

Unipolar Mania: Prevalence and Patient Characteristics

by

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Running title: *Unipolar mania*

Submitted to: *Acta Psychiatrica Scandinavica* as a research report, October, 2024 [250-word abstract, 3480-word text, 36 references, 2 tables, 2 figures]; revised as **ACP-2024-12505-R1**, February 2025.

Author contributions: MM: conceptualization, literature review, writing – original draft, writing – review & editing; AM: conceptualization, literature review, writing – original draft, writing – review & editing; LT: conceptualization, data collection and organization, writing – original draft, writing – review & editing; RJB: conceptualization, data screening and organization, formal analysis, literature review, writing – original draft, writing – review & editing.

Acknowledgments: Supported by a grant from the Aretaeus Foundation of Rome (to LT) and by a grant from the Bruce J. Anderson Foundation and the McLean Private Donors Psychiatric Research Fund (to RJB).

Disclosures: No author or immediate family member has financial relationships with commercial organizations that might appear to represent potential conflicts of interest with the material presented.

Data availability statement: Data that support the findings of this study are available on reasonable request from the corresponding author but are not publicly available due to privacy or ethical restrictions.

Ethical Statement: Written, informed consent was provided by all participants for collection and analysis of clinical data to be presented anonymously in aggregate and anonymous form in accordance with requirements of Italian law and with the Helsinki Declaration.

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Abstract

Objectives: Recurrent [hypo]mania without major depressive episodes (“unipolar mania” [UPM]), is an uncommon form of major affective disorder related to bipolar disorder (BD). We characterized UPM patients and estimated prevalence of their characteristics based on prolonged times-at-risk.

Methods: Using standard bivariate and multivariate statistics we compared characteristics of 63 consecutive UPM patients to 1210 other BD patients over prolonged, close, prospective follow-up at expert mood disorder centers.

Results: UPM was uncommon (4.95% of 1273 BD cases during 18.2 years at risk) with a 2.5-fold excess of men and 93.4% considered type I BD. UPM cases had earlier initial clinical interventions than other BD patients, and more psychotic features with first-episodes. Fewer UPM patients were married but did not have fewer children and were more unemployed. UPM cases experienced more morbidity (episodes and hospitalizations/year and %-time ill) than other BD patients and made more follow-up clinic visits/year. They were less likely to be suicidal and had less general medical comorbidity but did not differ in substance abuse. They had lower ratings of depressive symptoms, used mood-stabilizers more and as expected received antidepressants 27-times less than other BD patients. Observed rates of UPM declined with longer observation times.

Conclusions: UPM was uncommon (4.95% of BD cases; 0.31% with hypomania only). Compared to ordinary BD, UPM had significantly greater morbidity and unemployment but lower risk of suicidal behavior or general medical disorders associated with bipolar depression. This unusual disorder needs greater recognition, clarification of its nosological status, and efforts to optimize its treatment.

Key words: bipolar disorder, hypomania, mania, unipolar

Significant Outcomes

- Cases of (hypo)mania without major depressive episodes (UPM) were uncommon; they accounted for 4.95% of all bipolar disorder (BD) cases studied, 2.5-fold more in men and almost all (93.4%) diagnosed with type I BD.
- UPM patients experienced greater psychiatric morbidity (more recurrences and hospitalizations per year and greater percentage of time ill) and more unemployment but lower rates of suicidal behavior and general medical comorbidities than other BD patients.
- Observed prevalence of UPM declined with longer follow-up, suggesting that depressive episodes may emerge with prolonged observation.

Limitations

- The infrequency of UPM cases (n=63) limits the statistical power and generalizability of the findings.
- Long follow-up (18.2 years overall, 9.18 years with UPM) may alter the risk of observing depressive episodes and affect the accuracy of UPM classification.
- Study findings may not generalize to other locations; UPM patients were treated in specialized centers, where care provided may not be representative of other clinical settings.

