The interplay between depression, anxiety and physical health

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2014

document version
Publisher's PDF, also known as Version of record

Chapter 5

Impact of pain on the course of depressive and anxiety disorders

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Published in: Pain. 2012 Feb;153(2):429-36.

ABSTRACT

The combination of pain and depression or anxiety is commonly seen in clinical practice. Little is known about the influence of pain on psychopathology over time as previous studies were mainly cross-sectional. The objectives of this study are to determine the impact of pain on the course of depressive and/or anxiety disorders and investigate to what extent the association between pain and course of these mental disorders is mediated by psychiatric characteristics. Data from the Netherlands Study of Depression and Anxiety, collected between 2004 and 2009, were used. 1,209 participants with a depressive and/or anxiety disorder at baseline were followed for two years. Baseline pain was assessed by location, duration, use of pain medication and severity (Chronic Pain Grade). Course of depressive and anxiety disorders was assessed by CIDI and Life Chart Interview. A higher number of pain locations (OR=1.10; p=.008), joint pain (OR=1.64; p<.001), ≥90 days of pain (OR=1.40; p=.009), daily use of pain medication (OR=1.57; p=.047) and a higher chronic pain grade (OR=1.27; p<.001) were associated with worse course of depressive and anxiety disorders. These associations were largely mediated by baseline severity of the mental disorder. However, joint pain remained associated with a worse course independent of baseline psychiatric characteristics. This study shows that patients with pain are more prone towards a chronic course of depressive and anxiety disorders. More attention to pain seems necessary when diagnosing and treating these disorders. Future research should focus on treatment modalities for this co-occurrence, with joint pain in particular.

INTRODUCTION

Physical pain, both short-term and chronic, is frequently reported by patients with depressive and/or anxiety disorders[1-5]. Yet, studies focusing on the influence of pain in subjects with a depressive or anxiety disorder are relatively scarce[6;7]. Bair et al[8] reviewed the literature on comorbidity of depression and pain and found 14 studies of depressed patients in whom pain symptoms were assessed, and the mean prevalence of pain was 65% (15-100%). Fewer studies have investigated this relationship for anxiety disorders, mostly focused on post-traumatic stress and panic disorders. Recently, Asmundson et al.[6] reviewed 3 studies in which 20 to 70% of panic disorder patients reported chronic pain. These reviews and more recent cross-sectional studies have concluded that the combination of a depressive or anxiety disorder with pain is associated with poorer clinical outcome and increased health care use and costs than either condition alone[6;8-11].

The course of depressive and anxiety disorders varies widely. In about 40% of cases these disorders have a short duration, but over 40% of patients have a recurrent disorder and 5-30% of patients suffer from a chronic depressive or anxiety disorder[12-14]. Currently, studies are focusing on the identification of factors predicting the course of depressive disorders. Identified factors associated with an increased risk of recurrence, chronicity or treatment resistance of depressive disorders are greater severity of the index episode, more residual depressive symptoms, early age of disorder onset and psychiatric comorbidity[13;15;16]. Furthermore, some evidence for a poorer course has been found in randomized controlled trials in patients a with depressive disorder and comorbid pain[17;18]. One trial, which evaluated the effect of a collaborative stepped-care program for late-life depression, found that greater pain severity was associated with higher levels of severity of depressive symptoms and lack of remission of the depressive disorder[19]. A treatment trial for participants with panic disorder and generalized anxiety disorder showed that disabling pain was associated with more severe anxiety symptoms over time and a lower likelihood of responding to treatment[20]. Although some cross-sectional studies and treatment trials show that pain might influence depressive and anxiety disorders, to the best of our knowledge, no large study has longitudinally examined the impact of pain on the course of depressive and anxiety disorders. In addition, the extent to which the effects of pain are independent of or accounted for by other confirmed clinical course determinants – such as severity, duration and age of onset of the depressive or anxiety disorder - has not been determined yet. Therefore, the objectives of this study were to: (1) examine the influence of pain on the 2-year course of depressive and/or anxiety disorders, and (2) investigate to what extent the association between pain and course of these mental disorders is mediated by or independent of other clinical psychiatric characteristics (such as severity, duration, age of onset).

