ORIGINAL RESEARCH

Prevalences of comorbid anxiety disorder and daily smartphone-based self-reported anxiety in patients with newly diagnosed bipolar disorder

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ABSTRACT

Background Around 40% of patients with bipolar disorder (BD) additionally have anxiety disorder. The prevalence of anxiety in patients with newly diagnosed BD and their first-degree relatives (UR) has not been investigated.

Objective

To investigate (1) the prevalence of a comorbid anxiety diagnosis in patients with newly diagnosed BD and their UR, (2) sociodemographic and clinical differences between patients with and without a comorbid anxiety diagnosis and (3) the association between smartphone-based patient-reported anxiety and observer-based ratings of anxiety and functioning, respectively.

Methods We recruited 372 patients with BD and 116 of their UR. Daily smartphone-based data were provided from 125 patients. SCAN was used to assess comorbid anxiety diagnoses.

Findings In patients with BD, the prevalence of a comorbid anxiety disorder was 11.3% (N=42) and 10.3% and 5.9% in partial and full remission, respectively. In UR, the prevalence was 6.9%. Patients with a comorbid anxiety disorder had longer illness duration (p=0.016) and higher number of affective episodes (p=0.011). Smartphone-based patient-reported anxiety symptoms were associated with ratings of anxiety and impaired functioning (p<0.001).

Limitations The SCAN interviews to diagnose comorbid anxiety disorder were carried out regardless of the participants' mood state.

Clinical implications

The lower prevalence of anxiety in newly diagnosed BD than in later stages of BD indicates that anxiety increases with progression of BD. Comorbid anxiety seems associated with poorer clinical outcomes and functioning and smartphones are clinically useful for monitoring anxiety symptoms.

Trial registration number ClinicalTrials.gov Registry (NCT02888262).

INTRODUCTION

Bipolar disorder (BD) is characterised by alterations in mood and energy as well as a range of symptoms, including anxiety symptoms. In BD, the lifetime prevalence of anxiety disorders has in two meta-analyses been estimated to be 40.5% (39 studies including 13 409 patients) and 45% (40 studies including 14 914 patients with BD, ranging from 8% to 88%), respectively.[1 2] In comparison, the current global prevalence of any anxiety disorder in the general population is approximately 7.3% (ranging from 0.9% to 28.3%).[3] The high variability in the prevalence of anxiety diagnosis most likely represents the heterogeneous study populations and methods applied for assessing anxiety across institutions and nations. Further a proportion of patients with BD may experience subsyndromal anxiety symptoms during remitted phases and during episodes without fulfilling the criteria for anxiety diagnosis.[4 5] The co-occurrence of anxiety symptoms is related to worsening of clinical outcomes in patients with BD, such as increased self-reported stress,[4] shorter periods with remission[6] impaired functioning, reduced quality of life,[4] more severe mood episodes[7 8] and a higher risk of suicide attempts.[8 9] Also, anxiety disorders and anxiety symptoms in offspring of patients with BD have been associated with increased risk of onset of a mood disorder.[10] Consequently, anxiety is important to acknowledge both in patients in remission and in individuals with risk of developing BD. Smartphones offer a unique method to monitor daily anxiety symptoms for a long term and unobtrusively and are likely to be a feasible method to detect anxiety symptoms during remission and in high-risk individuals.

No study has previously investigated the prevalence of a comorbid anxiety diagnosis and daily self-reported anxiety symptoms in patients with newly diagnosed BD and their first-degree relatives and the association with clinical characteristics and functioning.

This study aimed to investigate (1) the prevalence of anxiety diagnosis in patients with newly diagnosed BD and their first-degree relatives, (2) the differences in sociodemographic data and clinical characteristics in patients with and without a comorbid anxiety diagnosis and with and without smartphone-based self-reported anxiety, (3) the association between smartphone-based patient-reported anxiety and anxiety ratings on validated observer-based rating scales and (4) finally, we aimed to investigate the association between smartphone-based patient-reported anxiety and

impairment in functioning in patients with newly diagnosed BD.

We predicted that: (1) the prevalence of a comorbid anxiety diagnosis and symptoms would be lower in patients with newly diagnosed BD than in previously reported studies with samples of patients with varying duration of illness; (2) the prevalence of a comorbid anxiety diagnosis would be associated with the severity of mood symptoms; (3) patients with newly diagnosed BD and a comorbid anxiety diagnosis or self-reported anxiety would have more severe illness characteristics and impaired functioning; (4) smartphone-based patient-reported anxiety level would be associated with the observer-based rating of anxiety levels and (5) higher level of smartphone-based patient-reported anxiety would be associated with a lower level of functioning.

METHODS

Study design

The present study is part of the larger ongoing Bipolar Illness Onset (BIO) Study.[11] Participants included in this report were included in the study from June 2015 to February 2020. All participants were assessed at baseline and then annually and additionally, if they experienced new episodes.

