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Bipolar Disorder with frequent mood episodes in the National Comorbidity Survey Replication (NCS-R)

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Abstract

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Virtually nothing is known about the epidemiology of rapid cycling bipolar disorder (BPD) in community samples. Nationally representative data are reported here for the prevalence and correlates of a surrogate measure of DSM-IV rapid cycling BPD from the National Comorbidity survey Replication (NCS-R), a national survey of the US household population. DSM-IV disorders were assessed in the NCS-R with the WHO Composite International Diagnostic Interview (CIDI). Although the CIDI did not assess rapid cycling, it did assess the broader category of 12-month BPD with frequent mood episodes (FME), having at least four episodes of mania/hypomania or major depression in the 12 months before interview. Roughly one-third of NCS-R respondents with lifetime DSM-IV BPD and half with 12-month BPD met criteria for FME. FME was associated with younger age-of-onset (of BP-I, but not BP-II) and higher annual persistence (73% of the years since first onset of illness with an episode) than non-FME BPD. No substantial associations of FME vs. non-FME BPD were found with socio-demographics, childhood risk factors (parental mental disorders, other childhood adversities), or comorbid DSM-IV disorders. However, FME manic episodes had greater clinical severity than non-FME episodes (assessed with a fully-structured version of the Young Mania Rating Scale) and FME hypomanic episodes had greater role impairment than non-FME episodes (assessed with the Sheehan Disability Scales). Whether these indicators of severity merely reflect attenuated effects of rapid cycling or independent effects of sub-threshold rapid cycling warrants further study given the high proportion of lifetime cases that met criteria for FME.

Keywords

Bipolar Disorder; Rapid-cycling bipolar disorder; Mania; Hypomania; National Comorbidity Survey Replication (NCS-R); Comorbidity; Treatment

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The natural history of bipolar disorder (BPD) consists of distinct manic, hypomanic, depressive, and mixed mood episodes that can morph immediately from one pole to another or are separated by periods of subsyndromal symptoms and euthymia.1–4 Polarity, frequency, duration, and intensity of mood episodes (along with psychosis) are highly variable, both within and between individuals.1 Effective treatments can decrease the frequency, duration, and intensity of mood episodes, but most people with bipolar disorder will continue to experience fluctuations in mood and persistent depressive symptoms. Clinical evidence suggests that about one-third of patients who recover from a mood episode stay recovered,5 while 5–40% have some, but not all, years during which they meet criteria for rapid cycling (four or more mood episodes within a year).6–8

Rapid cycling has been studied in patients accrued through diverse clinical samples (bipolar I, II, inpatient and outpatient, with index manic or depressive episodes) and has been associated with an earlier age-of-onset and greater illness burden.9 Clinical samples could be expected, however, to have a greater proportion of patients with rapid cycling than those in the general population, as rapid cycling would be expected to have a higher burden of disease and greater distress and, as a result, a higher probability of seeking help than those without rapid cycling, leading to bias in estimates of prevalence and correlates.10 It is impossible to correct for this kind of bias by weighting cases in the same way one can correct for frequency-based bias in studies of patients in point-in-time studies of primary

care visits.11 The use of general population samples is needed to generate estimates that are free of selection bias in a situation of this sort.

The prevalence and correlates of rapid cycling in the community are unknown. Assessing rapid cycling in large community samples presents a challenge because it can be difficult to gather the data needed to obtain a precise and valid count of onset and offset of episodes, as well as clearly delineated 2 month periods of partial or full remission or a switch to another episode of opposite polarity in community samples. Nevertheless, available data from the US National Comorbidity Survey Replication (NCS-R),12 provide some relevant information. Although these data do not allow DSM-IV rapid cycling BPD to be operationalized, the NCS-R data can be used to define cases of BPD with frequent mood episodes (FME) as a proxy measure for rapid cycling. FME was simply defined as self-report of four or more separate major depressive episodes or mania/hypomania episodes within a year. This report presents, to the best of our knowledge, the first nationally representative general population data on the prevalence and correlates of BPD with FME.

METHODS

Sample

The NCS-R is a nationally representative survey of mental disorders among English-speaking household residents ages 18 and older in the continental US. Interviews were carried out with 9282 respondents between February 2001 and April 2003. Verbal informed consent was obtained prior to data collection. Consent was verbal rather than written to maintain consistency with the baseline NCS. The response rate was 70.9%. Respondents were given a $50 incentive for participation. A probability sub-sample of hard-to-recruit pre-designated respondents was administered a brief telephone non-respondent survey and results were used to weight the main sample for non-response bias. Non-respondent survey participants were given a $100 incentive. The Human Subjects Committees of Harvard Medical School and the University of Michigan both approved these recruitment and consent procedures. The NCS-R interview was administered in two parts. Part I included a core diagnostic assessment of all respondents (n=9282). Part II included questions about correlates and additional disorders administered to all Part I respondents who met lifetime criteria for any core disorder plus a roughly one-in-three probability sub-sample of other respondents (n=5692). A more detailed discussion of NCS-R sampling and weighting is presented elsewhere.13

Bipolar disorder

NCS-R diagnoses are based on Version 3.0 of the World Health Organization's Composite International Diagnostic Interview (CIDI),14 a fully structured lay-administered diagnostic interview. DSM-IV criteria were used to define mania (duration of at least one week), hypomania (duration of at least four days), and major depressive episode (MDE). The requirement that symptoms do not meet criteria for a Mixed Episode (Criterion C for mania/hypomania and Criterion B for MDE) was not operationalized in making these diagnoses. Respondents were classified as having lifetime BP-I if they ever had a manic episode and as having lifetime BP-II if they ever had a hypomanic but not manic episode and ever had an

episode of MDE. Mixed episodes were not assessed, leading to a likely over-estimation of number of lifetime episodes of mania/hypomania and MDE due to double-counting. Diagnoses of both BP-I and BP-II excluded cases with plausible organic causes.

Clinical reappraisal interviews for BPD using the lifetime non-patient version of the Structured Clinical Interview for DSM-IV (SCID)15 were administered to a probability sub-sample of 50 NCS-R respondents. CIDI cases were over-sampled and the data weighted for this over-sampling. As described in more detail elsewhere,16 CIDI-SCID concordance (κ) was good for a diagnosis of BP-I/II (.69), with sensitivity of .87, specificity of .99, and area under the receiver operating characteristic curve of .93. CIDI-SCID concordance is higher for BP-I (.88) than BP-II (.50), but the McNemar test is consistently insignificant (χ^2_1 = 0.1–0.3, p = .56–.75). The latter documents that CIDI prevalence estimates are unbiased in relation to SCID prevalence estimates.

Age-of-onset of manic/hypomanic episodes and of MDE were assessed with retrospective self-reports at the syndrome level in the CIDI. These retrospective reports were not validated. Course of illness was also assessed retrospectively by asking respondents to estimate the number of years in which they had at least one episode of mania/hypomania and the number of years in which they had an episode of MDE. Again, these self-reports were not validated. Annual persistence was defined as the number of self-reported years with an episode divided by the number of years between self-reported AOO and current age.