METHODS

Study sample

The present study is part of the Netherlands Study of Depression and Anxiety (NESDA), an eight-year ongoing cohort study in which 2,981 participants, recruited from community, general practice and secondary mental health care, are being monitored to investigate the long-term course and consequences of depressive and anxiety disorders. Penninx et al.[21] provide a detailed description of the NESDA study design and sampling procedures. At baseline, healthy controls, persons with a prior history, and persons with a current depressive and/or anxiety disorder, aged between 18 and 65 years, were included. Exclusion criteria were not being fluent in Dutch and a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. The Ethics Committee of participating universities accredited the research protocol and a written informed consent was obtained from all participants. Specially trained research staff conducted the interviews.

All 2,981 participants were screened for depression and anxiety in the baseline interview using the DSM-IV based[22] Composite International Diagnostic Interview (CIDI, version 2.1), a highly reliable and valid instrument for assessing depressive (Minor and Major Depressive Disorder, Dysthymia) and anxiety (Social Phobia, Generalized Anxiety Disorder, Panic Disorder, Agoraphobia) disorders[23;24].

For this study, the sample was restricted to subjects with a depressive and/or anxiety disorder who were symptomatic in the month prior to baseline as confirmed in the CIDI recency questions or the Life Chart Interview[25] (LCI, see below). Of the eligible participants (n=1,456), 1,209 (83.0%) participated in the two-year follow-up interview and were included in this study. Baseline data collection took place between 2004 and 2007, with a follow-up assessment two years later. Non response was significantly higher among those with younger age, lower education, non-North European ancestry and depressive disorder, but was not associated with gender or anxiety disorder[26].

Measurements

Pain Assessment

To assess pain, two measures were included without a time element: a) the specific pain location, b) the number of pain locations. Three other measures were used to define pain with inclusion of a time element c) duration of pain for ≥ 90 days d) use of pain medication and e) chronic pain severity determined by the chronic pain grade[27] (CPG). For convenience we further regarded the pain variables with a time element as the "chronic pain" variables. First, to locate specific pain, a) an inventory was made of pain symptoms of joints in the extremities, back, neck, abdomen, chest, head and orofacial area in the last six months. Then, b) the number of pain locations (0-7) was assessed. The participant was asked to choose the most painful of those, to which all subsequent questions applied. To measure c) duration of pain, the number of days in pain in the last 6 months (0-180) was assessed and divided into greater or equal to 90 days and less than 90 days, since existing literature usually defines pain to be chronic if lasting more than 3 months[28]. For d), use of pain medication, the participant was asked whether he or she used medication for pain in the past six months, the use was divided in daily, weekly to monthly, and sporadic to no use. Next, e) chronic pain severity was graded by measuring the intensity and disability caused by pain using the CPG scale developed by von Korff et al[27]. The CPG instrument measures pain intensity based on the mean of the average, worst and present pain on a 0-100 scale. In addition, it assesses pain disability based on the mean of interference (0-100 scale) with usual activities, work/housework activities and family/social activities and the number of days (0-180) unable to carry out usual activities due to pain in the prior six months. For disability caused by pain, an overall 0-6 score was created by assigning 0-3 points for disability score (0-29, 30-49, 50-69, 70-100 rating) and adding 0-3 points for number of disability days (0-6, 7-14, 15-30, >31 days). Based on earlier work and on an observed hierarchical relationship between pain intensity and disability[27], the CPG was classified as:

- grade 0: no pain symptoms
- grade 1: low pain intensity-low disability (intensity <50, <3 disability points)
- grade 2: high intensity-low disability (intensity ≥50, <3 disability points)
- grade 3: high disability-moderately limiting (3-4 disability points regardless of intensity)
- grade 4: high disability-severely limiting (5-6 disability points regardless of intensity).

