaxis was 65%, whereas it was 88% in the patients with a depressive sway ( $P = 0.023$ ); however, the difference disappeared this time as well (79% and 88%, respectively,  $P = 0.28$ ) when the unipolar mania group was excluded (Table 4).

## DISCUSSION

The present study's findings confirm our previous finding that fewer unipolar mania patients respond to lithium prophylaxis than do those with classical bipolar disorder (Yazıcı et al. 2002), which is expected, as the two studies were conducted at the same center; however, there were some not unexpected changes in the unipolar and bipolar patient groups during the 9 years between the two studies. In addition, to the best of our knowledge the present study is the first to investigate the response profiles to valproate prophylaxis in these two groups of patients, which was observed to be similar in both groups. These data suggest that valproate could be the first choice for prophylactic treatment in unipolar mania patients. The response profiles of these groups to carbamazepine prophylaxis, on the other hand, were not investigated due to an insufficient number of patients treated with carbamazepine.

The present study aimed to determine if the reported differences between unipolar mania and classical bipolar disorder

**Table 4.** Response to lithium prophylaxis in the patients with a manic episode rate >80% and <50%

	M >80%	M <50%	P
Response to Li (UM included) responders/total group (%)	28/43 (65)	29/33 (88)	0.023
Response to Li (UM excluded) responders/total group (%)	15/19 (79)	29/33 (88)	0.28

M. Manic episode rate; UM: unipolar mania group; Li: lithium prophylaxis

are the result of manic preponderance in bipolarity or unipolar mania per se. When the difference in the response to lithium prophylaxis was investigated, comparison of the bipolar patients with a manic episode rate <50% and >50%, and <80% and >80% showed that the response rates were lower in the patients with manic preponderance and that the difference increased as the degree of preponderance increased; however, there was no difference when the unipolar mania group was excluded from the comparisons. These findings indicate that non-responsiveness to lithium prophylaxis was more strongly associated with unipolar mania than with manic preponderance in bipolarity.

The present study has some limitations that should be considered while evaluating the results. First, the present study was conducted retrospectively and the number of patients was limited. Additionally, unipolar mania has been reported to be more severely psychotic (Pfohl et al. 1982; Yazıcı et al. 2002) and how this may have affected the results requires further investigation. Angst et al.'s study (2004) does not present clear data regarding the response to maintenance treatment, although they did report that the manic group had longer durations of euthymia with and without maintenance treatment. In fact, their definition of prophylactic treatment was >6 months, most patients received combination treatment, and types of response were not assessed. Additionally, they did not evaluate unipolar mania as a separate group and preponderance of manic episodes was based on the severity of the episodes, that resulted in hospitalization but not the manic episode rate. As such, direct comparison of their findings and those of the present study may not be valid; however, their findings inspired us to determine if the differences between unipolar mania and bipolar disorder was related to manic preponderance in bipolarity.

In conclusion, based on the present results fewer patients with unipolar mania responded to lithium prophylaxis than did those with bipolar disorder, and this difference was associated with true unipolar mania rather than manic preponderance in bipolarity. On the other hand, the response to valproate prophylaxis was similar in the unipolar mania and bipolar disorder groups. This difference between the unipolar mania and classical bipolar disorder patients observed in the present study requires further investigation via cross-cultural studies

with larger patient populations, and in this respect the addition of unipolar mania as a course specifier of bipolar disorder in the diagnostic systems could be an important step.

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