Respondents with lifetime BPD were defined as 12-month cases if they had an episode of MDE or mania/hypomania at any time in the 12 months before interview. Respondents with 12-month BPD were asked how many episodes of mania/hypomania lasting four days or longer they had in the past 12 months and how many episodes of MDE lasting two weeks or longer they had in the past 12 months. These retrospective self-reports were not validated. Twelve-month BPD with frequent mood episodes (FME) was defined as having at least four self-reported episodes of MDE or mania/hypomania in the 12 months before interview.

Twelve month persistence was defined as the number of weeks that respondents reported they were in episode in the past year divided by 52 weeks/year. Lifetime persistence is the number of years that respondents reported that they had an episode divided by the number of years since age of onset.

Clinical severity was assessed among 12-month cases using a fully structured self-report version of the Young Mania Rating Scale (YMRS)17 for mania/hypomania and the self-report version of the Quick Inventory of Depressive Symptoms (QIDS)18 for MDE. The fully-structured respondent report version of the YMRS was developed from a fully-structured version originally designed for parent reports.19 Standard YMRS and QIDS cut-points used in previously published reports were used to define episodes as severe (including original YMRS and QIDS ratings of very severe, with ratings in the range 25+ on the YMRS and 16+ on the QIDS), moderate (15–24 on the YMRS; 11–15 on the QIDS), mild (9–14 on the YMRS; 6–10 on the QIDS), or not clinically significant (0–8 on the YMRS; 0–5 on the QIDS). Severity was assessed for the one month in the past year the respondents retrospectively described as “most severe.” No validation of the selection of these particular

months was made. YMRS and QIDS assessments are typically made for current episodes rather than for past episodes. No data were collected on the accuracy of these retrospective reports.

Role impairment among 12-month cases was assessed with the Sheehan Disability Scales (SDS).20 As with the YMRS and QIDS, the SDS scales asked respondents to focus on the one month in the past year when their mania/hypomania or MDE were most severe. The SDS questions asked respondents to rate how much the condition interfered during that month with their home management, work, social life, and personal relationships using a 0–10 visual analogue scale of none (0), mild (1–3), moderate (4–6), severe (7–9), and very severe (10).

Other disorders

Other core DSM-IV disorders assessed in the NCS-R included other anxiety disorders, mood disorders, impulse-control disorders, and substance disorders. Organic exclusion rules and diagnostic hierarchy rules were used in making all diagnoses. As detailed elsewhere,21, 22 blinded clinical reappraisal interviews using the non-patient version of the Structured Clinical Interview for DSM-IV (SCID)15 with a probability sub-sample of NCS-R respondents found generally good concordance of CIDI/DSM-IV diagnoses of anxiety, mood, and substance disorders with independent clinical assessments. Impulse-control disorder diagnoses were not validated, as the SCID clinical reappraisal interviews did not include an assessment of these disorders.

Other measures

Childhood adversities—Twelve dichotomously measured childhood adversities (CAs) were retrospectively assessed in the NCS-R. These include three types of interpersonal loss (parental death, parental divorce, and other loss of contact with parents), four types of parental psychopathology (mental illness, substance abuse, criminality, and violence), three types of harsh parenting (physical abuse, sexual abuse, neglect), and two other CAs (serious respondent physical illness, family economic adversity). The interpersonal losses were assessed with measures developed for the baseline NCS about parental death, divorces, and other parental separations (adoption, foster placement, living with other relatives instead of parents). Parental criminality, family economic adversity, and sexual abuse were also assessed with measures developed for the baseline NCS. Parental mental illness (major depression, generalized anxiety disorder, panic disorder, antisocial personality disorder) and substance abuse were assessed with the Family History Research Diagnostic Criteria (FHRDC) Interview23 and its extensions.24 Family violence and physical abuse of the respondent by parents were assessed with a modified version of the Conflict Tactics Scale. 25 Neglect, finally, was assessed using a battery of questions commonly used in studies of child welfare.26

Socio-demographics—We also consider the associations of BPD with five socio-demographic variables: sex, age at interview (18–34, 35–49, 50–64, 65+), marital status at the time of interview (married, previously married, never married), educational level (less than high school graduation, high school graduation of GED, some college without a four-

year degree, and graduation from college), employment status (working or self-employed, student, homemaker, retired, unemployed, and other, where the vast majority of respondents classified *other* were either unemployed or disabled at the time of interview), and household income, (low, low-average, high-average, and high). Household income was divided into four categories based on the distribution of the ratio of total household income before taxes in the year before interview divided by the number of household members. Following standard procedures in the welfare economics literature,27 all scores on that ratio variable were divided by the median value of that same variable. Respondents with scores of 0.5 or less (i.e., less than half the median income-per-family-member in the country) were classified as having low income. Respondents with values greater than 0.5 up to 1.0 were classified as having low-average incomes. Respondents with values of greater than 1.0 up to 3.0 were classified as having high-average incomes, while respondents with values greater than 3.0 were classified as having high incomes.

Suicidality—All Part II respondents were asked if they ever in their life seriously thought about committing suicide and, if so, the age when this first happened. Respondents who reported suicide ideation were then asked if they ever made a suicide plan and ever made a suicide attempt, again dating age of first occurrence of each among respondents with positive responses.

Treatment—All Part II respondents were asked about 12-month treatment of problems with emotions, nerves, or problems with substance use. These questions distinguished treatment by a psychiatrist, other mental health professional, general medical provider, human services professional, and complementary-alternative medical (CAM) provider (e.g., acupuncturist, chiropractor).

Analysis methods

Sub-group comparisons of proportions and means were used to compare the lifetime prevalence, persistence, severity, and treatment of BPD with and without frequent mood episodes (FME). Predictors (childhood adversities) and correlates (socio-demographics, comorbid DSM-IV/CIDI disorders) were studied using logistic regression analysis.28 In parallel with previous NCS-R studies of suicidality,29 the associations of BPD with and without FME with the subsequent (to the onset of BPD) first onset of suicidality were estimated using discrete-time survival analysis with person-year treated as the unit of analysis.30 Because the NCS-R sample design used weighting and clustering, all statistical analyses were carried out using the Taylor series linearization method,31 a design-based method implemented in the SUDAAN software system.32 Significance tests of sets of coefficients were made using Wald χ^2 tests based on design-corrected coefficient variance-covariance matrices. Statistical significance was consistently evaluated using two-sided design-based .05 level tests.

RESULTS

Prevalence, age-of-onset, and persistence

As reported previously,12 lifetime prevalence estimates for DSM-IV/CIDI BPD in the NCS-R are 1.0% for BP-I, 1.1% for BP-II, and 2.1% for overall BPD. These estimates include roughly one-third of lifetime cases that meet criteria for 12-month BPD with FME (0.3% BP-I, 0.4% BP-II, 0.7% overall BPD), another one-third that meet criteria for 12-month BPD without FME (0.3% BP-I, 0.4% BP-II, 0.7% overall BPD), and a final one-third that meet criteria for lifetime BPD without a 12-month episode (0.4% BP-I, 0.3% BP-II, 0.7% overall BPD). (Table 1)

The mean (SE) number of 12-month mood episodes overall was 7.1 (1.3), while the median was 3.1 (0.7), with the FME group reporting a higher mean of 12.6 (2.9) and median of 7.3 (0.7). Bipolar I FME consisted of a mean of 4.5 (0.6) manic or hypomanic episodes and a mean of 5.6 (1.0) depressive episodes within 12 months, Bipolar II FME consisted of a mean of 8.3 (4.2) hypomanic episodes and 6.5 (1.0) depressive episodes within the 12 months. (More detailed data on episode distributions are available on request.)

