

The Association between Affectivity, Perceived Stress and Pain in Patients with Bipolar Disorder

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Abstract

Objective: Patients with bipolar disorder commonly experience recurrent/chronic pain, usually associated with worsening of the psychic state. The primary aim of the study was to evaluate the association to state anxiety, depression, perceived stress and concurrent pain. A secondary aim was to determine the locations and characteristics of pain.

Method: A cross-sectional study was conducted on 87 bipolar type 1 and 50 bipolar type 2 patients (mean age 50.4 years; 63% women). HADS-A and HADS-D was used to determine the levels of anxiety and depression, the Perceived Stress Questionnaire (PSQ) was used to measure the perception of stress, and experience of pain was determined using a validated pain questionnaire including the duration, characteristics and location of pain.

Results: Eighty-six patients (63%) reported pain, and all but 5 of these had chronic pain (≥ 3 months). Patients with pain scored significantly higher on anxiety, depression and perceived stress, and significantly lower on well being than patients with no pain. In a logistic regression using different pain locations as the dependent variables and age, gender, HADS-D, HADS-A and PSQ index score as covariates, female gender was found to be significantly associated with abdominal pain (*adjusted OR 4.59; CI: 1.09-19.2*), thoracic spine pain (*adjusted OR 4.32; CI: 1.37-14.3*), shoulder pain (*adjusted OR 3.39; CI: 1.17-4.39*) and ≥ 3 pain locations (*adjusted OR 2.55; CI: 1.06-6.13*). In both males and females the experience of stress was significantly associated with the presence of any pain (*adjusted OR 5.56; CI: 1.61-19.2*), hip pain (*adjusted OR 5.52; CI 1.41-21.7*) and neck pain (*adjusted OR 3.37; CI: 1.10-10.3*). Finally, depressive mood is significantly associated with abdominal pain (*adjusted OR 12.1; CI: 2.18-67.9*) and knee pain (*adjusted OR 5.90; CI: 1.47-23.6*).

Conclusion: In patients with bipolar disorder the experience of stress and depressive mood, but not level of anxiety, is strongly related to pain.

Keywords: Abdominal pain; Anxiety; Bipolar disorder; Chronic pain; Depression; HADS; Headache; Irritable Bowel Syndrome; Neck Pain; Pain; Perceived stress questionnaire; Stress

Introduction

Bipolar disorder (BD) is characterized by alternating highly recurrent hypomanic/manic and depressive episodes [1]. BD is a common condition with reported lifetime prevalence in the population estimated at 2.4% [2] and 1.9% of people attending general physicians has BD [3]. Furthermore, in the last decade bipolar disorder has shown to be a chronic, progressive disorder with significant residual affective symptoms between episodes of depression and mania/hypomania rather than a classically cyclical illness [4]. Recovery from episodes normally takes months and in total patients suffers from various types of affective symptoms about 50% of the time even if they are appropriately treated receiving mood stabilizing medication [5]. The burden of total health care for patients with BD is estimated at two to four times higher than for age and sex matched controls [6].

Many studies have shown that pain is common in patients with BD and even more frequent than in major depression [7]. In a recent meta-analysis the prevalence of chronic pain was 23.7% in patients with BD [8], which is a two-fold increased risk compared to the general population. Pain is associated with impaired recovery of depressive episodes [9], lower quality of life [10] and an increased risk of suicide [11].

In patients with major depression about to be hospitalized, 92% complained of at least one painful symptom and 76% reported multiple painful symptoms [12]. The presence of bodily pain in patients with major depression also predicts a more prolonged and a more severe course of the depressive episode [13]. Physical symptoms decrease

with recovery and with treatment of depression [14] indicating a mechanistic link between pain and depression. Anxiety and depression are also common in patients with unexplained somatic syndromes associated with pain such as irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome [15,16] thus supporting a bidirectional mechanistic link between affectivity and pain.

There is need for a better understanding of the relationship between mood and pain in patients with BD. So far there is a lack of data in the literature on how pain correlates with mood in patients with BD. Also, previous studies lacked the employment of a proper validated pain assessment scale, and there is insufficient information within these studies concerning the pain characteristics, including the site and the modality of the pain [8].