Study participants

Patients with newly diagnosed BD were recruited from the Copenhagen Affective Disorder Clinic, Denmark. The clinic offers a 2-year programme to all newly diagnosed patients with BD in the entire Capital Region of Denmark.[12] All patients in the Capital Region are referred to the clinic when the diagnosis of a single manic episode or bipolar is made for the first time. The clinic receives patients from general practitioners, private psychiatrists in primary care and psychiatrists in secondary care following hospitalisation and from outpatient treatment. The criteria for inclusion were newly diagnosis with BD or a single manic episode according to the International Classification of Diseases (ICD) criteria and an age of 18–70 years. With permission from the patients with BD researchers contacted their first-degree relatives (siblings and children). The inclusion criterion for first-degree relatives was the age of 15–70 years and exclusion criteria were organic mental disorders, mental and behavioural disorders due to psychoactive substance use, schizophrenia or other psychotic disorders or BD.

Healthy control (HC) individuals without any current or prior treatment requiring psychiatric disorder in the individual or among the individual's first-degree relatives were recruited among blood donors from the blood bank at Rigshospitalet, Copenhagen University Hospital. The HC included in this paper was both from the BIO cohort and another study completed by our group, which used the same inclusion and exclusion criteria.[13] The control group from the other study was used because all participants provided smartphone-based daily recordings of anxiety. The HC was only used in the smartphone-based analyses.

Ratings of anxiety and questionnaires

At inclusion, a medical doctor or psychologist trained in diagnosing BD confirmed the diagnosis of BD and assessed any psychiatric comorbidities, including anxiety disorders, according to the ICD 10th version (ICD-10)[14] using the Schedules of Clinical Assessment in Neuropsychiatry (SCAN) interview.[15] Anxiety diagnoses included any diagnosis from F40.0 (agoraphobia) to F42.9 (obsessive-compulsive disorder). During the clinical interview, number of previous episodes was estimated based on retrospective patient reports. Previous episode includes hypomanic, manic, mixed and depressive episodes. The severity of depressive and manic symptoms for the past 3 days was clinically evaluated using the Hamilton Depression Rating Scale 17 items (HAMD-17)[16] and the Young Mania Rating Scale (YMRS),[17] respectively. For the HAMD-17, we used subitem 10 to assess psychiatric anxiety and subitem 11 to assess somatic anxiety. The Functional Assessment Short Test (FAST) was included to investigate whether changes in daily smartphone-based patient-reported anxiety symptoms were reflected in changes in functioning, as assessed by clinical researchers. FAST is specifically developed for BD and addresses six areas of functioning for the past 14 days: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationship and leisure time.[18] FAST scores 12, 20 and 40 are used as cut-offs for mild, moderate and severe functional impairment.[19]

The EuroQol-5 Domain (EQ-5D), a standardised measure of health status, was used to provide a simple and easily accessible measure of health across several disease areas.[20]

Smartphone-based patient-reported anxiety

Participants recruited after September 2016 were invited to download a smartphone-based application, Monsenso, on their smartphones.[21] It was voluntary to use the application and therefore smartphone-based recordings were not provided from all participants. The Monsenso app is available on both iPhone and Android smartphones. The patients with BD self-reported their mood, activity and sleep on a daily basis. In addition to these three measures, the participants could choose to rate daily anxiety symptoms and stress symptoms. Anxiety symptoms were rated on a scale from 0 ('no anxiety symptoms') to 4 ('high levels of anxiety symptoms') (0–4). Likewise, the level of overall daily stress was rated on a scale from 0 ('no stress') to 4 ('high levels of stress'). It was optional to report daily anxiety symptoms. Consequently, it was only a subpopulation of the patients with BD who provided smartphone-based recordings that provided daily self-reports of anxiety symptoms. Only three participants in the first-degree relative group provided daily self-reports of anxiety symptoms, due to the low number of participants we did not include data from this group in the analysis. Likewise, only a few of the HCs in the BIO study provided daily anxiety ratings and data from this group were therefore pooled with data from a previous study using a similar control group with similar inclusion and exclusion criteria.[13] The Monsenso system has a daily reminder function and self-reported data can be entered retrospectively for up to 2 days.

Statistical methods

All predictions and statistical analyses were planned a priori. Differences in demographic variables between two groups (patients with BD vs first-degree relatives, patients with BD with and without a comorbid anxiety diagnosis, patients with BD with and without daily patient-reported anxiety) were analysed using χ^2 for categorical variables and t-test or Mann-Whitney test for continuous variables depending on whether the assumptions of normality were met or not met. Continuous variables are presented as median (IQR) or mean (95% CI) and categorical data are presented as % (n) in the tables.

