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Research report

Presence and predictors of pain in depression: Results from the FINDER study

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ABSTRACT

Background: Patients with depression often experience pain. There is limited understanding of the relation between pain and other symptoms (depressive, anxious and non-painful somatic symptoms). This exploratory study assesses pain severity and interference of pain with functioning in a clinically depressed population and investigates the relation between the different groups of symptoms.

Methods: FINDER was a 6-month prospective, observational study investigating health-related quality of life of outpatients with depression initiating antidepressant treatment. Patients completed ratings on the Hospital Anxiety and Depression Scale (HADS), Somatic Symptom Inventory (SSI-28), and overall pain severity and interference of pain with functioning using Visual Analogue Scales (VAS) at baseline and at 3 and 6 months. Regression analyses identified factors associated with overall pain severity and interference of pain with functioning, at baseline and over the observation period.

Results: Of 3468 eligible patients at baseline, 56.3% experienced moderate to severe pain and 53.6% had moderate to severe pain-related interference with functioning. At 6 months of follow-up, these proportions decreased to 32.5% and 28.1%, respectively. Higher baseline SSI-somatic scores (non-painful) were strongly associated with greater pain severity and greater pain-related interference with functioning at baseline and over 6 months. Certain socio-demographic (increasing age, being unemployed) and depression-related factors (more previous episodes, longer duration of current episode) were also significantly associated with greater pain severity and interference over 6 months, while higher baseline severity of depression (HADS-D) and further education were associated with less severe pain or pain-related interference with functioning over 6 months.

Conclusions: Over half of depressed patients in this study experienced moderate to severe pain. Painful somatic symptoms appear to be closely related to non-painful somatic symptoms, more than to depressive or anxious symptoms suggesting that painful and non-painful somatic symptoms can be considered as one group of 'somatic symptoms,' all of them associated with depressive and anxious symptoms.

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1. Introduction

Epidemiological studies show that the prevalence of chronic painful physical symptoms is increased in patients with mood disorders and in patients with anxiety disorders, suggesting they are not specific to depressive disorders (Ohayon and Schatzberg, 2003; Demyttenaere et al., 2006, 2008). The question whether these painful physical symptoms are also associated with the non-painful physical symptoms found in depressed patients is not fully understood.

Co-morbid chronic painful (and non-painful) physical symptoms result in poorer recognition of depression (Kirmayer et al., 1993) and in poorer outcomes of depression (Ohayon and Schatzberg, 2003), and this may be due to several factors, including lower rates of help-seeking and longer delays before help-seeking when pain accompanies depression (Demyttenaere et al., 2006), or lower efficacy of antidepressant treatment on painful physical symptoms. Indeed, the effect size measured after 9 months of treatment with antidepressants has been shown to be lower for painful (and non-painful) physical symptoms than for non somatic depressive symptoms and for positive well-being (Greco et al., 2004). During antidepressant treatment, remitters and non-remitted responders had significantly more change than non-responders in both pain and non-pain physical symptoms suggesting that the changes in the latter two groups of symptoms occurs in parallel (Greco et al., 2004).

Moreover, the somatic symptoms being part of or associated with depression are not only influencing the outcome of depression. Indeed, several recently published papers even suggest that (in patients with myocardial infarction or with chronic heart failure) the so-called somatic/affective symptoms of depression are more predictive of overall mortality than the cognitive/affective symptoms of depression (De Jonge et al., 2006; Schiffer et al., 2009).

Although the recent literature focused on the 'comorbidity' of depression and anxiety and of depression (and anxiety) and painful physical symptoms, the relation between these different symptom clusters (including the non-painful physical symptoms) is not fully understood. The specificity of the comorbidity between somatoform clusters and other mental disorders should indeed be further clarified (Lieb et al., 2007).

Pain, like many other somatic symptoms, is always a subjective experience (from sensory to affective to cognitive to behavioural aspects); therefore, it is important to investigate not only pain severity and changes in pain severity but also interference of pain with functioning and changes in pain interference with functioning when presented with depression.

Factors Influencing Depression Endpoints Research (FINDER) is a multinational, longitudinal, observational study designed to increase understanding of the factors that influence health-related quality of life outcomes for clinically depressed outpatients receiving antidepressant (AD) medication in routine primary and secondary care. In this study, pain as well as its impact on functioning and factors associated with pain was assessed using patient-reported measures.