Mean age-of -onset (AOO) is somewhat earlier for respondents with 12-month BPD/FME (17.6) than others with either 12-month (19.6) or LT (20.7) BPD. (Table 2) These differences apply, though, only to BP-I, where mean AOO is substantially earlier for respondents with 12-month BPD/FME (14.4) than others (19.1–21.2; χ^2_1= 6.9–8.1, p = .004–.009). Mean AOO, in comparison, is unrelated to FME or recency among respondents with BP-II (18.4–22.8; χ^2_1 = 0.0–1.5, p = .21–.88).

Annual persistence is higher for respondents with 12-month BPD/FME (.74) than others with either 12-month (.61) or LT (.37) BPD. The difference between 12-month BPD/FME and other 12-month BPD is significant for BP-II (.75 vs. .56; χ^2_1= 8.2, p = .004) but not BP-I (.73 vs. .67; χ^2_1= 0.9, p = .35), while the difference between 12-month BPD/FME and other lifetime BPD is significant for both BP-I and BP-II (.73–.75 vs. .34–.40; χ^2_1= 41.1–58.7, p < .001). Mean number of weeks in episode in the past 12 months is also significantly higher for respondents with BPD/FME than others both for BP-I (32.1 vs. 18.8; χ^2_1= 5.3, p = .021) and BP-II (37.9 vs. 15.6; χ^2_1 = 11.5, p = .001).

Childhood predictors

BPD is significantly related to a wide range of retrospectively reported childhood adversities (CAs), with 85% of the ORs greater than 1.0 and 65% statistically significant. (Table 3) The significant ORs are all positive, have a median of 3.6, a range of 2.3–10.1, and an inter-quartile range (IQR; 25th–75th percentiles) of 2.9–4.4. These ORs are for the most part not significantly related to FME, as 28 of 32 comparisons of BPD/FME with other BPD are insignificant at the .05 level. In the four cases where differences are significant, two involve the OR being lower for 12-month BPD with than without FME (childhood physical abuse and parental mental illness), a third involves the OR for 12-month BPD/FME being lower than for other lifetime BPD (parental criminal behavior), and the last involves the OR for 12-month BPD/FME being higher than for other lifetime BPD (respondent severe childhood

physical illness). More detailed analyses (results are available on request) shows that all four of these significant differences are confined to respondents with BP-II.

We also examined the associations of BPD with respondent reports about five parental mental disorders. As with CAs, the vast majority (96%) of the ORs are greater than 1.0 and 64% are statistically significant at the .05 level. (Detailed results are available on request.) The significant ORs are all positive, have a median of 4.2, a range of 3.0–10.0, and an IQR of 3.8–4.5. These ORs are for the most part not significantly related to FME, as 18 of 20 comparisons of BPD/FME with other BPD are insignificant at the .05 level. One of the two cases where differences are significant involves the OR being higher for 12-month BP-I (with or without FME) than other lifetime BP-I (parental substance abuse), while the other involves the OR being lower for 12-month BP-II with than without FME (parental MDE).

Socio-demographic correlates

As reported in a previous publication,12 the socio-demographic correlates of BPD in the NCS-R are modest in magnitude but fairly consistent across the BPD spectrum in showing an inverse association of BPD with age and education and elevated prevalence of BPD among the previously married (compared to the currently married) and the unemployed-disabled (compared to the employed). BPD is unrelated to gender, race-ethnicity, and family income. (Results not presented, but available on request.) We examined the extent to which these socio-demographic correlates differ for 12-month BPD with and without FME. (Detailed results are available on request.) None of these differences was found to be significant at the .05 level either in the total sample or in separate analyses of BP-I and BP-II.

Severity and impairment

A significantly higher proportion of respondents with 12-month BPD were rated clinically severe in the presence vs. absence of FME (83.5% vs. 63.8%; χ^2_1= 4.9, p = .027). (Table 4) This pattern is more pronounced for BP-I (81.8% vs. 53.2%; χ^2_1= 2.5, p = .11) than BP-II (84.9% vs. 71.6%; χ^2_1= 1.9, p = .17), although it is not statistically significant in either of these sub-samples alone. Nor is the pattern significant when we look separately at the YMRS and QIDS. In disaggregated analysis, the pattern is only clear for YMRS among respondents with BP-I (80.3% vs. 46.9%; χ^2_1= 3.0, p = .08). Differences in the proportion of 12-month cases rated severe on the YMRS and QIDS depending on presence vs. absence of FME are much more modest and inconsistent in direction in the other comparisons (χ^2_1 = 0.0–0.5, p = .49–.90).

Severe role impairment due to 12-month mania/hypomania was reported by 73.1% of those with 12-month BP-I and 64.6% of those with BP-II. These reports are unrelated to FME among respondents with BP-I (72.5% vs.74.1%; χ^2_1 = 0.0, p = .88), but are significantly higher among those with FME for respondents with BP-II (79.4% vs.49.3%; χ^2_1= 3.9, p = .049). (Table 5) Severe role impairment due to 12-month MDE among respondents with BPD was reported by even higher proportions of 12-month cases: 89.3% of those with BP-I and 91.4% of those with BP-II. These reports are unrelated, though, to FME (χ^2_1= 0.0–0.1, p = .83–.96).

A similar pattern is found in reports of days out of role in the past 12 months due to BPD. (Detailed results are available on request.) The mean number of such days is unrelated to FME among respondents with BP-I (χ^2_1= 0.1–3.1, p = .08–.81) and among respondents with BP-II associated with MDE (χ^2_1= 0.2, p = .66), but is significantly higher for BP-II with than without FME associated with hypomania (52.6 vs. 16.7; χ^2_1= 4.8, p = .028).

We also examined the associations of BPD with subsequent (to first onset of BPD) first onset of lifetime suicideal ideation, plans, and attempts. (Detailed results are available on request.) Among respondents with 12-month BP-I, FME is associated with non-significantly elevated odds of both suicide plans [4.5 (2.5–8.1) vs. 1.3 (0.4–4.7); χ^2_1= 3.4, p = .07] and attempts [3.9 (2.0–7.4) vs. 0.5 (0.1–4.0); χ^2_1= 3.6, p = .06]. In comparison, FME is unrelated to odds of suicidal ideation among respondents with 12-month BP-I (χ^2_1= 0.9, p = .34) and to odds of any of the suicidality outcomes among respondents with 12-month BP-II (χ^2_1= 0.0–2.1, p = .15–.98).

Comorbidity with other DSM-IV disorders

As reported in a previous paper,12 the vast majority of NCS-R respondents with a history of BP-I (97.7%) and BP-II (95.8%) had a lifetime history of at least one other DSM-IV/CIDI disorder. The ORs of BPD with these comorbid disorders are uniformly significant and quite high both for BP-I (5.2–13.7) and for BP-II (2.6–16.7). Significant ORs for overall BPD have a range of 2.0–24.0, a median of 8.3, and an IQR of 4.1–10.9. None of these ORs differs significantly as a function of FME among respondents with 12-month BPD either in the total sample (Table 6) or in the sub-samples of respondents with BP-I and BP-II. (Detailed results are available on request.) The vast majority of the ORs are significantly higher, though, among respondents with 12-month BPD than others with lifetime BPD, although this is equally true for 12-month cases without FME as those with FME.