We employed a linear mixed-effect regression model with smartphone-based anxiety as the dependent variable and observer-based ratings and other smartphone measures (patient-reported mood, activity and stress) as fixed factors. Due to the longitudinal design of the study, some participants provided

Table 1 Prevalence of comorbid anxiety diagnosis in patients with newly diagnosed bipolar disorder (BD) and first-degree relatives at baseline

	Patients with BD	First-degree relatives
All participants, n	372	116
Age at inclusion	29 (24; 36)	26 (22; 33)
Sex, women, % (n)	65.3 (243)	56 (65)
HAMD-17 total	9 (5; 15)	2 (0; 4)
YMRS total	3 (0; 7)	0 (0; 2)
FAST	21 (11; 31)	2 (0; 6)
Depressive episode at baseline, % (n)*	30.1 (112)	
Hypomanic/manic episode at baseline, % (n)†	6.2 (23)	
Illness duration‡, years	10 (6; 16)	
Untreated BD§, years	4 (1; 11)	
Patients with one or more SCAN diagnosis at baseline, % (n)	11.3 (42)	6.9 (8)
Agoraphobia, % (n)	3.5 (13)	0.0 (0)
Social phobia, % (n)	2.2 (8)	1.7 (2)
Specific phobias, % (n)	4.6 (17)	1.7 (2)
Panic disorder, % (n)	3.8 (14)	2.6 (3)
Generalised anxiety disorder, % (n)	1.1 (4)	2.6 (3)
Obsessive compulsive disorder, % (n)	1.1 (4)	0.9 (1)
HAMD item 10 subjective anxiety symptoms	1 (0; 2)	0 (0; 0)
HAMD item 11 objective anxiety symptoms	0 (0; 1)	0 (0; 2)
Participants in partial remission¶, n	232	112
Patients with one or more SCAN diagnosis in partial remission	10.3 (24)	5.4 (6)
Agoraphobia, % (n)	2.6 (6)	0.0 (0)
Social phobia, % (n)	0.9 (2)	0.9 (1)
Specific phobias, % (n)	4.3 (10)	1.8 (2)
Panic disorder, % (n)	1.7 (4)	0.9 (1)
Generalised anxiety disorder, % (n)	1.7 (4)	1.8 (2)
Obsessive compulsive disorder, % (n)	1.3 (3)	0.0 (0)
Participants in remission**, n	101	96
Patients with one or more SCAN diagnosis in remission, % (n)	5.9 (6)	4.4 (4)
Agoraphobia, % (n)	0.0 (0)	0.0 (0)
Social phobia, % (n)	0.0 (0)	1.0 (1)
Specific phobias, % (n)	4.0 (4)	2.1 (2)
Panic disorder, % (n)	1.0 (1)	0.0 (0)
Generalised anxiety disorder, % (n)	0.0 (0)	1.0 (1)
Obsessive compulsive disorder, % (n)	1.0 (1)	0.0 (0)

Continuous variables are presented as median (IQR); categorical data are presented as % (n).
*Depressive episode at baseline defined as HAMD-17≥14 and YMRS≤14.
†Hypomanic/manic episode defined as HAMD-17≤14 and YMRS≥14.
‡Illness duration was defined as the time from the first episode to the time of inclusion.
§Untreated BD was defined as the time from the first mania, hypomania or mixed episode to time of diagnosis.
¶Participants in partial remission at baseline: HAMD-17 and YMRS<14.
**Participants in remission at baseline: HAMD-17 and YMRS<7.
FAST, Functional Assessment Short Test; HAMD-17, Hamilton Depression Rating Scale 17 items; SCAN, Schedules of Clinical Assessment in Neuropsychiatry; YMRS, Young Mania Rating Scale.

repeated measurements of HAMD-17, YMRS and FAST and smartphone-based self-reported symptoms. To account for this, the participants' identification numbers were included as a random factor in a linear mixed-effect model. In this way, this model enables us to account for both the variation of the variable of interest within the participants (intraindividual variation) and between individuals (interindividual variation). For all analyses, an unadjusted model and a model adjusted for age and sex were employed. Also, model assumptions were checked using QQ plot and histogram of residuals for all analyses.

Smartphone-based recordings of anxiety symptoms are a new area of research; therefore, due to the exploratory nature of the study, adjustment for multiple testing was not applied. The level of statistical significance was set to p values below 0.05. All statistical analyses were performed using SPSS software (V.25.0; IBM Corp., Armonk, New York, USA).