The aims of the present exploratory analyses were to examine the severity of overall pain and the interference of pain with ability to undertake normal activities both at baseline (untreated) and over the 6-month observation period in clinically depressed outpatients. We also investigated the relation between pain severity and interference of pain with functioning with other symptom clusters (non-painful somatic symptoms, anxious and depressive symptoms) and socio-demographic and clinical variables at baseline and over 6 months.

2. Methods

2.1. Study design

FINDER was a 6-month, observational, multi-centre, multinational study conducted in 12 European countries: Austria, Belgium, France, Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Sweden, Switzerland and the UK. Recruitment commenced in May 2004 and was completed in September 2005. The study had a non-interventional design which means that all treatment decisions were at the discretion of the participating physician. The study was approved in all countries according to local requirements for ethics and/or regulatory approvals for observational studies. Patients gave written informed consent for the provision and collection of data regarding care and outcomes during the observation period. The study design and baseline characteristics of the FINDER study population have been described in detail elsewhere (Garcia-Cebrian et al., 2008; Bauer et al., 2008) and will be briefly described here.

2.1.1. Patients

Patients were eligible for inclusion in the study if they presented within the normal course of care and were diagnosed by their physician as suffering from depression, were about to start pharmacological treatment for either a first or subsequent episode of depression (the index episode), and were aged at least 18 years. Patients were not simultaneously participating in a different study that includes an investigational drug or procedure.

2.2. Data collection and assessments

Data were collected by investigators (either primary care physicians or specialists — psychiatrists or neurologists — 437 investigators/study sites) or with patient rated scales at baseline (the routine visit at which the patient agreed to enter the study) and at 3 (±1 month) and 6 months (±1 month) post-baseline during visits that were part of the routine clinical care of the patient. At baseline, data were collected on patient socio-demographics and psychiatric history. Investigators recorded whether patients had any of a selection of co-morbid chronic medical or functional conditions. At baseline, data on healthcare resource utilisation, psychotherapy and medication taken (antidepressants, analgesics and pain-related medication, both over-the-counter and prescribed) were collected. Antidepressants taken from baseline were at the choice of the investigator and were grouped into: selective serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants (TCAs); serotonin norepinephrine reuptake inhibitors (SNRIs); others (including monoamine oxidase inhibitors [MAOIs]); and combinations (of SSRIs, TCAs, SNRIs, MAOIs and others).

2.3. Patient reported outcomes

Pain was assessed using Visual Analogue Scales (VAS) for overall pain severity and for interference of pain with the ability to perform daily activities during the past week (i.e., functioning). The VAS scale ranged from 'no pain' (0) to 'as severe as imaginable' (100). Moderate to severe pain was defined as a score >30 mm on the overall pain VAS (Collins et al., 1997). The corresponding anchors for the interference VAS were 'not at all' to 'complete disability.' Moderate to severe interference was determined to be present if the score was higher than 30.

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was completed at baseline and at 3 and 6 months as a measure of severity. The HADS consists of seven items for depression (HADS-D) and seven items for anxiety (HADS-A), assessing how the patient felt during the past week. Each item is scored on a 4-point scale from 0 to 3, leading to subscale scores for HADS-D and HADS-A of between 0 and 21.

Somatic symptoms (including both painful and non-painful items) were measured using the 28-item Somatic Symptom Inventory (SSI-28), where each item was rated according to how much it bothered the patient over the preceding week on a scale from 1 (not at all) to 5 (a great deal) (Barsky et al., 1986). The pain subscore (SSI-pain) was derived by calculating the average score over 7 pain-related items, and the somatic subscore (SSI-somatic) used the remaining 21 items.

2.4. Analysis

Two pain groups were defined using the overall pain VAS rating: (1) ≤30 mm was defined as having no/mild pain; and (2) >30 mm was defined as having moderate to severe pain (Collins et al., 1997). Descriptive summary statistics (means, standard deviations [SDs], frequencies, percentages) were used to describe the patients in the two pain groups.