Treatment

As reported in a previous paper,12 treatment of 12-month BPD in the year before interview was quite high in relation to treatment of other DSM-IV/CIDI disorders:33 67.3% BP-I and 65.8% BP-II. There is no significant difference in probability of receiving any 12-month treatment of BPD among those with versus without FME either in the total sample (χ^2_1= 1.8, p = .17) or in sub-samples of respondents with BP-I (χ^2_1 = 1.4, p = .24) or BP-II (χ^2_1 = 0.8, p = .38). (Detailed results are available on request.) In addition, there is no significant association between FME and 12-month treatment in any of the separate treatment sectors examined in the NCS-R (χ^2_1= 0.0–2.7, p = .10–.97).

DISCUSSION

The results reported here are limited by the use of fully structured lay-administered CIDI interviews rather than clinician-administered interviews, although the clinical reappraisal study found good concordance of CIDI diagnoses with blinded clinical diagnoses based on the SCID. Another limitation is that the CIDI did not assess rapid-cycling BPD. This led us to focus on the broader category of BPD with frequent mood episodes. The less flexible assessment of BPD in the CIDI compared to clinical interviews also could have led to over-

estimation of comorbidity and bias in retrospective recall of persistence. No data are available on the accuracy of these reports. The CIDI assessments of age-of-onset, numbers of lifetime and 12-month episodes, and “most severe” month of disorder in the past 12 months were also based on self-report with no validation.

The less flexible nature of the CIDI than clinical interviews also could have led to bias in the estimated clinical severity of BPD in the fully-structured versions of the YMRS and QIDS assessments. Again, no data were collected on the accuracy of these reports. Both these assessments were based on retrospective reports about symptoms in the “most severe” month of the past year rather than on either cross-sectional reports about current episodes or longitudinal reports. We have no way to know the validity of these retrospective reports. In the case of the YMRS, the full-structured equivalent of the original semi-structured clinical assessment was derived from a previously developed fully-structure parent report version19 and we do not have independent confirmation of the strength of concordance of this version with blinded semi-structured clinical interviews using the original YMRS.

Another noteworthy limitation is that FME was assessed only for 12-month cases (in the past year). This limitation means at least two things. First, we do not know how many additional lifetime cases of BPD had FME at some other year in their life. Second, we don’t know how many people with current FME had it relatively stably over the course of their illness vs. only in one (the past) year. As respondents with 12-month FME reported that they had an episode of either depression or mania/hypomania in approximately three-fourths of all years since first onset, we have to assume that some respondents with lifetime but not 12-month BPD also had a lifetime history of FME BPD. The same might be true of some respondents with 12-month non-FME BPD. Because clinical severity focused on the most severe months in the past 12 months, it is possible that by approaching severity for just a single month the CIDI minimized differences that might exist in the severity of respondents across the sub-samples. No information was available to assess time between episodes or if episodes immediately switched from on pole to another. It is possible that respondents reported phases of continuous episodes rather than distinctly different episodes and counted them as such. True FME may be less frequent than found in this study and could have more severe shorter distinct episodes.

In the context of these limitations, this first report of FME BPD in a community sample found that roughly one-third of respondents with lifetime BPD met criteria for 12-month FME BPD. Those with FME had several distinguishing characteristics: a younger age-of-onset (of BP-I, but not BP-II); higher annual persistence; greater likelihood of having had an episode in the past year (for BP-II, but not BP-I); and, not surprisingly, a higher mean number of weeks in episode within the past year (37.9 weeks versus 15.6 for non-FME BPD) among 12-month cases. The mean number of episodes for FME was about 12 with a median of about 7. Thus, many people with FME could experience monthly or nearly monthly mood episodes. No substantial differences were found, in comparison, in childhood adversities or parental mental disorders to distinguish those with FME compared to non-FME 12-month BPD. The fact that people with 12-month FME differ from people with other 12-month BPD in a number of ways suggests that the 12-month FME cases have some level of stability (i.e., they are not a random year in FME and have non-FME BPD in other

years) or else these differences in external variables would not exist. But because some cases not called FME this year presumably could have FME in other years, perhaps even in the vast majority of other years, the patterns we find in external correlates are attenuated and can be considered lower bounds on the association of stable FME with these correlates. Future research is needed to assess the stability of FME and to examine correlates of stable FME, sporadic FME, and stable non-FME.

The roughly 33% of all respondents with lifetime BPD in the current sample who met criteria for 12-month FME is similar to the 25.8% prevalence of rapid cycling found among cases of BPD in the landmark Collaborative Depression Study (CDS)34 but higher than the prevalence of rapid cycling among cases of BPD in either the EMBLEM study (17.3%; range of 2.2% to 23.0% across different European countries)35 or the Stanley Bipolar Network study (17.6%).8 Similarly, the proportion with young age-of -onset of FME (about 56% before the age of 17 vs. 42% for other 12-month BPD) is somewhat higher than in the CDS (about 30% of rapid cycling patients and 15.6% of non-rapid cycling patients had onset of their bipolar disorder before the age of 17), while the EMBLEM study found no difference in age-of-onset between patients with rapid cycling versus other BPD. These results suggest that early age-of-onset might be a risk factor for lifetime FME, but with some inconsistencies in the pattern over studies.

Our finding that FME in 12-month BPD is unrelated to sex is consistent with two reports36, 37 but inconsistent with the finding that rapid cycling is more common among women than men in the CDS and EMBLEM studies as well as in the STEP-BD study 38 This inconsistency could be due to the relationship between sex and FME BPD being different for FME than for the narrower category of rapid cycling BPD. Another possibility is that the inconsistency is due to the kind of selection bias mentioned in the introduction: that is, to FME being more strongly associated with help-seeking among women than men. This latter possibility is indirectly inconsistent, though, with the fact that no strong evidence was found for differences in patterns of 12-month treatment among respondents with 12-month FME BPD versus non-FME BPD.

FME was associated with greater overall clinical severity (as measured by the YMRS and QIDS) compared to other 12-month BPD. When examined by subtypes, though, only manic episode symptom severity was greater in BP-I with FME. Severity of role impairment (as measured by the Sheehan Disability Scale) was greater for FME than other BPD, but this was limited to hypomania in BP-II. This result suggests that severe role impairment in mania/hypomania can be caused either by the high clinical severity of mania or by the frequent occurrence of hypomania. The overall severity of clinical symptoms and role impairment was greater with depression than mania/hypomania, consistent with findings from the CDS.2, 3, 34, 39 This complex series of results regarding episode severity contrasts with the more consistent finding in the clinical literature that rapid cycling is associated with increased severity.38, 40 The more complex NCS-R pattern might be due to selection bias in clinical studies, but is more likely due to FME being more heterogeneous with respect to severity than rapid cycling BPD.