FINDINGS

Sociodemographic and clinical characteristics

We included 372 patients with BD. A total of 11.3% (N=42) of the patients with newly diagnosed BD and 6.9% (N=8) of their first-degree relatives had a SCAN verified anxiety diagnosis at baseline. For 93.2% of the patients, BD diagnoses were made within the preceding 2 years. Out of the 42 patients with BD and a comorbid anxiety diagnosis, 29 patients had one anxiety diagnosis and 13 patients with BD had 2–4 anxiety diagnoses at baseline. When including only participants without a mood episode, ie, in partial or full remission based on scores on the HAMD-17 and YMRS, the percentages of patients with BD with an anxiety disorder were 10.3% and 5.9%, respectively, and for first-degree relatives the percentages were 5.4% and 4.4%, respectively (table 1). There was no statistically significant difference in the prevalence of comorbid anxiety diagnosis between patients with newly diagnosed BD and their first-degree relatives neither in analysis including all participants regardless of mood episodes nor in partial or full remission (all p values>0.05).

As seen from table 2, comparing patients with and without an anxiety diagnosis, the patients with an anxiety diagnosis had an earlier onset of BD (median (IQR) age 19 (17; 22) vs age 21 (17; 27), p=0.044), more years with untreated BD (7 (2; 15) years vs 4 (1; 10), p=0.043), longer illness duration (14 (8; 19) years vs 9 (5; 15), p=0.016), more days on sick leave the previous year (days 163 (58; 308) vs 60 (15–173), p=0.009), lower functioning (p=0.001) and reported a lower level of health status (p=0.032). There was no difference between patients with and without anxiety diagnosis in relation to prescribed medication, BD type I or II, education level or civil status. When adjusting for age and sex, the difference in self-reported health status (EQ-5D, p=0.066) was no longer statistically significant (results not presented in the tables). In post hoc exploratory logistic regression analyses, we included anxiety diagnosis as a dependent variable and BD type, age at onset, illness duration, number of prior total episodes, prior psychosis and stressful life events as covariates. Longer illness duration (OR=1.097, 95% CI=1.015 to 1.186, p=0.019) and BD type II (OR=2.450, 95% CI=1.009 to 5.951, p=0.048) predicted the presence of a comorbid anxiety diagnosis.

Table 3 illustrates the difference in sociodemographic and clinical characteristics between patients with and without smartphone-based daily patient-reported anxiety symptoms. In total 252 patients with BD provided self-reported data. Of these, 132 patients with BD self-reported their anxiety symptoms for a total of 19 945 days with a median number of days for each participant on 94 days (43; 178) (median(IQR)). Seven of the patients with BD rated 0 equaling to no anxiety symptoms. Therefore, these seven patients were pooled together with the patients who did not provide information about daily self-reported anxiety. Patients with self-reported anxiety symptoms had more frequently an anxiety diagnosis according to the SCAN interview, more days with sick leave the previous year (68 (20; 210) days vs 40 (10; 120) days, p=0.019), longer illness duration (11.0 (6.3; 16.0) years vs 8.0 (3.0; 13.0) years p=0.001) and were less often in remission at baseline (23.4% vs 36.2%, p=0.026) compared with patients without self-reported anxiety symptoms. When adjusting for age and sex, there was no longer

Table 2 Differences in sociodemographic and clinical characteristics in patients with newly diagnosed bipolar disorder (BD) with and without anxiety diagnosis

	BD With anxiety diagnosis	BD Without anxiety diagnosis	BD with anxiety diagnosis versus BD without anxiety diagnosis (p)
Participants, % (n)	11.3 (42)	88.7 (330)	
Age, years	29 (24; 35)	29 (24; 37)	0.66
Female sex, % (n)	76.2 (32)	63.9 (211)	0.12
Education, years	14 (12; 16)	15 (13; 17)	0.12
Sick days last year, days	163 (58; 308)	60 (15; 173)	**0.009**
Full-time employment, % (n)	28.6 (12)	30.9 (100)	0.76
Student, % (n)	42.9 (18)	37.3 (121)	0.50
Civil status, single	38.1 (16)	51.1 (165)	0.11
HAMD-17	11 (8; 16)	8 (5; 15)	0.09
HAMD-17 item 10	1.33 (1.01; 1.66)	0.86 (0.75; 0.97)	**0.004**
HAMD-17 item 11	1.10 (0.75; 1.44)	0.58 (0.48; 0.68)	**0.001**
YMRS	4 (2; 7)	3 (0; 6)	0.17
FAST, total score	27 (19; 42)	20 (11; 31)	**0.001**
EQ-5D*	0.79 (0.74; 0.86)	0.80 (0.75; 1.00)	**0.032**
EQ-5D VAS	59.0 (52.7; 65.3)	64.9 (62.7; 67.2)	0.076
Alcohol weekly	2 (0; 6)	2 (0; 7)	0.42
Stressful life events	3 (1; 4)	2 (1; 3)	0.059
BD type II, % (n)	78.6 (33)	66.9 (221)	0.13
Age of onset, years	19 (17; 22)	21 (17; 27)	**0.044**
Illness duration, years†	14 (8; 19)	9 (5; 15)	**0.016**
Untreated BD, years‡	7 (2; 15)	4 (1; 10)	**0.043**
Suicide attempts, number	0 (0; 1)	0 (0; 0)	0.95
No. of prior depressive episodes	10 (5; 20)	5 (3; 10)	**0.002**
No. of prior hypomanic episodes	5 (2; 16)	4 (2; 15)	0.63
No. of prior manic episodes	0 (0; 1.5)	1 (0; 2)	0.10
No. of prior mixed episodes	0 (0; 0)	0 (0; 1)	0.06
No. of prior total episodes	20 (10; 46)	12 (6; 26)	**0.011**
Prior psychosis	0 (0; 1)	0 (0; 0)	0.48
Remission at inclusion§, % (n)	14.3 (6)	28.9 (95)	0.06
Partial remission at inclusion¶, % (n)	63.2 (24)	57.2 (208)	0.50
Prescribed medication at baseline			
Lithium, % (n)	19.0 (8)	30.6 (101)	0.12
Antiepileptic treatment, % (n)	57.1 (24)	51.2 (169)	0.47
Antipsychotic treatment, % (n)	40.5 (17)	34.8 (115)	0.47
Antidepressant treatment, % (n)	11.9 (5)	13.0 (43)	0.89
No psychotropic medication, % (n)	14.3 (6)	18.5 (61)	0.51