Multivariate linear regression analysis was performed to identify variables independently associated with (a) severity of overall pain (overall pain VAS) at baseline, and (b) interference of pain with ability to perform normal activities (pain interference VAS) at baseline. The independent variables included in the regression analyses were: *continuous baseline variables*: HADS-A, HADS-D, overall pain VAS [for analysis of interference of pain only], SSI-somatic score, age, body mass index (BMI), number of dependants (the number of dependents that the patient has, including those living with the patient, e.g. children of elderly relatives, and those who may be living away from home but are still dependents, such as students), duration of current depressive episode, age at first depressive episode, number of previous episodes of depression in the 24 months before baseline; *categorical variables*: gender, marital status (married/domestic partner, other), education (none/mandatory, further), occupational status (working for pay, unemployed, other), smoking (yes, no), medical conditions (known to be painful, non-painful, none: recorded from a pre-specified list of two groups of disorders: (1) a defined co-morbid physical condition known to cause pain — the presence of angina, malignant disease (cancer), neuropathic disorder, rheumatological disorder and/or (2) who indicated yes to suffering any physical trauma in the last 24 months from which pain effects still exist, termed 'painful medical condition,' a defined co-morbid physical condition not associated with pain (by not confirming the presence of any of t he conditions listed for the explained pain group; diabetes, hypertension, asthma were considered non-painful conditions) termed 'non-painful medical condition' and (3) no medical condition), functional conditions (collected from a pre-specified list including chronic fatigue, irritable bowel syndrome, atypical chest pain, irritable bladder, fibromyalgia and chronic pelvic pain), any psychiatric illness in the 24 months before baseline (yes, no) and country. The full models containing all of these variables were reduced by backward elimination methods to include only those independent variables that were statistically significantly associated with the outcome variable at $p \leq 0.05$.

Similarly, repeated measures regression analyses were performed for the two dependent variables over 6 months, including the same independent variables as above, but adding the baseline score for the dependent variable, the group of antidepressant taken between baseline and 3 months (combinations, other drugs, SNRIs, SSRIs, TCA), the class of analgesic taken between baseline and 3 months (no analgesic treatment, simple, NSAIDs, opioids), and the overall pain VAS at baseline (for analysis of pain interference only). Independent variables are sorted in order of the strength of the association with the outcome in each case (based on the *p*-values). Due to the exploratory nature of the analysis there were no adjustments made for multiple comparisons.

2.4.1. Analysis of loss to follow-up

We performed an analysis to determine whether patients lost to follow-up after 3 months differed systematically in their initial pain response (i.e. the change between baseline and 3 months in pain severity) from patients who had assessments at the end of 6 months. For this purpose, we compared the baseline characteristics and change scores from baseline to 3 months for overall pain severity for two groups of patients: Group 1 = patients with data at 3 months only; and Group 2 = patients with data at both 3 and 6 months (i.e. at all visits) or at 6 months only. This analysis is further supported by the results of a logistic regression analysis performed to identify those variables significantly associated with loss to follow-up.

All analyses were conducted using SAS version 8.2.

3. Results

There were 3468 patients with a clinical diagnosis of depression in the study, of whom, 3308 had a non-missing overall pain rating at baseline and were, thus, eligible for inclusion in the current analysis. Of these patients, 1861 (56.3%) had moderate to severe pain (based on overall pain VAS >30 mm) at baseline, and 1447 (43.7%) had no/mild pain. Of the 1861 patients with moderate to severe pain, 1311 (70.4%) had no recorded physical explanation for the pain. Table 1 summarises the baseline characteristics of the patients with and without moderate to severe pain at baseline. There were some differences between pain groups in socio-demographics, but few differences in psychiatric history. There were more comorbid chronic medical and functional conditions and higher baseline scores of depression and anxiety (HADS) among patients with moderate/severe pain compared to those with no/mild pain.

Fig. 1 presents the VAS frequency distribution at baseline and at 6 months of (a) overall pain severity and (b) interference of pain with ability to perform daily activities (i.e. functioning).

Table 1
Patient characteristics at baseline by pain group.