Respondents with 12-month FME BPD did not have significantly elevated risk of suicidality subsequent to the first onset of their disorder than respondents with non-FME 12-month BPD. Nor was FME BPD found to be associated with significantly elevated lifetime comorbidity of other DSM-IV/CIDI disorders compared to non-FME 12-month BPD. These results are indirectly inconsistent with the higher risk of suicidality35 and comorbidity8, 38, 41 found in clinical studies of rapid cycling BPD. As with the other discrepancies noted in the last paragraph, these discrepancies with the clinical literature could be due to selection bias in clinical studies, but are more likely due to FME being more heterogeneous than rapid cycling BPD with respect to elevated risk of suicidality and comorbidity. This latter possibility would be expected to result in a sign pattern of elevated risk related to FME, as rapid cycling BPD is a subset of FME that should lead to elevated rates of suicidality and comorbidity in attenuated form among people with FME. Such a pattern can, in fact, be seen in the NCS-R data (detailed results available on request) both on both suicidality (higher ORs of FME than other 12-month BPD with suicide plans and attempts) and comorbidity (higher ORs of FME than other 12-mo BPD with 7 of 8 anxiety disorders and 3 of 4 behavioral disorders).

Given the higher estimate of relative prevalence of FME among cases of BPD in the NCS-R than of rapid cycling among cases of BPD in clinical studies, the weaker evidence of elevated severity-comorbidity of FEM among cases of BPD in the NCS-R than of rapid cycling among cases of BPD in clinical studies is most plausibly interpreted as due to attenuated effects of rapid cycling among respondents classified in the broader category of FME BPD. The unresolved question is whether FME without rapid cycling is distinct from non-FME BPD with regard to the significant correlates examined here. We have no way of knowing from the NCS-R data whether this is true, as we cannot distinguish between FME with and without rapid cycling. Any attempt to make this distinction in future community epidemiological research will need to begin by developing a more refined fully-structured assessment of at least four characteristics of 12-month BPD episodes: onset and offset, partial versus complete remission, duration of time between episodes, and mixed episodes. We suggest that the assessment of these four characteristics be limited to a 12-month recall period because we saw in the current report that much stronger differences are found between 12-month cases (with or without FME) and other lifetime cases than between 12-month cases with and without FME. This restriction of the retrospective recall period to twelve months might make it possible to develop a valid fully-structured assessment of these four characteristics, but careful methodological research will be needed to document the consistency of these classifications with blinded clinical assessments before carrying out a large-scale epidemiological study that uses these measures. Until that time, the results reported here should not be taken to imply that the broader category of BPD with FME has any clinical meaning beyond the already established distinction between cases of BPD with and without rapid cycling.

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References

1. Alvarez-Ariza M, Mateos-Alvarez R, Berrios GE. A review of the natural course of bipolar disorders (manic-depressive psychosis) in the pre-drug era: Review of studies prior to 1950. J Affect Disord. in press.
2. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003; 60:261–269. [PubMed: 12622659]
3. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002; 59:530–537. [PubMed: 12044195]
4. Judd LL, Schettler PJ, Akiskal HS, Coryell W, Leon AC, Maser JD, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry. 2008; 65:386–394. [PubMed: 18391127]
5. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2006; 163:217–224. [PubMed: 16449474]
6. Azorin JM, Kaladjian A, Adida M, Hantouche EG, Hameg A, Lancrenon S, et al. Factors associated with rapid cycling in bipolar I manic patients: findings from a French national study. CNS Spectr. 2008; 13:780–787. [PubMed: 18849897]
7. Kupka RW, Luckenbaugh DA, Post RM, Leverich GS, Nolen WA. Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. J Clin Psychiatry. 2003; 64:1483–1494. [PubMed: 14728111]
8. Kupka RW, Luckenbaugh DA, Post RM, Suppes T, Altshuler LL, Keck PE Jr, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. Am J Psychiatry. 2005; 162:1273–1280. [PubMed: 15994709]
9. Bauer MS, Calabrese J, Dunner DL, Post R, Whybrow PC, Gyulai L, et al. Multisite data reanalysis of the validity of rapid cycling as a course modifier for bipolar disorder in DSM-IV. Am J Psychiatry. 1994; 151:506–515. [PubMed: 8147448]
10. Oepen G, Baldessarini RJ, Salvatore P, Slater E. On the periodicity of manic-depressive insanity, by Eliot Slater (1938): translated excerpts and commentary. J Affect Disord. 2004; 78:1–9. [PubMed: 14672791]
11. Schwartzbaum J, Ahlbom A, Feychting M. Berkson's bias reviewed. Eur J Epidemiol. 2003; 18:1109–1112. [PubMed: 14758866]
12. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007; 64:543–552. [PubMed: 17485606]

13. Kessler RC, Berglund P, Chiu WT, Demler O, Heeringa S, Hiripi E, et al. The US National Comorbidity Survey Replication (NCS-R): design and field procedures. Int J Methods in Psychiatr Res. 2004; 13:69–92. [PubMed: 15297905]
14. Kessler RC, Ustun TB. The World Mental Health (WMH) survey initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). Int J Methods Psychiatr Res. 2004; 13:93–121. [PubMed: 15297906]
15. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Biometrics Research. New York State Psychiatric Institute; New York, NY: 2002. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP).
16. Kessler RC, Akiskal HS, Angst J, Guyer M, Hirschfeld RM, Merikangas KR, et al. Validity of the assessment of bipolar spectrum disorders in the WHO CIDI 3.0. J Affect Disord. 2006; 96:259–269. [PubMed: 16997383]
17. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978; 133:429–435. [PubMed: 728692]
18. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003; 54:573–583. [PubMed: 12946886]
19. Gracious BL, Youngstrom EA, Findling RL, Calabrese JR. Discriminative validity of a parent version of the Young Mania Rating Scale. J Am Acad Child Adolesc Psychiatry. 2002; 41:1350–1359. [PubMed: 12410078]
20. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997; 27:93–105. [PubMed: 9565717]
21. Kessler RC, Abelson J, Demler O, Escobar JI, Gibbon M, Guyer ME, et al. Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMHCIDI). Int J Methods Psychiatr Res. 2004; 13:122–139. [PubMed: 15297907]
22. Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of- onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005; 62:593–602. [PubMed: 15939837]
23. Endicott, J.; Andreasen, N.; Spitzer, RL. Family History Research Diagnostic Criteria. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1978.
24. Kendler KS, Silberg JL, Neale MC, Kessler RC, Heath AC, Eaves LJ. The family history method: whose psychiatric history is measured? Am J Psychiatry. 1991; 148:1501–1504. [PubMed: 1928463]
25. Straus MA. Measuring Intrafamily Conflict and Violence: The Conflict Tactics (CT) scales. J Marriage Fam. 1979; 41:75–88.
26. Courtney, ME.; Piliavin, I.; Grogan-Kaylor, A.; Nesmith, A. Foster youth transitions to adulthood: A longitudinal view of youth leaving care. Institute for Research on Poverty; Madison, WI: 1998.
27. Solow, R. Inequality and Poverty. W. W. Norton and Company; New York, NY: 1967.
28. Hosmer, DW.; Lemeshow, S. Applied Logistic Regression, Second Edition. Wiley & Son; New York, NY: 2001.
29. Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. Epidemiol Rev. 2008; 30:133–154. [PubMed: 18653727]
30. Willett JB, Singer JD. Investigating onset, cessation, relapse, and recovery: why you should, and how you can, use discrete-time survival analysis to examine event occurrence. J Consult Clin Psychol. 1993; 61:952–965. [PubMed: 8113496]
31. Wolter, K. Introduction to Variance Estimation. Springer-Verlag; New York, NY: 1985.
32. Research Triangle Institute. SUDAAN: Professional Software for Survey Data Analysis. 8.01. Research Triangle Institute; Research Triangle Park, NC: 2002.
33. Wang PS, Lane M, Kessler RC, Olfson M, Pincus HA, Wells KB. Twelve-month use of mental health services in the U.S: results from the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry. 2005; 62:629–640. [PubMed: 15939840]

34. Coryell W, Solomon D, Turvey C, Keller M, Leon AC, Endicott J, et al. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry. 2003; 60:914–920. [PubMed: 12963673]

35. Cruz N, Vieta E, Comes M, Haro JM, Reed C, Bertsch J. Rapid-cycling bipolar I disorder: course and treatment outcome of a large sample across Europe. J Psychiatr Res. 2008; 42:1068–1075. [PubMed: 18262204]

36. Shulman, KI.; Schaffer, A.; Levitt, A.; Herrmann, N. Effects of gender and age on phenomenology and management of bipolar disorder: a review. In: May, M.; Akiskal, H.; Lopez-Ibor, JJ.; Sartorius, N., editors. Bipolar Disorder. John Wiley & Sons; New York, NY: 2002. p. 359-397.