Introduction

Unipolar mania (UPM) does not include depressive episodes but usually is included in the diagnostic group of “bipolar” disorders (BD). First theorized by Karl Leonhard (1904–1988) [Leonhard 1957a, 1957b], the concept of UPM evolved from the description by Emil Kraepelin (1856–1926) of ordinary (“manic-depressive insanity”) in the 1890s [Trede et al. 2005]. It has been proposed to be part of a spectrum of major affective disorders evidently related to BD, though its status as a separate and distinct disorder remains uncertain [Pfohl et al. 1981; Bartoli et al. 2023; Chang et al. 2023]. Certainly, UPM is unique among mood disorders in lacking a component of major depressive episodes, which are more prevalent and contribute importantly to medical co-morbidity, disability, and risk of suicide in ordinary BD [Tondo et al. 2021]. UPM as a distinct nosological entity is supported by studies finding that UPM patients compared with ordinary BD patients were more frequently male, younger at illness-onset, had more psychotic features and psychiatric hospitalizations but possibly decreased risk of suicidal behavior and low rates of other co-occurring psychiatric disorders [Bartoli et al. 2023].

Nevertheless, UPM is not recognized as a separate disorder other than as a subtype of type I BD (BD1) in standard, international diagnostic systems. It is also plausible that a small proportion of BD patients might experience recurring *hypomanic* episodes in the absence of depressive episodes. Such cases would not meet criteria for a diagnosis of BD type II (BD2) according to current classification systems given the lack of a major depressive episode. Although probably uncommon and potentially less clinically relevant (individuals with recurrent hypomanias may not seek help), it remains of interest to assess whether unipolar hypomania can be incorporated in the construct of UPM. Of interest, a recent UK Biobank study on disrupted rest/activity rhythms in UPM included patients categorized as having unipolar hypomania [Sangha 2022].

With some exceptions [Angst et al. 2019], UPM patients have had significantly more hyperthymia, as the presence of at least two hypomanic symptoms continuously for at least two years [Yazici et al. 2002] or higher ratings of hyperthymic temperament [Perugi et al. 2007]. Greater hyperthymia accords with the possibly low suicidal risk with UPM [Miola et al. 2021].

In addition, UPM patients were less likely to report a family history of depression than those with BD [Bartoli et al. 2023], whereas other evidence, controlling for age and sex, found no significant differences in family history of MDD, mania or other mental disorders between UPM patients and those with ordinary BD [Angst et al. 2019].

Two early studies of UPM patients characterized their clinical presentations and identified characteristics associated with particular treatment responses, which did not differ from those of other BD patients [Abrams et al. 1979; Nurnberger et al. 1979]. However, a more recent study found that UPM patients responded less well to lithium monotherapy than other BD patients [Yazici et al. 2002]. Overall, the preceding findings concerning a relatively rare syndrome represent tentative characterizations based mainly on evidence of limited quantity and variable quality [Bartoli et al. 2023]. In addition, much research on UPM has been based on cross-sectional observations without prospective, long-term assessments, and with relatively small samples potentially biased toward including UPM cases. Brief exposure times may sometimes be too limited to rigorously exclude risk of depressive episodes and diagnosis of ordinary BD. Moreover, available knowledge leaves questions about the validity and clinical utility of UPM as a conceptual entity.

Aims of the Study

Given the concern about the nature of UPM and its uncertain nosological status, we compared characteristics of UPM and ordinary BD patients based on years of exposure prior to entry at the study site as well as on their systematic, prospective follow-up for several additional years. We aimed to characterize UPM patients as well as estimating their prevalence based on prolonged times-at-risk.

Methods

Subjects

The study involved consecutive, consenting adults evaluated and followed at specialized outpatient clinics for assessment and treatment of mood disorders—the Lucio Bini Mood Disorders Centers in Cagliari, Sardinia, and Rome, Italy. Study subjects were clinically diagnosed with BD1 (n=649), or BD2 (n=624), updated to meet DSM-5-TR criteria [APA 2022].