The CPG has shown to be generalizable across different anatomical sites and has previously proven to be a reliable and valid pain scale in both chronic pain populations and the general population[27;29].

Course of depressive and/or anxiety disorder

To assess the course of depressive and anxiety disorders, a face-to-face follow up assessment with a CIDI interview was first conducted after two years to assess psychiatric status based on the presence of CIDI DSM-IV diagnosed depressive or anxiety disorders (6-month recency: over the last six months).

To define the clinical course trajectory of the index disorder over the two years, the interviewers then completed the LCI for all persons with detected symptoms at the 2-year CIDI interview. Using a calendar method, life events were recalled to refresh memory, after which the depressive and anxiety symptoms were determined, for each month separately, during the previous two years. In addition, for each month with reported symptoms, severity was assessed. Symptoms on LCI were only considered to be present when at least of mild severity. Using both the CIDI and the LCI results, we defined four categories on the basis of depressive and/or anxiety symptoms over time:

a) early sustained remission: remission within six months and no recurrence of any symptoms during follow-up, b) late sustained remission: remission after six months without recurrence, c) remission with recurrence: recurrence of depressive or anxiety symptoms after initial remission, d) chronic course: at least mild symptoms during the entire follow-up period. Based on the LCI we defined remission of the index disorder as reporting no symptoms for three consecutive months[30].

Covariates

Covariates were selected a priori on the basis of previously reported associations between both pain and depressive and/or anxiety disorders. Socio-demographic characteristics included age, sex and years of education[31]. We also assessed the number of chronic diseases[19]. Self-reports were used for ascertainment of the presence of coronary artery disease, cardiac arrhythmia, heart failure, stroke, chronic lung disease, diabetes mellitus, thyroid disease, epilepsy, migraine or other headache, multiple sclerosis, neuropathy, osteoarthritis, rheumatoid arthritis, intestinal disorders, ulcer and cancer for which participants were currently under physician control or currently treated. We discerned seven groups of chronic diseases (based on the International Classification of Primary Care [ICPC])[32]; cardiovascular, pulmonary, endocrine, neurological, musculoskeletal or digestive disorder or cancer.

We considered several clinical characteristics of the depressive and/or anxiety disorder to be possible mediating variables in the relationship between chronic pain and course of depression and anxiety disorders. A mediator is an intervening variable that may account (statistically) for the relationship between the independent (pain) and dependent variable (course of depression and anxiety)[33]. Previous studies have shown that patients with pain have worse severity of depression and anxiety, and also that severity of the index episode, residual symptoms and early age of disorder onset influence course[19;20;30]. For these reasons we hypothesized that the impact of pain on the course of depression and anxiety might be mediated by clinical characteristics of the mental disorder. Age of onset of the index disorder was derived from the CIDI; for those with co morbid disorders the earliest age was used[23;24]. Information on duration of symptoms in the four years prior to baseline was assessed using the LCI at baseline[25]. Severity of depressive symptoms at baseline was measured using the 16-item Quick Inventory of Depressive Symptomatology -Self-Report, in which no pain items are included[34] (QIDS-SR). Severity of anxiety symptoms at baseline was measured using the 14-item self-report Fear Questionnaire, also not containing pain items[35;36] (FQ). We did not take into consideration whether the mental disorder was recurrent or first-onset, or whether persons were treated with antidepressant medication or psychological treatment, since a previous study showed no significant differences in course trajectories for these variables[30].