	No/mild pain ($n=1447$)	Moderate/severe pain]($n=1861$)
Female, %	66.0	69.8
Age, years	44.8 (14.5)	48.3 (14.7)
Further education, %	53.8	43.4
Paid employment, %	56.6	45.2
BMI, kg/m^2	24.8 (4.8)	26.0 (5.5)
Duration of current depressive episode, weeks	13.6 (16.2)	13.7 (17.0)
Duration of depression, years	8.0 (10.1)	8.9 (10.6)
Any psychiatric illness in last 24 months, %	52.3	58.0
Any current chronic medical condition, %	31.2	51.1
Painful	13.1	29.9
Non-painful	20.9	25.1
Any current chronic medical condition, %	31.2	51.1
Any current functional syndrome, %	30.4	47.6
HADS depression score (0–21)	11.6 (4.6)	12.9 (4.3)
HADS anxiety score (0–21)	12.2 (4.1)	13.6 (3.8)
Overall pain VAS (0–100)	11.6 (10.4)	61.4 (17.5)
Pain interference with functioning VAS (0–100)	16.0 (20.8)	57.2 (26.5)
SSI-28	1.9 (0.5)	2.6 (0.7)
SSI-pain	1.8 (0.6)	2.8 (0.8)
SSI-somatic	1.9 (0.6)	2.5 (0.7)

Data presented as mean (SD) unless indicated otherwise.
No/mild pain = an overall pain VAS rating of ≤30 mm, moderate/severe pain = an overall pain VAS >30 mm.
BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; SSI, Somatic Symptom Inventory; VAS, visual analogue scale.

As previously mentioned at baseline, 56.3% had moderate/severe pain. In addition, 53.6% of patients had moderate to severe interference of pain with functioning (VAS >30 mm). At 6 months, VAS pain ratings were available for 2700 patients and the frequency distribution figure shows that the proportion of patients with moderate to severe pain and interference of pain with functioning had fallen to 32.5% and 28.1%, respectively.

There was a relationship between overall pain and interference of pain with functioning such that of the 1861 patients with moderate to severe pain at baseline, 81.7% also demonstrated interference of this pain with daily activities. Likewise, of the 1447 patients without moderate to severe overall pain at baseline, only 17.6% had significant pain interference with functioning. This relationship endured over the observation period, with 74.1% of those patients with moderate to severe pain over 6 months reporting significant interference of pain with functioning.

3.1. Factors associated with pain at baseline

Table 2 summarises the independent variables significantly associated with overall pain severity at baseline. A higher SSI-somatic score, any presence of concurrent medical conditions, and a higher BMI were associated with greater pain severity at baseline, while having further education was associated with lower pain severity (Table 2).

The independent variables significantly associated with greater interference of pain with functioning at baseline (Table 2) were greater severity of overall pain, higher SSI-somatic score, higher HADS depression score, higher BMI, and occupational status (not working for pay). Having further education, increasing age and being female were associated with less interference of pain with functioning at baseline.

3.2. Factors associated with pain over 6 months

The following independent variables were significantly associated with greater overall pain severity over 6 months (Table 3): greater overall pain severity at baseline, higher SSI-somatic score at baseline, taking analgesics (especially opioids) between baseline and 3 months, any presence of concurrent medical condition, increasing age, longer duration of the current episode of depression, greater number of previous episodes of depression and being unemployed. More severe depression at baseline (i.e. a higher HADS-D score) and a higher educational level were associated with lower overall pain severity over the 6-month observation period.

Table 4 summarises the independent variables significantly associated with interference of pain with functioning over 6 months. Positive associations (i.e. associations with greater interference of pain) were observed for taking analgesics (especially opioids) between baseline and 3 months, a higher baseline SSI-somatic score, greater overall pain severity and interference of pain at baseline, longer duration of the current episode of depression, presence of a painful medical condition, greater age, a higher number of previous episodes of depression, being unemployed, and a greater BMI. Having further education, more severe depression at baseline (a higher HADS-D score) and being married or having a partner were associated with less pain interference with functioning over 6 months.

Individual groups of ADs taken between baseline and 3 months were not significant compared to no treatment over 6 months for either pain severity or interference of pain with functioning although AD group was retained in each model because there were significant differences between other pairs of AD groups. In general, those taking a combination of AD treatments had worse pain severity and interference of pain over 6 months than the other AD groups.