37. Tohen, M.; Angst, J. Epidemiology of bipolar disorder. In: Tsuang, M.; Tohen, M., editors. Textbook in Psychiatric Epidemiology. 2. Wiley; New York, NY: 2002. p. 427-444.

38. Schneck CD, Miklowitz DJ, Calabrese JR, Allen MH, Thomas MR, Wisniewski SR, et al. Phenomenology of rapid-cycling bipolar disorder: data from the first 500 participants in the Systematic Treatment Enhancement Program. Am J Psychiatry. 2004; 161:1902–1908. [PubMed: 15465989]

39. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry. 2005; 62:1322–1330. [PubMed: 16330720]

40. Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R. Rapid cycling bipolar disorder-- diagnostic concepts. Bipolar Disord. 2008; 10:153–162. [PubMed: 18199234]

41. MacKinnon DF, Zandi PP, Gershon ES, Nurnberger JI Jr, DePaulo JR Jr. Association of rapid mood switching with panic disorder and familial panic risk in familial bipolar disorder. Am J Psychiatry. 2003; 160:1696–1698. [PubMed: 12944349]

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Table 1

Twelve-month and lifetime (LT) prevalence estimates of DSM-IV/CIDI bipolar disorder (BPD) with and without frequent mood episodes (FME) in the total sample (n = 9,282)

	Twelve-month BPD							
	FME		No FME		Other LT BPD[1]		Any LT BPD	
	%	(se)	%	(se)	%	(se)	%	(se)
Any BPD	0.7	0.1	0.7	0.1	0.7	0.1	2.1	0.2
BP-I	0.3	0.1	0.3	0.1	0.4	0.1	1.0	0.1
BP-II	0.4	0.1	0.4	0.1	0.3	0.0	1.1	0.1

[1]FME is defined only for 12-month cases. Lifetime cases with no 12-month episodes consequently are not distinguished by the presence-absence of FME.

Table 2

Age-of-onset and course of DSM-IV/CIDI bipolar disorder with and without frequent mood episodes (FME)

	Twelve-month BPD				Other LT BPD[1]		Any LT BPD		Twelve-month FME versus	
	FME		No FME						Other 12-month BPD	Other LT BPD
	Mean	(se)	Mean	(se)	Mean	(se)	Mean	(se)	χ^2_1	χ^2_1
I. Any BPD										
Age-of-onset[2]	17.6	(1.2)	19.6	(1.7)	20.7	(1.3)	19.3	(0.7)	2.1	4.1*
LT persistence[3]	.74	(.03)	.61	(.04)	.37	(.03)	.58	(.02)	6.4*	83.0*
12-month persistence[4]	35.2	(3.2)	16.9	(3.7)	.	.	26.2	(2.5)	16.4*	--
(n)	(76)		(63)		(67)		(206)[5]			
I. BP-I										
Age-of-onset[2]	14.4	0.8	21.2	2.7	19.1	1.6	18.2	1.2	8.1*	6.9*
LT persistence[3]	.73	.03	.67	.04	.34	.03	.57	.02	0.9	58.7*
12-month persistence[4]	32.1	4.0	18.8	4.2	.	.	25.8	2.8	5.3*	--
(n)	(35)		(30)		(36)		(101)[5]			
III. BP-II										
Age-of-onset [2]	20.3	1.9	18.4	1.9	22.8	2.4	20.3	0.9	0.0	1.5
LT persistence[3]	.75	.03	.56	.06	.40	.04	.58	.03	8.2*	41.1*
12-mo persistence[4]	37.9	4.6	15.6	5.3	.	.	26.5	3.7	11.5*	--
(n)	(41)		(33)		(31)		(105)[5]			

*Significant difference between respondents with 12-month BPD/FME and respondents in the contrast category. The models used to test the significance of these differences controlled for age and sex. The models for BP-I/II additionally controlled for BP-I.

[1]FME is defined only for 12-month cases. Lifetime cases with no 12-month episodes consequently are not distinguished by the presence-absence of FME.

[2]Age-of-onset is defined as the earlier of the onsets of mania/hypo-mania and MDE

[3]Lifetime persistence is defined as the ratio of number of years in episode divided by number of years since first onset.

[4]Twelve-month persistence is defined as the number of weeks in episode (out of a maximum of 52) in the past 12 months among 12-month cases.

[5]The sample size on which twelve-month persistence is calculated is 139or any BPD, 65 for BP-I, and 74 for BP-II.

Table 3

Bivariate associations of retrospectively reported childhood adversities with DSM-IV/CIDI bipolar disorder (BP-I/II) with and without frequent mood episodes (FME) in the total sample (n = 9,282)

	Twelve-month BPD				Other lifetime BPD		Twelve-month FME versus	
	FME		No FME				Other 12-month BPD	Other LT BPD
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	χ^2	χ^2
I. Neglect and abuse								
Neglect	3.4*	(1.4–8.7)	2.9*	(1.1–7.5)	1.2	(0.3–6.0)	0.1	1.2
Physical abuse	3.2*	(1.6–6.4)	10.1*	(4.2–24.6)	2.3	(0.8–6.8)	5.4**	0.2
Sexual abuse	4.4*	(1.9–10.1)	6.2*	(2.5–15.5)	3.8*	(1.3–11.5)	0.5	0.1
Any	3.6*	(1.7–7.8)	6.4*	(2.5–16.5)	1.9	(0.8–4.6)	0.9	0.8
II. Loss								
Parent death	0.4	(0.1–1.6)	0.7	(0.2–3.3)	1.4	(0.8–2.5)	0.3	3.0
Parent divorce	2.4	(1.0–5.4)	1.1	(0.5–2.8)	0.9	(0.3–2.8)	0.9	1.7
Other major loss	2.6*	(1.1–6.4)	3.1*	(1.2–7.9)	0.9	(0.2–4.4)	0.1	1.1
Either	1.7	(0.8–3.4)	1.1	(0.5–2.4)	1.2	(0.5–2.7)	0.5	0.3
III. Parent violence and criminality								
Violence	3.6*	(1.5–8.8)	4.8*	(2.4–9.3)	2.7*	(1.1–7.1)	0.4	0.2
Criminal behavior	2.3*	(1.0–5.6)	4.2*	(1.6–10.8)	5.1*	(2.2–11.3)	1.5	4.1**
Either	2.9*	(1.3–6.5)	5.2*	(2.4–11.2)	3.2*	(1.5–6.7)	1.3	0.1
IV. Other adversity								
Family economic adversity	2.5*	(1.2–5.4)	3.2*	(1.5–6.9)	0.9	(0.2–3.3)	0.7	1.5
Respondent's severe physical illness	3.8*	(1.4–10.8)	1.0	(0.2–4.6)	0.4	(0.1–3.0)	1.6	4.2**
Parental mental illness	2.8*	(1.4–5.7)	6.5*	(2.8–14.8)	2.8*	(1.3–6.2)	3.8**	0.0
Any	2.9*	(1.4–6.1)	4.3*	(1.9–9.9)	1.8	(0.8–3.9)	1.3	0.7
V. Any childhood adversity								
Any	3.6*	(1.7–7.6)	2.7*	(1.1–6.8)	3.6*	(1.5–8.5)	0.2	0.0
(n)[1]		(5,563)		(5,550)		(5,553)		