Statistical analysis

We used descriptive statistics to assess the prevalence of pain and baseline characteristics. With logistic regression analyses we assessed the association between pain indices and the presence of depressive and anxiety disorders after two years, before and after adjustment for basic covariates (age, sex, level of education, and number of chronic diseases). Based on earlier evidence[2;8;13;15], we subsequently tested whether psychiatric clinical characteristics are possible mediators of the associations between the pain variables and course of depression and anxiety that could at least partly explain why pain variables are associated with course outcomes. Testing for mediation using the causal steps approach involves four criteria that need to be fulfilled[33;37]. After associating pain to course outcomes, a second criterion concerns whether indeed pain variables are associated with clinical characteristics. For this purpose, their associations were examined using linear regression analyses. The third criterion, explores whether clinical characteristics are associated with depression and anxiety course, which has been demonstrated before[30]. To meet the final criterion, we tested whether, after entering clinical characteristics in final logistic regression analyses, the association between pain and outcome measures was significantly reduced (>10%).

Next to these analyses, associations between pain variables and course trajectories were also investigated using multinomial regression analyses, with early sustained remission as reference category. We also explored – following the above presented steps – to what extent associations between pain and course trajectories were mediated by clinical characteristics.

RESULTS

Characteristics of the 1,209 subjects are presented in Table 1. The mean age of the participants in the study was 42.1 years (SD=12.3) and 66.0% was female. At baseline, 22.1% had a depressive disorder only, 40.3% an anxiety disorder only and 37.6% had a comorbid disorder. The mean number of pain locations was 3.68 (SD=1.7). Headache was the pain location most frequently mentioned, least mentioned was orofacial pain. Almost half of the patients (41.4%) had at least 90 days of pain in the past 6 months. Pain medication was used daily by 10.3% of participants. The mean chronic pain grade (CPG) was 1.90 (SD=1.1). Of the participants only 35 patients (2.9%) had grade 0 and they were therefore combined with those who had grade 1. Of all participants, 27.1% was suffering with high disability from chronic pain (grades 3 and 4) indicating that they had severe chronic pain. Spearman correlations between the CPG and the number of pain locations (0.36, p<.001), and the CPG and days in pain (0.49, p<.001) were modest in magnitude, indicating that these reflect partly different concepts.

Two thirds (61.5%) had a 6-month recency diagnosis of depressive and/or anxiety disorder after two years. Within six months after baseline 24.6% recovered from their depressive and/or anxiety disorder, 13.4% recovered after more than 6 months, 18.5% had at least one relapse during follow-up and 43.5% had a chronic course for two years.

Table 2 shows the basic adjusted logistic regression analyses assessing the association between pain variables and psychiatric outcome. These results were similar compared to the unadjusted analyses. Pain of the joints showed a significant association with having a depressive and/or anxiety disorder after two years (OR=1.64; 95%CI=1.29-2.10). No associations were found for the other locations. The number of pain locations was also significantly associated with having a disorder after two years (per location increase: OR=1.10; 95% CI=1.03-1.18). Chronic pain as measured by ≥ 90 days of pain (OR= 1.40; 95% CI= 1.09-1.79), the daily use of pain medication (OR=1.57; 95% CI=1.01-2.44) and CPG (per grade increase: OR=1.27; 95% CI=1.12-1.43) turned out to be strong pain predictors of the presence of depressive and/or anxiety disorders at the 2-year follow-up. To examine whether findings differed between the depressive, anxiety disorder and comorbid disorder, we conducted subanalyses with the outcomes depressive disorder (n=483), anxiety disorder (n=564) and comorbid disorder (n=303) at the 2 year follow-up separately. Results were very comparable for the single disorders indicating that pain has a rather similar impact on the course of depressive versus anxiety disorders. When using comorbidity as the indicator of course, some stronger associations were found (e.g. CPG (OR=1.37; 95%CI=1.21-1.55), ≥ 90 days of pain (OR=1.57; 95%CI=1.19-2.08) and pain of the neck (OR=1.32; 95%CI=1.00-1.73)). This suggests that pain variables may even be of more importance when a more severe course outcome is examined.

Table 1: Baseline sample characteristics.