3.3. Loss to follow-up analysis

Of the 3468 patients at baseline, 343 (9.9%) had no follow-up data, 271 (7.8%) had data at 3 months only (Group 1, see Methods section), and 2854 (82.3%) had data at both 3 and 6 months ("all visits," Group 2) or 6 months only (Group 2, see Methods section).

Examination of the changes in overall pain ratings during the first 3 months of treatment in Group 1 and Group 2 revealed no systematic differences (data not shown).

The logistic regression model comparing the patients lost to follow-up after 3 months with those who had 6-month data identified three variables that were significantly associated with loss to follow-up: country ($p<0.001$), younger age at first depressive episode ($p=0.001$) and higher SSI-somatic score at baseline ($p=0.019$). Overall pain severity was not retained in the model and, therefore, was not significantly associated with the likelihood of remaining in the study. This provides some evidence that the results on the pain outcomes will not be systematically biased due to missing information on the patients lost to follow-up.

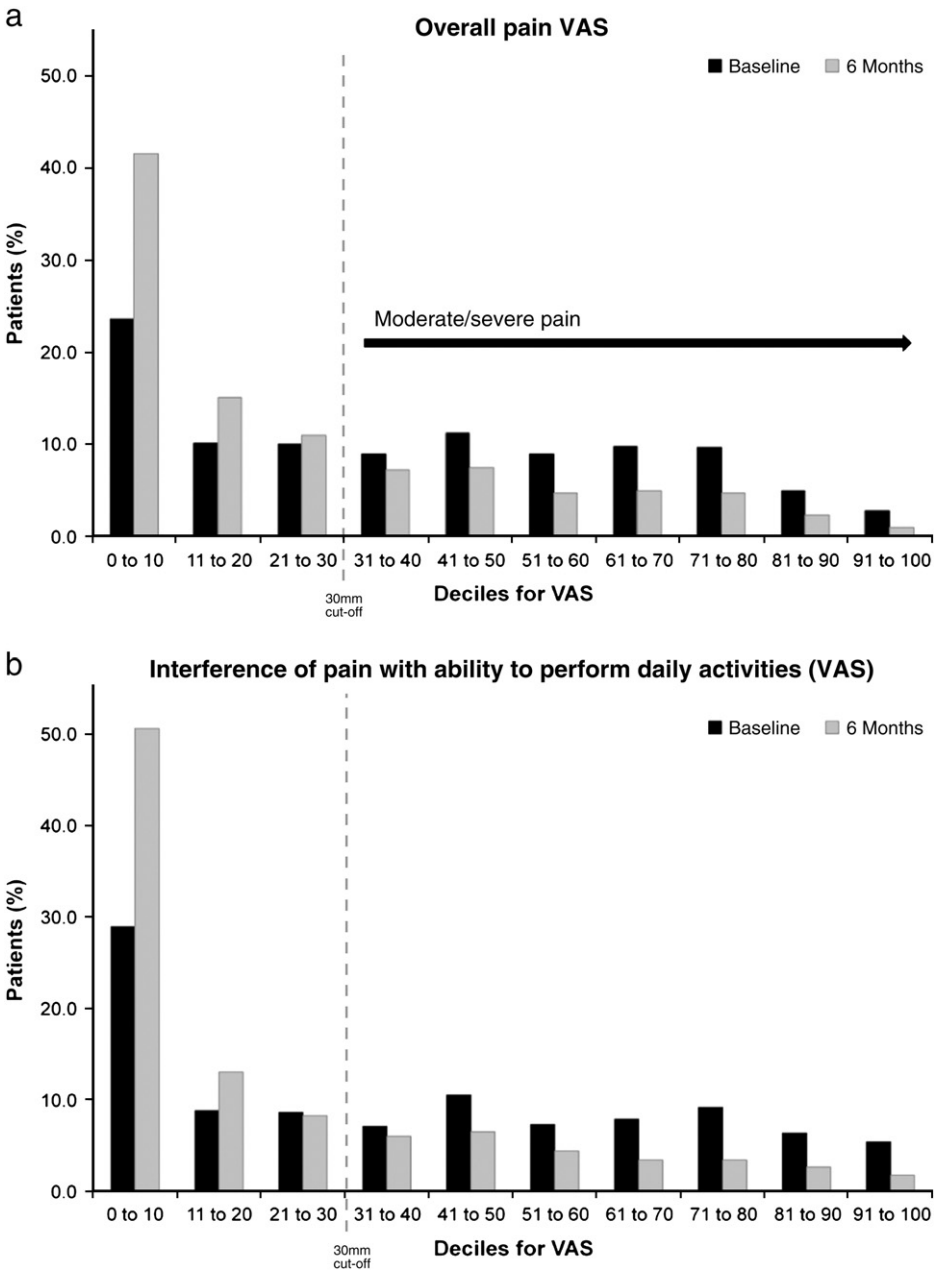

Fig. 1. VAS frequency distribution of overall pain severity and interference of pain with ability to perform daily activities at baseline and at 6 months.

4. Discussion

A first important finding of this naturalistic study is the presence of pain in a high proportion of patients in this population of help-seeking patients with clinically diagnosed depression. Indeed, more than half of the patients had moderate to severe pain (during the past week), which is consistent with previously published data on the relation between depression and more chronic pain (Ohayon and Schatzberg, 2003; Bair et al., 2003, 2004; Demyttenaere et al., 2006). One-third of the patients continued to report moderate to severe pain at the end of the observation period. The severity of pain was reflected in the high likelihood of pain interfering with daily activities both at baseline (in 81.7% of patients with pain) and over 6 months of follow-up (in 74.1% of patients with pain).

An second important finding of this study is the close relationship between painful symptoms and non-painful somatic symptoms, as assessed with the Somatic Symptom Inventory which asked how much individual symptoms bothered patients: e.g. nausea or vomiting, feeling faint or dizzy, trouble with vision. A higher score for somatic symptoms was one of the strongest predictors of higher overall pain at baseline as well as over 6 months, and suggests that these groups of symptoms are

Table 2