The primary aim of this study was to evaluate how symptoms of anxiety, depression and perceived stress relate to concurrent pain in patients with BD. A secondary aim was to determine the site and

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characteristic of pain in patients with BD and its relation to mood and stress.

Material and Methods

Study design

The study design was cross sectional.

Study participants

Outpatients with a bipolar type 1 or 2 diagnosis were considered for participation in the study, which is part of the multiple-outcome research project, the Umeå Bipolar project. The patients were treated at a specialized outpatient affective unit at Umeå University Hospital. The inclusion criteria were adults, outpatients diagnosed with BD type I or II according to DSM-IV criteria [17]. Exclusion criteria were dementia, intellectual disability, relatedness as well as any other feature that would compromise the ability to fulfil the study protocol such as not having Swedish as a mother tongue, several visual or auditory disabilities.

The present study has its focus on pain, and we included all types of pain (explained and unexplained) for two reasons. First, it is difficult in a proper well-founded manner to separate explained and unexplained pain, and secondly, the aim was to explore how patients with BD experience all types of pain in relation to symptoms of anxiety/depression. Information on number of hypo-/manic/depressive episodes and the history of the duration and start of stabilizers for bipolar disorder was taken from medical records. Information regarding socio demographic variables and concurrent medication was recorded from questionnaires.

Ethics

All patients and control subjects gave written consent to participate in the study. The local committee for human ethics, Umeå University, approved the study.

Evaluation of symptoms of anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) developed by Zigmond and Snaith in 1983 [18], is a highly sensitive instrument to screen for symptoms of anxiety and depression among patients with somatic conditions. It consists of 7 items each for anxiety and depression, each using a 4-point Likert scale. We used the HADS scale because it has a high sensitivity in detecting symptoms of anxiety and depression, it is well validated, and it is simple to fill in, which facilitates a higher response rate [19,20]. The accepted cut-off level of 8 points or more for the depression part of HADS (HADS-D) was used to define patients suffering from a moderate or severe depressive mood, and the cut-off level of 9 points or more were used for the anxiety part of HADS (HADS-A) to define patients suffering from moderate and severe anxiety.

Evaluation of pain

We used a validated pain questionnaire [21] designed to evaluate pain conditions for patients referred to a Multidisciplinary Pain Centre (at Karolinska Hospital, Stockholm). The pain questionnaire comprises demography, history of pain, and present status of the pain (continuous or recurrent). The patients were asked "When was the first time you felt the pain you have at present?", "Is your present pain continuous and/or recurrent?" "If the pain is continuous, since when has it been continuous?". Visual analogue scales (VAS) were used for evaluating pain intensity (at present and average pain last week) and overall present health status. In the questionnaire, the location, distribution

and quality of pain are presented in a pain drawing, which also includes pain descriptors. The pain descriptors were: Nagging, Stabbing, Burning, Sweltering, Throbbing, Prickling, Scurrying and Other. From the pain-drawing figure, thirteen body areas were defined (Head, Neck, Thoracic spine, Lower Spine, Shoulder, Arm, Hand, Thorax, Abdomen, Sexual organ, Hip, Knee and Foot).

Evaluation of stress

We used the Perceived Stress Questionnaire (PSQ) which was developed to measure general stress perceived during the past year and emphasizes cognitive perceptions more than emotional states or specific life events [22]. The PSQ consist of 30 items using a 4-point Likert scale (0-3 points). A PSQ index, varying from 0 (the lowest level) to 1 (the highest level) is calculated by dividing the total raw score with 90 [22]. We used the estimated PSQ index of >0.34 to define moderate level of perceived stress [23].

Statistics

All analyses were carried out using SPSS, version 23. Student T-test was used for comparison between groups with respect to continuous data and Mann-Whitney test was used with respect to ordinal data. Chi-square test was used for crosstabs analyses and Fischer exact test was used in the crosstabs analyses when the number of cases was small (<10). Spearman test was used for correlations.