Characteristics	Population (n=1,209)
Sample characteristics	
Female gender, %	66.0
Age in years, Mean (SD)	42.1 (12.3)
Education in years, Mean (SD)	11.8 (3.3)
Number of chronic diseases, Mean (SD)	0.65 (0.9)
Baseline clinical characteristics	
Depressive disorder, %	22.1
Anxiety disorder, %	40.3
Co-morbid disorder, %	37.6
QIDS score, Mean (SD)	11.6 (5.0)
Fear questionnaire score, Mean (SD)	34.0 (20.3)
Duration of symptoms prior to index episode (% of time of prior 4 years), Mean (SD)	58.5 (35.0)
Age of onset of mental disorder, Mean (SD)	21.0 (12.6)

Table 1 continued.

Pain characteristics	
Number of pain locations, Mean (SD)	3.68 (1.7)
0-1, %	11.1
2-3, %	35.0
4-5, %	38.5
6-7, %	15.5
Pain location, %	
Neck	60.4
Back	67.8
Head	76.6
Orofacial	18.1
Abdominal	57.9
Joints	51.9
Chest	35.6
Duration of pain (days), Mean (SD)	
≥ 90 days, %	41.4
Use of pain medication, %	
Never to sporadic	56.9
Monthly, weekly	32.8
Daily	10.3
Chronic Pain Grade, Mean (SD)	1.90 (1.1)
Grade 0-1, %	49.7
Grade 2, %	23.2
Grade 3, %	14.3
Grade 4, %	12.8
Outcome characteristics	
Psychiatric disorder after two years, %	61.5
Clinical course trajectory, %	
Early recovery (<6 months)	24.6
Late recovery (≥ 6 months)	13.4
Remission and recurrence	18.5
Chronic course	43.5

Abbreviation: QIDS-SR= Quick Inventory of Depressive Symptomatology-Self Report

Table 2: Associations between pain variables and the presence of a depressive and/or anxiety disorder at 2-year follow up [a].

Baseline variable	Depressive and/or anxiety disorder at 2-year follow-up [b]	
	OR (95% CI)	p
Number of pain locations (total)	1.10 (1.03-1.18)	.008
0-1	reference	
2-3	1.08 (0.73-1.61)	.709
4-5	1.16 (0.78-1.73)	.460
6-7	1.79 (1.10-2.89)	.018
Pain location		
Neck	1.12 (0.88-1.42)	.353
Back	0.99 (0.77-1.28)	.959
Head	1.20 (0.91-1.59)	.207
Orofacial	1.14 (0.84-1.55)	.394
Chest	1.19 (0.92-1.53)	.181
Abdominal	1.16 (0.90-1.48)	.249
Joints	1.64 (1.29-2.10)	<.001
Duration of pain		
≥ 90 days	1.40 (1.09-1.79)	.009
Use of pain medication		
Never to sporadic	reference	
Monthly, weekly	0.91 (0.70-1.18)	.460
Daily	1.57 (1.01-2.44)	.047
Chronic Pain Grade (continuous)	1.27 (1.12-1.43)	<.001
Grade 1	reference	
Grade 2	0.87 (0.83-1.49)	.490
Grade 3	1.66 (1.15-2.40)	.007
Grade 4	2.02 (1.34-3.04)	.001

a Using logistic regression analyses

b Adjusted for age, gender, years of education, number of chronic diseases

As stated previously, we examined whether psychiatric clinical characteristics mediated the association between pain and course of the depressive or anxiety disorder. Therefore, as a first criterion, in Table 2 we have shown the association between pain and psychiatric outcome (see above). The second criterion of mediation, which involves assessing whether there is an association between pain and the clinical characteristics, is shown in Table 3. These clinical characteristics were previously shown to be associated with depression and anxiety outcome[30]. All pain variables were associated with baseline depression severity, and that number of pain locations, several pain locations, pain for 90 days or more and chronic pain grade, were significantly associated with baseline anxiety severity. However, pain was not associated with duration of depressive and anxiety symptoms prior to baseline assessment and hardly associated with the age of onset of the mental disorder, except for abdominal pain which was associated with younger age of onset. Duration of symptoms and age of onset were consequently not regarded as mediators in the final step.