Some were diagnosed with UPM or hypomania based on repeated assessments at intake and during prospective follow-up to exclude episodes of major depression. Assessments were carried out by the same mood disorder expert (LT) using semi-structured interviews to support construction of individual life-charts. Acquired clinical data were recorded systematically and converted to digitized form. Study participants provided written informed consent at clinic entry for potential anonymous reporting of clinical data in aggregate analyses, in accordance with requirements of Italian law [IMEH 2014].

Clinical measures

We assessed various demographic, descriptive, and clinical factors of interest. Psychometric assessments at clinic intake included affective temperament scored with the 39-item version of the self-assessment Temperament Evaluation of Memphis, Pisa, Paris and San Diego autoquestionnaire (TEMPS-A) [Akiskal et al. 2005], depression severity using the 21-item Hamilton Depression Rating Scale (HDRS₂₁) [Hamilton 1960], likelihood of lifetime presence of BD with the Mood Disorder Questionnaire (MDQ) [Hirschfeld et al. 2000], current [hypo]manic symptomatic status with the Young Mania Rating Scale (YMRS) [Young et al. 1978], anxiety with the Hamilton Anxiety Rating Scale (HARS) [Hamilton 1959], and global functioning with the Global Assessment of Functioning (GAF) [Aas 2010].

Among *illness course-related variables* we included: ages at first symptoms, syndromal illness-onset, first diagnosis and first treatment as well as type of first lifetime episode (manic or hypomanic [“(hypo)manic”], depressive, with or without mixed manic-depressive, psychotic, or anxious features). Morbidity measures included observed annual frequency of illness-episode recurrences (all episodes, [hypo]manias) and the average estimated total percentage of time ill and in [hypo]mania during follow-up as well as by retrospective assessment for comparison.

Data analysis

Data are presented as proportions (%) or means with 95% confidence intervals [CI].

Sociodemographic and selected clinical data were analyzed for differences between subjects with versus without UPM using contingency tables (χ^2) for categorical measures and analysis of variance (*t*-test) for continuous measures. These subgroup comparisons were ranked by the

statistical significance of differences of measures between UPM subjects versus ordinary BD patients. Statistical significance was limited to guiding selection of initial measures for further analyses and the Bonferroni-adjusted minimum p -value for significance was ≥ 0.0025 (Table 1). Analyses employed commercial software: *Statview.5* (SAS Institute, Cary, NC) for spreadsheets, and *Stata.17* (StataCorp, College Station, TX) for analyses.

Results

Characteristics of the study sample

A total of 1273 consenting adult subjects considered to have DSM-5-TR BD were included in this study (649 BD1, 624 BD2). All patients were of Caucasian ethnicity; they were at risk from illness-onset for an average of 18.2 years [CI: 17.4–18.9] overall, and 9.18 years [6.30–12.1] for those with UPM. Cases of unipolar mania or hypomania [“(hypo)mania”] without episodes of major depression (UPM) were uncommon ($n=63$, 4.95% [3.82–6.29] among all 1273 “bipolar disorder” [BD] patients. UPM patients were 14.2-times more likely to experience mania than hypomania alone and so require diagnosis of BD1 ($n=59/63$, or 93.6%), whereas only 4/1273 (0.314%) had recurrences of hypomania without major depressive episodes. UPM also was 2.54-times more prevalent among men (7.42% [5.35–9.97]) than women (2.92% [1.81–4.42]). No UPM patients showed rapid-cycling (≥ 4 episodes in any year) during prospective assessment, but their mean recurrence rate of [hypo]manias/year averaged 2.57 [CI: 0.58–4.56] compared to 0.80 [0.55–1.04] for ordinary BD patients ($t=2.56$, $p=0.004$), or 3.23-times higher.

Factors larger or more prevalent with unipolar (hypo)mania

As summarized in Table 1, UPM subjects exceeded other BD patients in several measures. As already noted, these differences included a great excess of BD1 diagnoses and only rare cases with recurrent hypomania only, as well as greater risk among men than women. The UPM cases had selectively higher ratings of hyperthymic temperament (lower for cyclothymic, dysthymic and anxious types, and not different for irritable temperament), were more likely to be unemployed, and were evaluated 73% more frequently during follow-up than other BD patients (16.8 [7.57–26.1] vs. 9.71 [8.56–10.9] clinic visits/year).