A two-sided p-value less than 0.05 was regarded significant. Means and standard deviations were used for continuous variables. Medians and inter quartile range (IQR) were used for ordinal variables. No correction for multiple testing was applied. A logistic regression (SPSS/analyze/regression/binary logistic) was used for adjusting for possible confounders to reported present pain. In the regression model age was regarded as continuous variable. HADS-D was categorized into two groups according to the accepted "cut-off" at ≥ 8 points, HADS-A was categorized into two groups according to the accepted "cut-off" at ≥ 9 points [19,20] and PSQ index was categorized into two groups according the estimated moderate level of perceived stress (PSQ index >0.34) [23]. The Hosmer-Lemeshow test was used to test the accuracy of the logistic regression model.

Results

Basic characteristics of the study population

One-hundred-thirty-seven patients (87 bipolar type 1 and 50 bipolar type 2) between 20 and 84 years of age fulfilled the inclusion criteria and accepted participation. All patients were on stable drug treatment for at least three months prior to the study. There was a majority of women (63%). Sixty-four percent of the patients were of BD type 1. Sixty-three percent of the patients reported any type of pain at present or during the last week. Twenty percent of the patients were depressed (HADS-D ≥ 8) and 27% of the patients (HADS-A ≥ 9) had anxiety.

The characteristics of pain

Most commonly the patients localised their pain to the neck, shoulder and spine (the thoracic and lower regions) (Table 1). More than half (69%) of the patients with pain reported more than one pain location. The pain descriptors the patients used most to described the pain was "nagging" and "stabbing" (Table 1). More than half (56%) of the patients with pain used more than one pain descriptor.

The patients with pain

Eighty-six patients (63%) reported pain, and all but 5 of these

Pain location	
Head	18% (n = 25)
Neck	29% (n = 40)
Shoulder	20% (n = 28)
Arm	12% (n = 17)
Hand	9% (n = 12)
Thorax	7% (n = 10)
Abdomen	12% (n = 17)
Sexual organ	2% (n = 2)
Thoracic spine	20% (n = 27)
Lower spine	31% (n = 43)
Hip	17% (n = 23)
Knee	20% (n = 27)
Foot	18% (n = 24)
Number of pain locations	
1	20% (n = 27)
2	14% (n = 19)
≥ 3	29% (n = 40)
Pain descriptors	
Nagging	39% (n = 53)
Stabbing	25% (n = 34)
Burning	14% (n = 19)
Sweltering	13% (n = 18)
Throbbing	11% (n = 15)
Prickling	6% (n = 8)
Scurrying	4% (n = 6)
Other	11% (n = 15)
Continuous	19% (n = 26)
Recurrent	44% (n = 60)
Number of pain descriptors	
1	28% (n = 38)
2	18% (n = 24)
≥ 3	18% (n = 24)

Table 1: The prevalence of pain in different bodily locations and the prevalence of different pain descriptors among patients with bipolar disorder (n=137).

had chronic pain (≥3 months duration). The patients with pain had significantly higher scores of anxiety, depression and perceived stress, and had significantly lower scores on well being than patients with no pain (Table 2). The patients with pain also tended to have more depressive episodes the last five years in comparison to patients without pain. The patients who reported pain had a significant longer delay to the start of stabilizer treatment for bipolar disorder. Also the median years on stabilizer treatment was shorter in the patients with pain. There were no differences in age, sex, body mass index (BMI), educational level, marital status or bipolar type between the patients with pain and the patients without pain (Table 2). Patients with pain took more drugs than patients with no pain, particular drugs for insomnia and analgesics (including non-steroid anti-inflammatory drugs) were more commonly used by patients with pain.

The association between pain and depression

Only 4 of the 28 depressed patients (HADS-D ≥ 8) had no pain. There was a significant low to moderate correlation between HADS-D score and pain intensity, pain duration, the number of pain locations and the number of used pain descriptors (Table 3).

The pain location that showed the strongest association with depression was abdominal pain (Table 4). Abdominal pain was six times more common in the depressed patients compared with patients with low depression scores. Also, pain localized to the knee was significantly more common in the patients with present depression when adjusted for covariates (Table 4). The pain descriptors “Prickling”, “Stabbing” and “Burning” was significantly more often noted by the depressed patients but in a logistic regression analysis adjusted to covariates age, gender, HADS-A and PSQ index there was no significant association.