[*] Significant association between the childhood adversity and BPD at the .05 level, two-sided test. The models used to test the significance of these differences controlled for age and sex. A separate model was used for each of the three BPD sub-samples (i.e., 12-month FME, other 12-month BPD, other LT BPD), each compared to respondents without a history of BPD. This is why sample sizes differ somewhat in the three columns of the table.

[**] Significant difference between the OR for respondents with 12-month BPD/FME and the OR for other respondents with BPD in the contrast category.

[1] Logistic regression models were used to generate the results in this table. A separate model was used for each of the three BPD sub-samples (i.e., 12-month FME, other 12-month BPD, other LT BPD), each compared to respondents without a history of BPD. This is why sample sizes differ somewhat in the three columns of the table. Childhood adversities were assessed in Part II, which is why the sample sizes are smaller than in Table 1.

Table 4

Clinical severity of worst 12-month DSM-IV/CIDI bipolar disorder (BPD) episode with and without frequent mood episodes (FME)

	Any bipolar						Bipolar I						Bipolar II					
	FME			No FME			FME			No FME			FME			No FME		
	%	(se)		%	(se)	χ^2	%	(se)		%	(se)	χ^2	%	(se)		%	(se)	χ^2
I. Mania/hypo-mania[1]																		
Severe/Very Severe	66.3	(6.9)		53.7	(8.4)	0.9	80.3	(8.6)		46.9	(15.3)	3.0	54.1	(9.9)		57.2	(11.4)	0.0
Moderate	25.2	(6.7)		34.7	(9.4)	0.2	19.7	(8.6)		35.3	(15.2)	295.9*	30.0	(9.6)		34.4	(12.1)	0.7
Mild	5.2	(3.0)		11.6	(6.0)		0.0	(0.0)		17.8	(12.0)	.	9.7	(5.5)		8.5	(6.6)	
None	3.3	(3.0)		0.0	(0.0)	.	0.0	(0.0)		0.0	(0.0)	.	6.2	(5.4)		0.0	(0.0)	.
(n)	(56)			(30)			(27)			(12)			(29)			(18)		
II. MDE[1]																		
Severe/Very Severe	50	77.8	(6.1)	20	79.9	(7.0)	0.0	20	74.1	(10.5)	7	62.6	(12.9)	0.3	30	80.4	(7.7)	13	91.1	(6.4)	0.5
Moderate	11	19.2	(5.7)	5	14.5	(6.6)	0.3	5	21.2	(10.0)	3	23.3	(14.0)	0.8	6	17.7	(7.3)	2	8.9	(6.4)	79.5*
Mild	2	3.1	(2.2)	2	5.5	(3.7)	.	1	4.8	(4.7)	2	14.1	(8.0)	.	1	1.8	(1.7)	0	0.0	(0.0)	.
None	0	0.0	(0.0)	0	0.0	(0.0)	.	0	0.0	(0.0)	0	0.0	(0.0)	.	0	0.0	(0.0)	0	0.0	(0.0)	.
(n)	(63)			(27)			(26)			(12)			(37)			(15)		
III. Either mania/hypo-mania or MDE (higher of two scores)[1]																		
Severe/Very Severe	59	83.5	(4.9)	27	63.8	(8.6)	4.9*	26	81.8	(7.9)	11	53.2	(11.6)	2.5	33	84.9	(6.5)	16	71.6	(10.9)	1.9
Moderate	9	12.8	(4.3)	14	28.8	(9.0)	0.5	5	14.1	(6.9)	7	32.4	(14.1)	0.9	4	11.8	(5.8)	7	26.3	(10.7)	0.2
Mild	3	3.7	(2.2)	4	7.3	(4.6)	.	1	4.1	(4.0)	3	14.5	(9.5)	.	2	3.3	(2.2)	1	2.2	(2.2)	.
None	0	0.0	(0.0)	0	0.0	(0.0)	.	0	0.0	(0.0)	0	0.0	(0.0)	.	0	0.0	(0.0)	0	0.0	(0.0)	.
(n)[2]	(71)			(45)			(32)			(21)			(39)			(24)		

*Significant difference between 12-month BPD/FME and other 12-month BPD. Significance tests were based on cumulative categories. The significance tests for "moderate" consequent compare severe-moderate versus mild-none. The models used to test the significance of these differences controlled for age and sex. In the case of the models for any BPD (i.e., BP-I/II), we also included a control for BP-I.

[1]Clinical severity of mania/hypo-mania was assessed with a fully-structured version of the Young Mania Rating Scale. Clinical severity of MDE was assessed with the self-report version of the Quick Inventory of Depressive Symptoms. See the text for a description of cut-points. The results in Part III represent the higher of the two severity scores for respondents who had both mania/hypo-mania and MDE in the past 12 months.

[2]Sample sizes are somewhat smaller than in Table 2 because of missing values on the severity scales.

Table 5

Severity of role impairment associated with worst 12-month DSM-IV/CIDI bipolar disorder (BPD) episode with and without frequent mood episodes (FME)