[Table 1 about here]

First-lifetime episode types differed markedly between UPM and other BD patients (Table 1). UPM cases were much more likely to start with psychotic, manic or hypomanic episodes, were much less likely to present with mixed manic-depressive, anxious or other syndromes (mostly substance abuse) and, as expected, did not start with a depressive episode, though depressive first-episodes are common with BD1 [Salvatore et al. 2021]. Morbidity was consistently greater among the UPM patients (as episodes/year or %-of-time ill), with a much greater risk of psychiatric hospitalization, based on prospective as well as retrospective assessment (Table 1). However, measures of morbidity were much greater prior to entry into clinical care at the specialized study centers. For example, rates of hospitalization/year were 12.1-times higher before clinic entry than during prospective follow-up (1.69 vs. 0.14). In addition, the proportion of time in [hypo]mania was 3.56-times lower (13.9% vs. 49.5%) after clinic entry, and the recurrence rate was 2.44-fold less (1.45 vs. 3.54 [hypo]manias/year). There also were consistent and important differences in the treatment of UPM patients, including more use of lithium, anticonvulsants and antipsychotics than for other BD patients, adding to the impression that their illnesses were less treatment-responsive but suggesting that specialized care provided added benefit.

Factors less frequent or smaller with unipolar [hypo]mania

First lifetime episode types *less* associated with UPM included a lack of depressive episodes or of (hypo)manic episodes with mixed features [dysphoric (hypo)mania], with no difference in overall risks of anxiety disorders or other types of co-occurring psychiatric illness (Table 1). Age at onset of illness and time between illness-onset and first diagnosis or treatment did not differ between UPM and BD patients. Notable but unsurprising, use of antidepressants was 27-times less among UPM than other BD patients (Table 1, Figure 1). UPM patients averaged 10.2 years younger currently than other BD subjects and they had been ill 9.42 years less. Consistent with their tendency toward (hypo)mania, the UPM subjects had 2.82-times lower ratings of depressive *symptoms* at intake than other BD patients.

Several other factors also were lower or less frequent among the UPM patients (Table 1, Figure 1). These included 1.40-times lower rates of marriage, and less frequent family history of

any psychiatric illness or of mood disorders, with no difference in family history of suicide. Of particular note, risk of suicide attempt was 4.77-times *lower* with UPM patients, despite their already noted greater psychiatric morbidity. Risks of substance abuse were similar with UPM and ordinary BD patients (29.5% vs. 21.7%, respectively). Also of note, rates of comorbid general medical disorders were 1.92-times *lower* with UPM patients (32.0% vs. 61.3%), consistent with a more important relationship of medical illnesses as well as suicidal behavior with bipolar depression [Baldessarini et al. 2020].

Factors that did not differ significantly between the subgroups are summarized in footnotes for Table 1.

Multivariable modeling

Owing to the relatively small number of cases of UPM, the feasibility of extensive multivariable logistic regression modeling of factors associated with this diagnosis was limited. Nevertheless, three factors remained significantly and independently associated with that diagnosis: lack of suicidal behavior, BD1 diagnosis, and lower risk of general medical comorbidity (Table 2).

[Table 2 about here]

Summary of differences between UPM and other BD patients

Based on data in Table 1, we summarized differences between UPM and other BD patients as relative rates (RR) among UPM/other BD cases, with separate reporting the 14 factors that were more associated, and nine others that were less associated with UPM (Figure 1, panels A and B). Most strongly associated with UPM versus ordinary BD were BD1 diagnosis and presence of psychotic features with first episodes, and least with hyperthymic temperament (Figure 1A). Factors that were less associated with UPM than ordinary BD cases ranged from antidepressant treatment to psychiatric illness in first-degree relatives (Figure 1B).

[Figure 1 about here]

Effect of observed rate of UPM with longer observation

Based on data provided by a recent review of reports on UPM [Bartoli et al. 2023] combined with data from the present study (14 observations), we regressed the proportion of subjects diagnosed with UP versus the length of observations involved, to nearly two decades (Figure 2).