The association between pain and anxiety

Out of 37 patients with a high HADS-Anxiety score (≥9) 78% (n = 29) reported pain that was significantly more frequent than the patients with a low anxiety score. The patients with a high anxiety score were

Parameters	Bipolar patients with pain (n=86)	Bipolar patients without pain (n=51)	P-value
Mean age, years (SD)	50.4 (13.5)	50.5 (16.0)	0.96
Body mass index, kg/m ² (SD)	27.6 (6.18)	26.2 (5.58)	0.18
Female gender	65% (n = 56)	59% (n = 30)	0.46
Educational level			
Primary	18% (n = 15)	16% (n = 8)	0.82
Secondary	41% (n = 35)	33% (n = 17)	0.44
University	42% (n = 36)	51% (n = 26)	0.33
Marital status			
Living with a partner	60% (n = 52)	69% (n = 35)	0.32
Divorced/Separated	14% (n = 12)	10% (n = 5)	0.6
Single	24% (n = 20)	33% (n = 10)	0.60
Widow(er)	2% (n = 2)	2% (n = 1)	1.0
Bipolar type			
Type 1	63% (n = 54)	65% (n = 33)	0.82
Type 2	37% (n = 32)	35% (n = 18)	
Mean age at onset, years (SD)	20.6 (8.99)	24.9 (11.6)	0.015
Stabilizer Treatment delay, median years (IQR)	19 (21)	9.0 (13)	0.001
Median years on Stabilizer treatment (IQR)	1.9 (7.9)	3.5 (10.1)	0.048
Median number of periods with hypomania/mania the last five years (IQR)	1 (2)	1 (1)	0.31
Median number of periods with depression the last five years (IQR)	2 (3)	1 (3)	0.062
Suicide attempts, median (IQR)	0 (1)	0 (1)	0.52
Drug treatment			
Lithium	44% (n = 38)	53% (n = 27)	0.33
Anti-epileptics	35% (n = 30)	29% (n = 15)	0.51

Neuroleptics	21% (n = 18)	26% (n = 13)	0.54
SSRI	12% (n = 10)	16% (n = 8)	0.61
SNRI	8% (n = 7)	6% (n = 3)	0.75
Benzodiazepines	13% (n = 11)	8% (n = 4)	0.42
Medication for insomnia	24% (n = 21)	8% (n = 4)	0.021
Analgesics	15% (n = 13)	4% (n = 2)	0.05
Median Number of drugs taken (IQR)	3 (4)	2 (3)	0.018
Median duration of pain (months) (IQR)	84 (164)	0 (0)	<0.001
VAS scales (0-100), median (IQR)			
For Well Being	78 (34)	96 (12)	<0.001
For Present Pain	25 (36)	0 (0)	<0.001
For Pain Last Week	32 (36)	0 (0)	<0.001
Scores on questionnaires			
HADS-Anxiety median (IQR)	5.5 (7)	4 (6)	0.007
HADS-Depression, median (IQR)	4 (7)	2 (3)	0.005
HADS-Anxiety ≥ 9 points	34% (n = 29)	16% (n = 8)	0.03
HADS-Depression ≥ 8 points	28% (n = 24)	8% (n = 4)	0.005
PSQ index (0-1) (IQR)	0.32 (0.20)	0.18 (0.18)	<0.001
PSQ index >0.34	45% (n = 38)	14% (n = 7)	<0.001

Note: Student T-test was used for comparison between groups with respect to continuous data and Mann-Whitney test was used with respect to ordinal data. Chi² test was used for crosstabs analyses and Fischer exact test was used in the crosstabs analyses when the number of cases was small (<10).
SD: Standard deviation. IQR: Intra-Quartile range. HADS: Hospital Anxiety and Depression Scale. VAS: Visual Analogue Scale. PSQ: Perceived Stress Questionnaire. SSRI: Selective Serotonin Reuptake Inhibitors. SNRI: Serotonin and Noradrenalin Reuptake Inhibitor.

Table 2: The basal characteristic of patients with bipolar disorder with pain versus without present pain.