Finally, Table 4 displays the associations between pain and having a depressive and/or anxiety disorder at 2-year follow up after additional adjustments for the depression and anxiety severity; QIDS-SR score and Fear score. Table 4 only displays the pain variables that were significantly associated with course outcome in Table 2. Most associations between pain indices and course lost significance, which appeared to be mainly due to the influence of QIDS-SR score for depression severity. However, having pain of the joints (OR=1.53; 95% CI=1.18-1.98) was still significantly associated with having a depressive and/or anxiety disorder at the 2-year follow up. We checked our causal steps approach[37] by using the approach by Preacher and Hayes[38], which estimates both a direct and an indirect effect through a mediator variable. This approach showed similar results with confirming both significant direct effects and indirect effects through depression severity for joint pain on the course of depression and anxiety.

In addition to examining the course at the two year follow up, we conducted analyses for the association between pain variables and clinical course trajectories over two years (data not shown). The results of multinomial logistic regression analyses showed that the number of pain locations, the specific pain locations and daily use of pain medication did not predict course trajectories, although pain of the joints was borderline significantly associated with a high risk of a recurrent course (OR=1.39; 95% CI=0.96-2.01). Of the chronic pain variables, pain for 90 days or more was associated with having a chronic course (OR=1.51; 95% CI=1.11-2.05) and a higher CPG was associated with having late recovery (borderline significant: OR=1.18; 95% CI=0.98-1.44) and a recurrent (OR=1.18; 95% CI=0.99-1.41) or chronic course (OR=1.20; 95% CI=1.04-1.39). The findings on course trajectories were no longer significant after further adjustments for severity of depression and anxiety.

Table 3: Adjusted [a] associations between pain variables and baseline clinical characteristics of the mental disorder.

Baseline variable	Duration of symptoms prior to index episode[b]		Age of onset of mental disorder[b]		Severity of depressive disorder[b]		Severity of anxiety disorder[b]	
	β	p	β	p	β	p	β	p
Number of pain locations	.024	.410	-.053	.059	.341	<.001	.123	<.001
Pain location								
Neck	.012	.684	-.053	.054	.224	<.001	.075	.009
Back	-.047	.106	-.016	.549	.146	<.001	.043	.136
Head	.014	.624	-.001	.967	.178	<.001	.059	.044
Orofacial	.024	.398	-.015	.572	.117	<.001	.036	.206
Chest	.040	.171	.013	.642	.208	<.001	.083	.005
Abdominal	.009	.760	-.061	.031	.215	<.001	.101	.001
Joints	.037	.220	-.050	.076	.141	<.001	.038	.197
Duration of pain								
≥ 90 days in pain	.007	.811	-.016	.569	.173	<.001	.096	.001
Use of pain medication								
Never to sporadic	reference		reference		reference		reference	
Monthly, weekly	.006	.828	.008	.775	.041	.165	.046	.124
Daily	-.034	.269	.049	.093	.148	<.001	.047	.128
Chronic Pain Grade	-.015	.613	.033	.243	.320	<.001	.178	<.001

a Adjusted for sex, age, years of education, number of chronic diseases
b Using linear regression analyses

Table 4: Associations between pain variables and the presence of a depressive and/or anxiety disorder at 2-year follow up now also adjusted for severity of depressive and anxiety symptoms[a].