There was a significant inverse correlation, with lower observed prevalence of UPM with longer observation time (slope = -2.69 [-5.18 to -0.21 , t -score = 2.36 , $p=0.036$]). This association may reflect increasing chances of encountering episodes of depression with longer observation.

[Figure 2 about here]

Discussion

This study estimated prevalence and explored clinical characteristics of patients diagnosed with UPM compared to other BD patients who had major depressive episodes in addition to (hypo)mania. Several significant differences were identified. The prevalence of UPM was 4.95% (63/1273) after long exposure times averaging 18.6 years overall and 9.18 years for UPM cases. Most UPM patients (93.4%) had final diagnoses of BD1, and only 6.35% (4/63) had hypomanias without depressions, at a prevalence of 0.315% (4/1273).

Previously reported prevalence rates of UPM have varied from a low of 1.10% to implausibly high values up to 65.3% despite exposure times of up to 20 years [Yazici et al. 2002; Solomon et al. 2003; Yazici 2014; Bartoli et al. 2023]. A new review of 14 studies [Bartoli et al. 2023] plus data from the present study (Table 1) yielded a relatively high overall mean rate of UPM among all BD subjects considered, of 31.4% [19.2–43.6] (range: 3.32% in France to 65.3% in Tunisia). There are suggestions that some regions and cultures, including relatively underdeveloped areas, may have unusually high rates of UPM [Wikstrom et al. 2023], but there are also exceptions with high rates in some highly developed areas [Sangha et al. 2022]. Similarly confusing, rates of UPM have varied markedly within the same countries: from 28.1% to 48.7% in Turkey (range of 1.73-fold) but from 5.88% to 52.7% in India (range of 8.96-fold) [Bartoli et al. 2023]. At the low end of the reported range of rates of UPM, even including some cases with mild depressions, a study by Angst and Grobler estimated a prevalence below 2% [Angst & Grobler 2015]. The basis of some unusually high prevalence rates for UPM is not readily explained.

One possibility is that longer observation times may increase chances of encountering depressive episodes, so that longer observation may result in lower prevalence estimates for UPM. For example, a report exploring the proportion of subjects with UPM who later experienced at least one major depressive episode during a 3-year follow-up period found that

about 18% of subjects thought to have UPM experienced such depressions [Baek et al. 2019]. Interestingly, retrospective follow-up analyses found that diagnostic stability of UPM increased with an increasing number of manic episodes [Angst & Grobler 2015]. Previous reports consistently recognized the need for long-term follow-up to confirm diagnosis of UPM [Shulman & Tohen 1994; Yazici et al. 2002; Solomon et al. 2003; Perugi et al. 2007]. Findings in the present study also support the view that observed rates of UPM declined with longer observation (Figure 2).

Moreover, given a lack of consensus about a definition of UPM based on number of recurrences of (hypo)mania and years at risk, several criteria to define the syndrome have been proposed. They include: [1] at least three manic episodes without major depression during at least five years of risk [Shulman & Tohen 1994]; [2] at least four manic episodes without major depression over at least 4 years [Yazici et al. 2002]; [3] at least three manic episodes and no depressions over at least 10 years [Perugi et al. 2007]. Using the third definition [Perugi et al. 2007], an investigation involving 1,411 BD1 patients found a prevalence for UPM of 5.00% [Baek et al. 2014]. With the stringent definition of ≥ 4 episodes of mania within at least 4 years [Yazici et al. 2002], the observed prevalence of UPM was 5.40% [Grover et al. 2021]. These rates are in close accord with the prevalence of 4.95% estimated in the present study, based on one or more episodes of mania (mean of 2.57/year, or 24 [hypo]manic recurrences) and none of major depression during an overall average of 18.2 years from illness onset, and of 9.18 years for UPM cases. An alternative proposal is that 20-years of exposure without major depression can adequately support the diagnosis of UPM regardless of the number of manic episodes [Solomon et al. 2003]. In addition, reported prevalence of UPM may be higher with smaller samples [Angst & Grobler 2015; Bartoli et al. 2023], possibly suggesting that small samples may over-represent UPM cases when they are the subjects of particular interest. Such definitional proposals require further investigation, though they indicate that longer years at risk and higher numbers of (hypo)manic recurrences are plausible elements of definitional criteria for UPM.