	Present pain (VAS)	Pain last week (VAS)	Pain duration (months)	Number of pain locations	Number of pain descriptors
HADS-Depression	0.286 (p = 0.001)	0.292 (p = 0.001)	0.209 (p = 0.014)	0.234 (p = 0.006)	0.237 (p = 0.005)
HADS-Anxiety	0.177 (p = 0.034)	0.208 (p = 0.015)	0.185 (p = 0.031)	0.234 (p = 0.006)	0.224 (p = 0.008)
PSQ index	0.344 (p<0.001)	0.363 (p<0.001)	0.280 (p = 0.001)	0.346 (p<0.001)	0.353 (p<0.001)

Note: HADS: Hospital Anxiety and Depression Scale. VAS: Visual Analogue Scale. PSQ: Perceived Stress Questionnaire.

Table 3: Spearman's correlation test used on pain variables and reported symptoms of affectivity and stress.

younger than the patients with a low anxiety score (mean age 45.2 years vs 52.3 years; $p = 0.010$). There was a significant low to moderate correlation between HADS-A score and pain intensity, pain duration, the number of pain locations and the number of used pain descriptors (Table 3). In a logistic regression analysis when adjusted to covariates age, gender, HADS-D and PSQ index there was no significant association between anxiety and pain variables (Table 4).

The association between pain and perceived stress

Forty-five out of 137 patients (33%) with bipolar disorder scored moderate to high on the PSQ index. There was a significant moderate correlation between PSQ index score and pain intensity, pain duration, the number of pain locations and the number of used pain descriptors (Table 3). In the logistic regression model analysis when adjusted to covariates age, gender, HADS-D and HADS-A, PSQ index was significant associated to the presence of any pain, hip and knee pain (Table 4).

Other factors associated to pain

Female gender was in the logistic regression model analysis when adjusted to covariates age, HADS-D, HADS-A and PSQ index associated to abdominal, shoulder and thoracic spine pain, as well as to more widespread pain (≥ 3 pain locations) (Table 4). Age and BMI (when added in a logistic regression model with the presented covariates above) was not associated to pain in patients with BD. Adding "taking drugs for insomnia" with the presented covariates in Table 4 in the logistic regression was not significant (Adjusted OR 2.33; CI:0.70-7.78). There were no significant interactions between PSQ index, HADS-D, HADS-A and gender in the logistic regression model.

Discussion

Chronic pain is commonly encountered in patients with bipolar disorder. Patients with chronic multisite pain are more likely to have a major depressive disorder and are at higher risk of bipolar disorder [7]. There is little published data on factors associated with pain in BD. The present study focus on how affectivity and perceived stress are related to pain. When anxiety, depression and stress scores competes in a logistic regression model we found that the presence of any reported pain were associated to perceived stress but not to symptoms of anxiety and depression. Failde et al. [24] conducted a similar cross-sectional study as ours, and after adjusting for several variables they found that older age, being separated or divorced, having a prior diagnosis of other types of depression, and having sleeping disorders was associated with pain but not depression score (measured by Hamilton scale score) [25]. In that study there was no instrument for evaluating stress. In consistent with Failde et al. insomnia (medications for insomnia) was associated with pain. However, we could not repeat the association of marital status and age with pain.

Interestingly, we found that pain was almost an obligate symptom (86% of the patients) in patients with BD who scored high on depression. Depressive mood was after adjusting for age, gender, anxiety and stress significant associated with abdominal and knee pain. We found no previous study evaluating the association between the localisation of pain and depression. Of interest therefore, we found a six-fold increased frequency of localised abdominal pain, highest among all body parts, among the patients with depressive mood. A cautious interpretation of this finding is that the abdominal area mostly taps into visceral stimuli and pain, which point to an association between a depressive mood and