Continuous variables are presented as median (IQR) or mean (95% CI) and p values are calculated based on differences in mean between the two groups using t-test for or Mann-Whitney U test. Categorical data are presented as % (n) and p values are calculated by using the χ^2 test.
*EQ-5D: a standardised measure of health status developed by the EuroQol Group.
†Illness duration was defined as the time from the first episode to the time of inclusion.
‡Untreated BD was defined as the time from the first mania, hypomania or mixed episode to time of diagnosis.
§Remission at inclusion: HAMD-17 and YMRS<7.
¶Partial remission at inclusion: HAMD-17 and YMRS<14.
EQ-5D, EuroQol-5 Domain; FAST, Functional Assessment Short Test; HAMD-17, Hamilton Depression Rating Scale 17 items; SCAN, Schedules of Clinical Assessment in Neuropsychiatry; VAS, visual analogue scale; ; YMRS, Young Mania Rating Scale.

a statistically significant difference in the YMRS score between the two groups (p=0.09).

The mean level of smartphone-based self-reported anxiety symptoms for patients with BD was 0.89 (0.77; 1.02) and when only looking at days where patients had self-reported neutral mood (−0.5, 0 or 0.5, a total of 15 869 days), mean self-reported anxiety was 0.73 (0.62; 0.84). In contrast, in the HC group, the mean level of self-reported anxiety symptoms was 0.01 (0.01; 0.01) and the percentage of days with a self-reported anxiety score >0 was 0.02% which is markedly lower than in patients where it was 49.5%.

Table 4 presents the association between smartphone-based patient-reported anxiety and clinically rated parameters of anxiety and functioning. We found that the mean anxiety level, calculated by taking the average score of daily self-reported anxiety the past 3 days, was positively associated with anxiety items on the HAMD-17 and functioning according to FAST (B=0.013, 95% CI: 0.004 to 0.023, p<0.001). A higher patient-reported anxiety score was associated with a 0.46 (−0.48; −0.45) decrease in mood score, 0.08 (−0.09; −0.07) decrease in activity score and a 0.42 (0.41; 0.43) increase in stress score, all at a statistically significant level (all p values<0.001).

DISCUSSION

Overall, we found that the current prevalence of comorbid anxiety disorder in patients with newly diagnosed BD was 11.3% and 6.9% in first-degree relatives. Additionally, illness

Table 3 Differences in sociodemographic and clinical characteristics between patients with and without smartphone-based self-reported anxiety symptoms