Among differences between UPM and other BD patients we found a 1.86-fold excess of men among UPM patients, whereas among ordinary BD patients with depressions, there was an excess of women (58.1% [55.3–60.9]; Table 1). The excess of men with UPM accords with

findings from previous studies [Baek et al. 2014; Angst et al. 2019], including a recent review [Bartoli et al. 2023], and this gender difference has been recognized at least since the 1970s [Abrams et al. 1979].

Several of the present findings indicate that UPM is associated with greater morbidity than in other forms of BD (Table 1, Figure 1). These include 3.5-to-over-4-times higher proportion of time during follow-up in (hypo)mania and more recurrences of such episodes/year, with 4.7-times more hospitalizations/year, despite greater use of mood-stabilizing treatments and close clinical follow-up (Table 1). With few exceptions [Perugi et al. 2007; Chang et al. 2023], such findings are consistent with previous reports as well as present findings of more manic episodes/year [Grover et al. 2021], more hospitalizations/year [Andrade-Nascimento et al. 2011; Gorgulu et al. 2021], and lesser responses to lithium treatment with UPM than with other BD patients [Yazici et al. 2002]. In the present study, UPM patients also were more likely to be unemployed, and had more follow-up clinic visits/year (Table 1). That measures of morbidity among UPM patients were lower during close follow-up at the specialized mood disorder centers of the present study than in years between illness-onset and clinic intake suggests that specialized clinical care can contribute to more favorable outcomes despite inferior responses to mood-stabilizing medicines.

Assessment of psychiatric family history indicates a significantly lower chance of a genetic transmission in UPM participants for any psychiatric disorder and for any mood disorder. The greater familial transmission for BD, as previously reported [Merikangas et al. 2014] was not found in the present data; however, the result may have been influenced by the low number of participants with such familial transmission.

Remarkably, the risk of suicide attempts was nearly five-times lower with UPM than among other BD patients (Table 1). This finding underscores the relative importance of depression and mixed affective features as contributors to suicidal risk among BD patients in general, and possible protective effects against suicide of relatively high scores for hyperthymic affective temperament [Miola et al. 2021, 2023]. The relatively low risk of general medical disorders among UPM patients is consistent with another recent study [Chang et al, 2023] and

points to the probable importance of depression as a risk factor for medical co-morbidity [Baldessarini et al. 2020].

Limitations

This study is limited by the relatively small sample of 63 UPM cases owing to the low prevalence of the condition. This sample may have been insufficient to detect some associated factors. Although the mean duration of observation was long (18.2 years overall, 9.18 years with UPM), it is possible that some depressive episodes had passed unnoticed. That UPM cases were less likely to be married or employed may have made it easier for depressive episodes to be missed. The absence of dropout rate data and the limited ethnic diversity (with all participants being Caucasian) may affect the study's generalizability, but the prolonged duration of observations may help mitigate potential ascertainment bias. The range of reported prevalence rates for UPM is so broad as to preclude meaningful comparison with the present estimate of 4.95%.

Conclusions

In this study, we observed that cases of [hypo]mania without episodes of major depression were uncommon. Clinically relevant are study findings that UPM cases were more severe than ordinary BD. Indeed, UPM cases received clinical attention earlier than other BD patients and experienced greater psychiatric morbidity with more recurrences and hospitalizations per year and greater percentage of time ill, despite more use of standard mood-stabilizing treatments. Interestingly, longer observation times were associated with lower estimated prevalence of UPM, presumably by increasing chances to observe depressive episodes. Despite a growing number of studies of UPM indicating their dissimilarities to forms of BD that include major depressive episodes, the nosological status of UPM remains uncertain and in need of additional research to establish criteria for its diagnosis and clarify its status as diagnostic entity in standard, international diagnostic systems and to define its optimal treatment.

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