Dependent variable	Age	Female gender	HADS- Depression ≥ 8	HADS-Anxiety ≥ 9	PSQ index >0.34
Any pain (n = 86)	1.02 (0.99-1.05)	1.66 (0.76-3.63)	1.78 (0.43-7.34)	0.93 (0.28-3.03)	5.56 (1.61-19.2)
Head (n = 25)	0.99 (0.95-1.03)	2.19 (0.79-6.10)	0.46 (0.12-1.84)	1.21 (0.35-4.23)	2.71 (0.71-9.56)
Neck (n = 40)	1.00 (0.97-1.03)	2.02 (0.87-4.05)	0.62 (0.19-2.03)	1.21 (0.41-3.59)	3.37 (1.10-10.3)
Shoulder (n = 27)	0.97 (0.94-1.01)	3.39 (1.17-4.39)	0.85 (0.23-3.17)	2.03 (0.60-6.92)	2.08 (0.58-7.40)
Arm (n = 16)	1.00 (0.96-1.04)	1.36 (0.44-4.22)	0.83 (0.17-3.98)	1.46 (0.34-6.24)	1.52 (0.33-6.99)
Hand (n = 12)	1.00 (0.96-1.05)	2.16 (0.53-8.70)	3.34 (0.56-19.8)	0.51 (0.09-2.84)	1.82 (0.31-10.8)
Thorax (n = 10)	1.00 (0.94-1.06)	0.51 (0.13-1.99)	0.25 (0.04-1.72)	2.69 (0.51-14.1)	3.34 (0.53-21.0)
Abdominal (n = 17)	1.02 (0.97-1.07)	4.59 (1.09-19.2)	12.1 (2.18-67.9)	0.90 (0.18-4.40)	0.94 (0.16-5.69)
Thoracic spine (n = 27)	0.97 (0.94-1.01)	4.32 (1.37-14.3)	1.21 (0.32-4.63)	1.15 (0.33-4.09)	1.32 (0.37-4.77)
Lower spine (n = 42)	1.00 (0.97-1.03)	1.20 (0.54-2.66)	3.00 (0.94-9.53)	0.72 (0.24-2.19)	1.72 (0.57-5.25)
Hip (n = 23)	1.02 (0.99-1.06)	1.34 (0.49-3.65)	1.09 (0.31-3.88)	1.19 (0.35-4.08)	5.52 (1.41-21.7)
Knee (n = 24)	0.98 (0.94-1.01)	1.49 (0.56-3.94)	5.90 (1.47-23.6)	0.78 (0.21-2.84)	0.72 (0.18-2.85)
Foot (n = 24)	1.02 (0.99-1.06)	2.41 (0.83-6.94)	2.79 (0.75-10.4)	1.11 (0.30-4.03)	1.91 (0.47-7.65)
≥ 3 pain locations (n = 40)	0.99 (0.96-1.02)	2.55 (1.06-6.13)	1.50 (0.46-4.90)	1.25 (0.42-3.74)	2.15 (0.70-6.59)

Note: The table presents adjusted odds ratios with 95% confidence intervals (in paragraph) for the covariates age, gender, HADS score and PSQ score and when using different pain locations as dependent variable. Age is used as a continuous variable and the other covariates as dichotomous variables.

HADS: Hospital Anxiety and Depression Scale, PSQ: Perceived Stress Questionnaire.

Table 4: Logistic regression analysis studying factors which may influence reported present pain in patients with bipolar disorder (n = 137).

visceral pain. Moreover, studies on patients with unipolar [26] when in a depressive mood, show significantly more functional gastrointestinal symptoms and in consistency patients with irritable bowel syndrome also report more anxiety and depressive symptoms than expected [15].

Location of pain in patients with BD was also reported by Failde et al. They reported five different sites of pain in patients with BD but they did not present data on abdominal pain [24]. They found that patients with BD mostly reported back pain (38%), followed by pain in limbs (35%), head (34%), neck (34%) and joints (33%) which are proportions in parity presented in our study. A recent review found that migraine was associated to more depressive episodes but in our study there were no difference in headache between patients with high or low scores on depression [27].

What is the link between stress, depression and pain? The association between stress and pain could be interpreted in two ways. Firstly, chronic stress and depression may lower pain threshold. Secondly, chronic pain may decrease stress tolerance and lead to depression.

The neurobiological mechanism of pain and depressive mood is complex, probably reciprocal and mostly unknown. The experience of pain involves a sensory component but also perception, cognition and higher brain centre processing [28]. The widespread pain reported by patients with bipolar disorder and major depression, may reflect abnormalities in higher brain-centre function or in an insufficient pain inhibition leading to that the bipolar patients reporting widely distributed pain.