Smartphone-based ratings of anxiety	BD With self-reported anxiety	BD Without self-reported anxiety or self-reported=0	P
Participants, n	125	127	
Anxiety diagnosis, SCAN, % (n)	14.4 (18)	4.0 (5)	**0.005**
Age, years	28 (24; 36)	27 (22; 35)	0.17
Female sex, % (n)	72.8 (91)	63.8 (81)	0.12
Education, years	15 (13; 17)	15 (12; 17)	0.14
Sick days last year, days	68 (20; 210)	40 (10; 120)	**0.019**
Full-time employment, % (n)	26.2 (32)	31.2 (39)	0.39
Student, % (n)	41.0 (50)	40.8 (51)	0.98
Civil status, single	48.4 (59)	54.8 (68)	0.31
HAMD-17	10.0 (6.3; 16.0)	8.0 (4.0; 15.0)	0.07
Hamilton anxiety item 10	1 (0; 2)	0 (0; 2)	**0.006**
Hamilton anxiety item 11	0 (0; 2)	0 (0; 1)	**0.011**
YMRS	4.0 (1.3; 8.0)	2.0 (0.0; 5.0)	**0.018**
FAST, total score¶	22.0 (14.0; 31.0)	20.0 (11.0; 31.5)	0.65
EQ-5D*	0.80 (0.75; 0.87)	0.80 (0.75; 1.00)	0.064
EQ-5D VAS	62.2 (58.5; 65.8)	65.9 (62.0; 69.7)	0.17
Alcohol weekly	2 (0; 6)	2 (0; 7)	0.72
Stressful life events	2 (1; 4)	2 (1; 3)	0.16
Bipolar disorder type II, % (n)	68.8 (86)	69.3 (88)	0.93
Age of onset, years	19.0 (16.0; 25.0)	20 (17.0; 26.0)	0.39
Illness duration, years*	11.0 (6.3; 16.0)	8.0 (3.0; 13.0)	**0.001**
Untreated BD, years†	6.0 (1.0; 12.0)	4.0 (1.0; 10.0)	0.20
No. of prior depressive episodes	6 (4; 13)	5 (3; 10)	0.07
No. of prior hypomanic episodes	5 (2; 14)	6.5 (2.0; 15.0)	0.38
No. of prior manic episodes	1 (0; 2)	1 (1; 2)	0.09
No. of prior mixed episodes	1 (0; 1)	1 (0; 3)	0.21
No. of prior total episodes	13 (7; 26)	13 (5; 30)	0.42
Prior psychosis	0 (0; 1)	0 (0; 0)	0.32
Remission, inclusion‡, % (n)	23.4 (29)	36.2 (46)	**0.026**
Partial remission, inclusion§, % (n)	59.7 (74)	69.3 (88)	0.11
Prescribed medication at baseline			
Lithium, % (n)	28.0 (35)	26.8 (34)	0.83
Antiepileptic treatment, % (n)	53.6 (67)	48.0 (61)	0.38
Antipsychotic treatment, % (n)	32.8 (41)	35.4 (45)	0.66
Antidepressant treatment, % (n)	10.4 (13)	17.3 (22)	0.11
No psychotropic medication, % (n)	22.4 (28)	18.1 (23)	0.39

All continuous variables are presented as median (first quartile, Q_1; third quartile, Q_3) or mean (95% CI) and p values are calculated based on differences in mean between the two groups using t-test for or Mann-Whitney U test. Categorical data are presented as % (n) and p values are calculated by using the χ^2 test.
*EQ-5D: a standardised measure of health status developed by the EuroQol Group.
†Illness duration was defined as the time from the first episode to the time of inclusion.
‡Remission at inclusion: HAMD-17 and YMRS<7.
§Partial remission at inclusion: HAMD-17 and YMRS<14.
¶Untreated BD was defined as the time from the first mania, hypomania or mixed episode to time of diagnosis.
BD, bipolar disorder; EQ-5D, EuroQol-5 Domain; FAST, Functional Assessment Short Test; HAMD-17, Hamilton Depression Rating Scale 17 items; SCAN, Schedules of Clinical Assessment in Neuropsychiatry; YMRS, Young Mania Rating Scale.

characteristics were more severe in patients with a SCAN verified anxiety diagnosis or with daily smartphone-based patient-reported anxiety symptoms compared with patients without an anxiety diagnosis or daily self-reported anxiety symptoms. Finally, we found that smartphone-based anxiety symptoms were associated with observer-based ratings of anxiety, patient-reported mood and stress and poorer functioning.

Current prevalence of an anxiety diagnosis in patients with newly diagnosed BD

The prevalence of a comorbid anxiety diagnosis, verified by SCAN interview, in patients with newly diagnosed BD was substantially lower than previously reported prevalences above 40% in the two recent meta-analyses.[1 2] Further, patients with a comorbid anxiety diagnosis had statistically significantly longer illness duration, untreated BD and higher number of prior affective episodes than patients without a comorbid anxiety diagnosis. In line with prior studies,[4 22 23] patients with a comorbid anxiety diagnosis reported statistically significantly more days on sick leave, lower functioning and lower self-reported health status compared with patients without a comorbid anxiety diagnosis. Overall, these findings show that the prevalence of comorbid anxiety disorders is low in newly diagnosed BD compared with other studies investigating anxiety diagnosis in later stages of BD, supporting that anxiety may increase with the progression of BD.[24] Also, the findings indicate that comorbid anxiety diagnosis should be routinely assessed in patients with BD to aid full remission and functioning between episodes.