Baseline variable	Depressive and/or anxiety disorder at 2-year follow-up[b]		
	OR (95% CI)	p	% change in log (OR)[c]
Number of pain locations (total)	1.04 (0.97-1.10)	.291	81
0-1	reference		
2-3	0.87 (0.57-1.32)	.507	-
4-5	0.83 (0.54-1.28)	.404	-
6-7	1.07 (0.64-1.80)	.801	90
Pain location			
Joints	1.53 (1.18-1.98)	.001	14
Duration of pain			
≥ 90 days	1.13 (0.86-1.47)	.379	64
Use of pain medication			
Never to sporadic	reference		
Monthly, weekly	0.81 (0.62-1.06)	.129	-
Daily	1.23 (0.77-1.96)	.397	55
Chronic Pain Grade (continuous)	1.09 (0.95-1.24)	.218	65
Grade 1	reference		
Grade 2	0.94 (0.69-1.28)	.678	-
Grade 3	1.26 (0.86-1.87)	.239	54
Grade 4	1.24 (0.80-1.93)	.344	70

a Adjusted for age, gender, years of education, number of chronic diseases and severity of index disorder (QIDS-SR and FQ)
b Using logistic regression analyses
c As compared to analyses without severity of the index disorder

DISCUSSION

This study investigated the relationship between pain and the two-year course of depressive and anxiety disorders in a large cohort. A higher number of pain locations, pain of the joints and longer duration of pain (for 90 days or more), daily use of pain medication and more severe pain at baseline were found to be associated with a significantly increased risk of still having a depressive or anxiety disorder after two years. Longer duration and higher severity of pain were significantly associated with having a chronic course of depressive and/or anxiety disorders. These relationships were largely mediated by a greater severity of the baseline depressive and/or anxiety disorder among those with pain, except for pain of the joints, which remained a significant predictor after considering severity.

Our results show that pain is associated with a worse course of depressive and/or anxiety disorders. The chronic pain variables are particularly strong predictors of chronicity of depression and anxiety course. First, the association between pain and course of depression and anxiety could be due to the disabling impact of pain, which could induce patients to limit daily activity and restrict physical and social role functioning[39-41]. Through these consequences, pain and psychiatric symptoms can reinforce each other, resulting in a downward spiral of worsening pain and deteriorating mental health. Another mechanism through which pain, specifically chronic pain, can perpetuate depressive and anxiety disorders is due to shared pathophysiological pathways, such as inflammatory processes, hypothalamic-pituitary-adrenocortical axis abnormalities and altered neurotransmitter receptivity in descending pathways of the central nervous system[42-45]. That severity of the index depressive and/or anxiety disorder mediated the effects of pain on depression and anxiety course is in line with this, since the most severe depression and anxiety patients will show the largest dysregulations of central stress systems. Our findings that pain was associated with worse course of comorbid depression and anxiety compared to a single depressive or anxiety disorder also reflected a difference in severity in these distinct clinical disorders. In line with our observations, pain has previously been shown to increase the experience and severity of mental health problems, which could also explain why a greater symptom severity plays an important role in the link between pain and course of depressive and anxiety disorders[16;19;20].

We found that pain of the joints in the extremities in particular was associated with poorer depression and anxiety course at the two-year follow-up, independent of severity of the index disorder. This is an important finding since population studies on chronic pain found that pain of the joints is frequently reported[31;46;47]. Several physical disorders may be responsible for joint pain, mostly osteoarthritis. The negative cognitive processes that play a role in the development or persistence of psychological symptoms perhaps also influence the way that persons with joint pain 'label' their pain. Pain may be a trigger for them to avoid activity, which in turn negatively influences both their mental symptoms and their pain. Since joint pain was the only pain location

impacting significantly on the course of depressive and anxiety disorders, we examined whether perhaps joint pain was associated with worse pain severity and disability (components of the CPG) compared to other pain sites. These explorative analyses (adjusted for the number of pain locations) indicated that patients with joint pain had higher scores on the severity (0-100 scale), 47.94 versus 45.61, p=0.046, and disability (0-6 points), 1.72 versus 1.48 p=0.061, compared to the other pain sites. The more severe and disabling pain caused by joint pain might therefore be associated with decreased quality of life as compared to pain in certain other sites[8;48]. In addition, pain of the joints is highly persisting and re-occurring[49-53], which may explain why this kind of pain in particular is associated with the persistence of psychiatric symptoms. There is an interesting circularity here that warrants further study.