	Any bipolar					Bipolar I					Bipolar II				
	FME		Other			FME		Other			FME		Other		
	%	(se)	%	(se)	χ^2	%	(se)	%	(se)	χ^2	%	(se)	%	(se)	χ^2
I. Mania/hypo-mania[1]															
Severe/Very Severe	76.1	(5.6)	57.9	(7.0)	3.1	72.5	(9.3)	74.1	(10.9)	0.0	79.4	(6.9)	49.3	(11.1)	3.9*
Moderate	21.6	(5.1)	28.2	(7.1)	1.5	27.5	(9.3)	25.9	(10.9)	.	16.1	(6.0)	29.5	(10.1)	1.5
Mild	1.4	(1.4)	4.0	(3.9)	3.0	0.0	(0.0)	0.0	(0.0)	.	2.8	(2.8)	6.1	(5.9)	3.0
None	0.9	(0.9)	9.8	(3.8)	.	0.0	(0.0)	0.0	(0.0)	.	1.8	(1.8)	15.1	(6.0)	.
(n)	(62)		(40)			(31)		(16)			(31)		(24)		
II. MDE[1]															
Severe/Very Severe	90.6	(4.3)	90.5	(5.4)	0.0	90.1	(5.8)	87.8	(8.6)	0.1	90.9	(4.7)	92.2	(7.1)	0.0
Moderate	8.2	(4.1)	9.5	(5.4)	28.0*	9.9	(5.8)	12.2	(8.6)	.	6.9	(4.1)	7.8	(7.1)	31.9*
Mild	1.3	(1.3)	0.0	(0.0)	.	0.0	(0.0)	0.0	(0.0)	.	2.2	(2.2)	0.0	(0.0)	.
None	0.0	(0.0)	0.0	(0.0)	.	0.0	(0.0)	0.0	(0.0)	.	0.0	(0.0)	0.0	(0.0)	.
(n)	(68)		(32)			(29)		(14)			(39)		(18)		
III. Either mania/hypo-mania or MDE (higher of two scores) [1]															
Severe/very severe	94.0	(3.4)	78.1	(8.9)	8.3*	94.8	3.6	78.1	8.9	3.9*	93.2	4.1	66.8	8.4	7.9*
Moderate	4.9	(3.2)	26.6	(9.1)	0.3	5.2	3.6	21.9	8.9	.	4.6	3.5	26.6	9.1	0.3
Mild	1.2	(1.2)	2.6	(2.5)	93.8*	0	0	0	0	.	2.1	2.1	2.6	2.5	98.6*
None	0	0	4.1	(4.3)	.	0	0	0	0	.	0	0	4.1	4.3	.
(n)1[2]	(76)		(56)			(35)		(26)			(41)		(30)		

*Significant difference between 12-month BPD/FME and other 12-month BPD. Significance tests were based on cumulative categories. The significance tests for "moderate" consequent compare severe-moderate versus mild-none. The models used to test the significance of these differences controlled for age and sex. In the case of the models for any BPD (i.e., BP-I/II), we also included a control for BP-I.

[1]Clinical severity was assessed with an expanded version of the Sheehan Disability Scales (SDS). The results represent the highest severity score across the SDS domains. The results in Part III represent the higher of the two severity scores for respondents who had both mania/hypo-mania and MDE in the past 12 months.

[2]Sample sizes are somewhat smaller than in Table 2 because of missing values on the severity scales.

Table 6

Lifetime comorbidity of DSM-IV/CIDI bipolar disorder (BPD) with and without frequent mood episodes (FME) with other DSM-IV/CIDI disorders[1]

	Twelve-month BPD				Other lifetime BPD		Twelve-month FTE versus	
	FME		No FME				Other 12-month BPD	Other LT B PD
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	χ^2_1	χ^2_1
I. Anxiety disorders								
Generalized anxiety disorder	11.4*	(6.3–20.6)	6.4*	(3.2–12.7)	4.1*	(2.2–7.5)	1.8	9.7**
Agoraphobia	4.9*	(1.3–19.1)	6.2*	(1.9–20.1)	9.2*	(3.8–22.2)	0.1	0.8
Specific phobia	10.9*	(6.2–19.3)	5.7*	(2.6–12.4)	5.4*	(3.0–9.7)	2.0	3.3
Social phobia	10.6*	(5.7–19.9)	8.4*	(4.6–15.2)	7.0*	(3.9–12.7	0.3	1.0
PTSD	9.0*	(5.5–14.6)	6.9*	(3.5–13.6)	5.38	(2.5–11.2)	0.5	2.2
OCD	11.3*	(3.2–40.3)	24.0*	(7.1–81.8)	10.2*	(2.2–46.2)	1.2	0.0
Panic disorder	12.0*	(5.4–26.2)	8.4*	(3.6–19.5)	2.9*	(1.2–7.0)	0.6	7.2**
Separation anxiety	11.7*	(6.3–21.8)	7.0*	(3.0–16.0)	3.6*	(1.8–7.1)	1.2	8.9**
Any anxiety disorder	40.8*	(10.7–154.9)	17.0*	(7.5–38.6)	8.1*	(2.7–23.9)	1.3	5.7**
II. Behavioral disorders								
ADHD	12.1*	(6.3–23.4)	12.4*	(6.1–25.4)	4.7*	(1.7–12.9)	0.0	4.5**
Oppositional-defiant disorder	8.3*	(4.1–16.8)	6.6*	(2.6–17.1)	4.2*	(1.7–10.3)	0.4	3.6**
Conduct disorder	3.4*	(1.4–8.0)	2.1*	(1.0–4.6)	2.2*	(1.0–5.2)	1.1	0.8
Intermittent explosive disorder	4.8*	(2.5–9.4)	3.0*	(1.4–6.7)	3.1*	(1.5–6.6)	1.2	1.0
Any behavioral disorder	8.9*	(4.6–17.3)	8.1*	(3.9–16.8)	6.5*	(2.4–17.6)	0.1	0.7
III. Substance disorders								
Alcohol abuse	4.3*	(2.4–7.5)	4.6*	(2.3–9.4)	3.2*	(1.4–7.2)	0.1	0.5
Alcohol dependence	4.5*	(2.2–9.20	5.4*	(2.4–11.9)	3.2*	(1.2–8.7)	0.2	0.6
Drug abuse	3.9*	(2.1–7.2)	4.7*	(2.4–9.1)	2.0*	(1.0–4.1)	0.2	2.6
Drug dependence	3.9*	(1.3–11.4)	3.2*	(1.3–8.1)	1.3*	(0.4–4.9)	0.2	4.4**
Any substance disorder	4.4*	(2.6–7.5)	5.4*	(2.7–10.7)	3.0*	(1.5–6.3)	0.3	1.1

	Twelve-month BPD				Other lifetime BPD		Twelve-month FTE versus	
	FME		No FME				Other 12-month BPD	Other LT B PD
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	χ^2_1	χ^2_1
IV. Any disorders								
Any disorder	104.1*	(10.9–994.8)	41.8*	(14.0–124.5)	8.9*	(2.1–37.0)	0.5	5.0**
Exactly one disorder	25.1*	(1.9–323.9)	9.38	(1.7–49.5)	3.8*	(0.7–19.8)	0.5	2.0
Exactly two disorders	42.5*	(2.7–658.5)	8.5	(0.9–81.0)	4.9*	(1.0–23.6)	0.9	2.4
Three or more disorders	243.2*	(25.7–2299.0)	95.7*	(32.5–281.4)	15.6*	(3.4–71.8)	0.5	6.1**

*Significant association between the BPD sub-sample and the comorbid disorder at the .05 level, two-sided test.

**Significant difference between the OR for respondents with 12-month FME and the OR for respondents with the BPD in the contrast category.

*1*The models used to generate the results in this table included three dummy predictor variables for the different types of BPD to predict each of the other disorders controlling for age and sex. Significance tests of pair-wise differences in the ORs of FME with either other 12-month BPD or other lifetime BPD were based on Wald χ^2 estimated in these models. The exception was the model for number of comorbid disorders (exactly one, exactly two, three or more), in which three separate sub-sample analyses were used to predict exactly one vs. none, exactly two vs. none, and three or more vs. none. Sample sizes differed because although most comorbid disorders were assessed in Part I of the NCS-R (n = 9,,282), others (PTSD, drug abuse and dependence) were assessed in Part II (n = 5,6,92), and yet others (ADHD, ODD, CD) in the sub-sample of the Part II sample in the age range 18–44 (n = 3,197). OCD, finally, was assessed in the random sub-sample of Part II respondents (n = 2,073).