Anxiety symptoms are often a prominent symptom during depressive episodes[25 26] and may decrease with remission of episodes.[27] Accordingly, we also found that the prevalence of comorbid anxiety diagnosis was lower in patients who at baseline were in partial (10.3%) or in full remission (5.9%). Further, in a meta-analysis investigating the prevalence of comorbid anxiety disorder, the prevalence of comorbid anxiety diagnosis was similarly lower in euthymic patients with BD (34.7%)[28] compared with the life-time prevalence in patients with BD (45%).[2] These findings stress the importance of aiming to treat patients with BD into remission as this may decrease anxiety symptoms as well.

In contrast to a recent meta-analysis,[1] we found a relatively low prevalence of generalised anxiety disorder and social phobia. This can partly be explained by that approximately one-third of the patients were not in remission when the SCAN interview was performed. Patients in an elevated mood state may likely under-report previous anxiety symptoms. Additionally, in patients with depression it can be clinically difficult to separate whether the reported anxiety symptoms are solely related to mood episodes or present between mood episodes. If the anxiety symptoms were solely related to mood episodes, it was not considered as a separate diagnosis even if the anxiety symptoms during the mood episode fulfilled the criteria for an anxiety diagnosis. This might have led to under-reporting of some of the anxiety disorders in our study since 30% of the patients were in a depressive state at the time of inclusion. Therefore, it is of interest to repeat the assessment of anxiety symptoms again in the present sample optimally when all the participants are in remission.

Current prevalence of anxiety diagnosis in first-degree relatives

In the first-degree relatives of patients with BD, the current prevalence of SCAN verified anxiety diagnosis was 6.9%. The prevalence is lower than what we expected for the group, this might be due to the method applied to verify anxiety diagnosis or that relatives with anxiety symptoms declined to participate in the study or already had developed a BD disorder or a psychotic disorder. Anxiety disorders and anxiety symptoms in offsprings of patients with BD are associated with increased risk of onset and earlier onset of a mood disorder.[10 29–31] Early recognition of anxiety symptoms in individuals at risk seems crucial creating a possibility that both early diagnosis and prevention may be possible.[32 33] Although promising results indicate that early

Table 4 Associations between smartphone-based self-reported anxiety* and clinically rated anxiety using the Hamilton Depression Rating Scale (HAMD) and functioning according to the Functional Assessment Short Test (FAST) and smartphone-based self-reported measurements

	Model 1†			Model 2†		
	B	95% CI	P	B	95% CI	P
Smartphone-based self-reported anxiety						
HAMD anxiety item 10, N=145‡	0.45	0.33 to 0.57	**<0.001**	0.45	0.33 to 0.57	**<0.001**
HAMD anxiety item 11, N=145	0.43	0.32 to 0.55	**<0.001**	0.44	0.32 to 0.55	**<0.001**
FAST, n=143	0.013	0.004 to 0.022	**0.007**	0.013	0.004 to 0.023	**0.007**
Self-reported mood, N=125	−0.46	−0.48 to −0.46	**<0.001**	−0.46	−0.48 to −0.45	**<0.001**
Self-reported activity, N=125	−0.08	−0.09 to −0.07	**<0.001**	−0.08	−0.09 to −0.07	**<0.001**
Self-reported stress, N=97	0.42	0.41 to 0.43	**<0.001**	0.42	0.41 to 0.43	**<0.001**

*Summary measures of smartphone-based anxiety were calculated for the same time period as addressed by the observer-based rating scales: FAST the past 14 days and for HAMD-17 the past 3 days.
†Model 1: Unadjusted. Model 2: Adjusted for age and gender.
‡Measure of anxiety symptoms: subitems 10 and 11 from the observer-based HAMD-17.

intervention for high-risk individuals will be beneficial, further research is required over longer follow-up periods to determine who will benefit from which types of interventions. Also, systematic monitoring of high-risk individuals using clinical interviews is expensive and not feasible. It has been suggested by us[34] and others[35] that remote electronic monitoring of symptoms in this group of individuals may be feasible and an unobtrusive way to identify those individuals who would benefit from clinical care. Unfortunately, our present sample size was too low to investigate sociodemographic differences in this group and too few first-degree relatives provided smartphone-based anxiety self-reports.

Smartphone-based monitoring of anxiety symptoms

Smartphone-based symptoms monitoring is a reliable method to monitor changes in symptoms continuously and fine-grained. It gives a unique opportunity to measure the daily fluctuations in symptoms and thereby increase our understanding of the nature and heterogeneity of BD. We found that daily smartphone-based patient reports of anxiety reflected observer-based ratings of anxiety using the anxiety-items on HAMD-17. This indicates that daily patient reports of anxiety symptoms may be a useful measure of anxiety symptoms in patients with newly diagnosed BD.