Treatment trials with antidepressants have shown to be effective in achieving remission in depressed and anxious patients and also in chronic pain patients. However, recent studies on patients with depression and/or anxiety and chronic pain have found poorer treatment response[17;18;20;42;43;54]. Cognitive behavioral therapies (CBT) may also be successful in treating either patients with chronic pain, depressive disorder or anxiety disorder, but data on treating patients with both pain and one of those psychiatric disorders are lacking[6;43;55]. Over the past years increasing attention has been paid to patients with depression and/or anxiety in collaborative care trials. Some of these studies have focused on musculoskeletal pain. One study showed that combined treatment with antidepressants and psychotherapy aiming at depression also resulted in decreasing pain intensity and decreased disability in osteoarthritis patients[56]. Another study showed better treatment response in the collaborative care intervention group than in the care-as-usual group, however, patients in the intervention group with arthritis had worse depression response[57]. A few small experimental studies have shown positive effects of adding an NSAID compared to placebo to an antidepressant on the short-term course of depressive disorders[58;59]. Future trials involving pain in depressed and anxious patients should evaluate the possible beneficial effects of addition of analgesics to psychotherapies and/or antidepressants to optimize treatment[60;61]. It is well possible that combined intervention strategies that target both the psychiatric condition as well as the pain condition are most effective in breaking the vicious cycle in which pain, depression and anxiety are reinforcing each other.

This longitudinal study has several strengths. To our knowledge, this is the largest cohort used to describe the relationship of pain and the course of both depressive and anxiety disorders, in participants recruited from community, general practice and secondary care, and our study therefore provides additional knowledge to earlier evidence from cross-sectional studies. In addition, various course outcomes were examined, and the mediating role of baseline clinical characteristics was considered.

Besides strengths this study also has some limitations. Firstly, this was an observational study, which limits inferences about causality between pain, depressive and/or anxiety disorders and the psychiatric clinical characteristics. Secondly, (changes in) the course and treatment of pain symptoms over time might also influence the course of depression and anxiety, these variables, however, were not further considered since it was our main goal to examine whether baseline pain predicts subsequent mental health course. Also, the study was conducted in a population of adults aged 18 to 65 years, and results could differ in aging populations, in which pain is more prevalent[62] and specific factors such as health status, cognitive function and psychosocial roles are changing[63]. Cognitive factors (e.g. perceived lack of control on life, negativism, lack of self-appreciation) that might mediate the impact of pain on the course of depressive and anxiety disorders, were not examined. NESDA provides information on the most common depressive and anxiety disorders, but does not allow us to generalize results to specific other disorders such as PTSD or bipolar depression. Another limitation is perhaps that pain was based on self-report rather than objective pain measures. It has repeatedly been found that depressed patients have reduced pain perception to skin surface applied stimuli, like heat and cold, though the few studies that examined deeper somatic stimuli[64-67], as measured by inducing ischemic muscle pain, have found a higher pain perception compared to healthy controls[64;65]. Studies investigating pain perception in anxiety disorders were not conclusive[66]. Thus, studies involving objective pain measures in depressed and/or anxious patients have shown indeterminate results. The experienced pain in our study sample may resemble the deeper somatic pain stimuli and therefore be due to lower thresholds in experienced pain. Lastly, course of the depressive and/or anxiety disorder was assessed over two years, which might be a rather short follow-up period. Whether pain determines chronicity over a longer period of time could be investigated in the future.

In sum, this large longitudinal study shows that the course of depressive and anxiety disorders is poorer when pain is present. Except for pain of the joints these relationships are mediated by a greater severity of the baseline mental disorder. These observations provide evidence for the importance of enquiring after pain symptoms in depressed and anxious patients in clinical practice and might suggest that treatment modalities should be specific for depressed and anxious patients with pain. More attention to pain seems necessary when diagnosing and treating patients with depressive and anxiety disorder.

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