Certain brain structures, i.e. hippocampus and amygdala have been suggested to be involved in the pathogenesis of pain in patients with depression [28,29]. These structures are involved in the pain

matrix that transmit and decode nociceptive information, generate, amplify or reduce the pain sensation, allow expression of defensive or distress behaviour as well as influencing affect regulation [29]. The hippocampus also plays a role in stress and anxiety regulation as well as in memory and learning processes. The brain structure additionally, participates in the processing and modification of nociceptive stimuli [28] and seems to integrate sensory, autonomic and affective information. Chronic pain, chronic stress and depression have been associated with hippocampal atrophy [30-33].

Affectivity and mood involves also the amygdale, which have bidirectional pathways with hippocampus. Amygdale is considered to provide an emotional value – either positive or negative – to sensory information, and to adaptive behavioral, affective responses and to emotional memory [29]. The central nucleus of amygdala receives nociceptive information from multiple sources, i.e. the brainstem, thalamus and the cerebral cortex and is believed to play a role in both hypoalgesia seen in acute stress and in hyperalgesia seen in chronic stress [29].

Interestingly, the patients with pain in our study showed a significant delay in stabilizer treatment for BD and had been treated for a shorter time with stabilizers than the patients with no pain. In addition, the patients with pain in our study tended to have a history of more depressive episodes in the past. An interpretation of these data could be that an untreated bipolar disorder and consequently a higher stress load may have an effect on the hippocampus and the amygdala leading to long-term or even permanent changes in these areas with subsequently hyperalgesia.

What are the options for treating unexplained pain in BD? One theory behind pain in depression is an insufficient pain inhibition by

monoamines [34]. It is well known that antidepressants have an effect on chronic pain [35,36]. For example, duloxetine, a selective noradrenalin and serotonin reuptake inhibitor (SNRI) is effective in treating affective disorders and pain conditions such as diabetic neuropathic pain [37]. In addition, in patients with major depression and pain treated with duloxetine, the depression remission rate for pain responders was twice the rate of remission on pain non-responders [38].

Our study was unpowered to show differences in the use of selective serotonin reuptake inhibitors (SSRI) and SNRIs among patients with and without pain.

Overall in this study the prevalence of any present pain in patients with BD (63%) was higher than the pooled prevalence of clinical pain in BD presented in a recent systematic review (29%) [8]. Possible reasons for this could be the use of more sensitive instruments to detect pain in our study (i.e. pain questions and pain drawings) or that this is a cross-sectional study focusing on present pain. However, 81 of 86 patients reported that the onset and duration of their present pain was more than 3 months ago, which by definition is chronic. In the Spanish cross-sectional study by Failde et al who used an interview confirmed by a VAS scale to estimate the prevalence of pain in patients with BD there was a pain prevalence of 51% [24].

There are some limitations in our study. The study design was mainly cross-sectional, which results in a lack of clear insight into the temporal relationships between stress/affectivity and pain. A prospective study design, analyzing pain in patients with affective disorder over time would be an appropriate way to move forward in elucidating the temporality of this relationship. Also, in studies comparing results from questionnaires, there is some risk of report bias (reporting the same type of dignity on different scales). However, we believe that the use of a pain chart in addition to the employment of questionnaires reduces the risk of such a potential bias. Finally, some subgroups analyses in the study may be interpreted cautiously due to a relative small number of subjects.

To conclude, perceived stressed is associated to the present of any pain overall as well to hip and neck pain in patients with BD. Depressive mood is associated with abdominal pain and knee pain. It is known that pain in patients with BD is associated with a lower quality of life [10] and with suicidal behaviour [11] and deteriorate the recovery of affective symptoms [9]. Hence, there are multiple reasons as to why it is important to identify chronic pain in these patients and to treat not only the psychiatric symptoms but also to involve coping strategies for stress as well as treatment of pain.

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Author contribution

PK and KFN constructed the study design, contributed in the acquisition of the data, analyzed the data, interpreted the data and wrote the manuscript. RA constructed the study design, contributed in the acquisition of the data, interpreted the data and wrote the manuscript. MM constructed the study design, interpreted the data and wrote the manuscript. All authors did a final approval of the version to be published.

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