The adherence to smartphone-based daily self-reports may decline during depressive and manic episodes,[36] therefore, the majority of patients reporting anxiety symptoms on smartphones will most likely be in partial or full remission. It is notable that despite being in partial or full remission most of the time, patients self-reported anxiety symptoms scored 1 or more 50% of the time. Interestingly, we also found that smartphone-based patient-reported anxiety was associated with an increased level of patient-reported stress and impaired functioning. Also, patients with self-reported anxiety symptoms had more days on sick leave, longer illness duration and fewer were in remission at inclusion compared with patients without daily self-reports of anxiety. These findings are of clinical importance and support previous findings concluding that anxiety symptoms are important to assess routinely during the clinical interview, in order to initiate treatment of anxiety symptoms and thereby potentially prevent worsening of the illness.[4 8 23 37]

Strengths

First, this is a large longitudinal observational study comprising 372 systematically recruited patients with newly diagnosed BD and 116 of their first-degree relatives. Second, the patients with BD were diagnosed at a specialised mood disorder clinic and all participants subsequently underwent a SCAN interview, by trained SCAN certified Ph.D. students with an MD or MSc psychology degree. Third, participants daily provided smartphone-based self-reports of mood, anxiety and stress—this is a unique way of monitoring anxiety symptoms daily and continuously, in real time and in naturalistic settings. Fourth, the system used in this study is a well-validated application suitable for long-term monitoring of symptoms.[21] Finally, the results from this study may be generalised to all patients with newly diagnosed BD because our patients were referred from the entire Capital Region of Denmark.

Limitations

First, the SCAN interview was carried out at baseline regardless of the participants' mood state. It would have been ideal to repeat parts of the SCAN interview during remission to investigate the prevalence of anxiety diagnosis at this point. Second, in table 2 when comparing clinical and sociodemographic differences between patients with and without a comorbid anxiety diagnosis, we included all anxiety diagnoses and did not differentiate between the different anxiety disorders. It is plausible that some anxiety diagnoses, such as social phobia, may impact functioning more than others. However, the sample of patients with comorbid anxiety did not allow for such subanalyses. Also, we used the SCAN interview and smartphone-based anxiety self-reports to assess anxiety. There are numerous ways to investigate the prevalence of anxiety diagnosis and symptoms in patients with BD, and it would have been interesting to include other parameters as well to verify anxiety diagnosis and to validate the smartphone-based anxiety measurement. Third, we excluded first-degree relatives with schizophrenia or other psychotic disorders or BD and therefore, the prevalence of anxiety disorder found in this study may not be representative of all first-degree relatives of patients with BD. Fourth, unfortunately, we could not include the control group in the BIO Study for this paper due to treatment requiring anxiety diagnosis being an exclusion criterion. It would have been preferable to have investigated the prevalence of anxiety diagnosis in a control group as well. Also, HC recruited among blood donors might represent a 'super healthy' control group, since there are strict criteria that blood donors must comply with to be eligible for blood donation.[38] Fifth, it was not mandatory to self-report anxiety symptoms on the smartphone application. It is therefore a limitation that we do not know why some participants filled out self-reported anxiety and some did not. In the present study, we assume that patient reports of anxiety were provided by patients who regularly or intermittently experience anxiety and therefore, we compared clinical and sociodemographic differences between participants with and without anxiety self-reports (or anxiety self-reports at 0 at all times). Half of the time the patients who

self-reported anxiety scored 0. It is probable that if we had included only participants with more severe anxiety symptoms the differences between the groups would have been larger. Also, we cannot draw any conclusions regarding adherence to daily anxiety reports, since it was solely on the participant's initiation that anxiety symptoms were reported. Finally, we cannot draw any conclusion regarding the causality between a comorbid anxiety diagnosis and clinical and sociodemographic differences, as comorbid anxiety diagnoses were assessed at inclusion only.

CONCLUSIONS

Overall, the study shows that the prevalence of anxiety was lower in patients newly diagnosed with BD compared with findings from other studies investigating later stages of BD. Further, these findings stress the importance of aiming to treat patients with BD into remission as this may decrease anxiety symptoms as well. The study supports smartphones as a useful tool for remotely monitoring anxiety symptoms on a daily basis both in patients with newly diagnosed BD and in first-degree relatives. Also, the smartphone-based recordings reveal that although patients are in partial or full remission, a substantial part of patients still experience anxiety symptoms which are important to address and treat since comorbid anxiety symptoms are associated with lower functioning and worsening of illness characteristics.

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Contributors LVK, RNJ and MF-J conceived the study. LVK and JEB obtained the required funding for the study and wrote the study protocol. LVK, MF-J, MV, JEB and MF were involved in optimising the study protocol. SS, KC, KSOS, HLK, IS and MV have been responsible for the recruitment of participants and have carried out the assessment and data collection. MF and SS have been responsible for data processing. Data analyses were done by SS and supervised by MF-J and LVK. Interpretation of the data has been done by SS under the supervision of LVK and MF-J. All authors have read, contributed to and approved the final version of the manuscript.

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