Linear regression: independent baseline variables significantly associated with severity of overall pain (overall pain VAS) and interference of pain with ability to perform daily activities (pain interference VAS) at baseline.

	Independent variable	Estimate	*F* value	*p* value
Severity of overall pain ($n=3062$)	SSI-somatic score	18.8	893	<0.001
	Medical conditions (reference: none)		56	<0.001
	Painful	12.1		
	Non-painful	4.9		
	Further education (reference: none/mandatory)	−3.3	11	<0.001
	BMI	0.3	11	<0.001
	Country (reference: UK)	–	4	<0.001
Pain interference ($n=3013$)	Severity of overall pain	0.7	2114	<0.001
	SSI-somatic score	7.0	113	<0.001
	HADS depression score	0.5	32	<0.001
	Further education (reference: none/mandatory)	−2.0	5	0.021
	BMI	0.2	5	0.024
	Age	−0.1	4	0.034
	Occupational status (reference: paid work)		3	0.037
	Unemployed	2.0		
	Other	2.1		
	Female sex (reference: male)	−1.6	4	0.046

Independent variables are sorted in order of the strength of the association with the outcome. Country was not statistically significant ($p=0.161$) for pain interference, but forced into the reduced model.
BMI = body mass index; SSI, somatic symptom inventory; HADS, hospital anxiety and depression scale.

closely related in a depressed population. Since it has been shown that the presence of painful symptoms compromises the outcome of antidepressant treatment (Ohayon and Schatzberg, 2003; Bair et al., 2003, 2004), the present findings suggest that non-painful physical symptoms should probably also be taken into account as possible predictors of treatment response in depression. A higher non-painful physical symptom score was also one of the strongest predictors of interference of pain with functioning at baseline and over 6 months, independent from overall pain severity. This suggests that non-painful physical symptoms aggravate the influence of pain on functioning, or that patients attribute the impaired functioning to the pain severity rather than to the severity of co-existing non-painful physical symptoms.

It is remarkable that the association between painful physical symptoms and non-painful physical symptoms is stronger than between painful physical symptoms and depressive or anxious symptoms (as assessed with the HADS). This suggests that they probably are better understood as one group of 'somatic' or 'somatoform' symptoms instead of focusing separately on the one (painful) or the other (non-painful) subgroup. Standard rating scales for somatic symptoms (like the SSI, the Patient Health Questionnaire-somatization subscore or the Symptom Check List-somatization subscore) indeed cluster them into one group of symptoms. One could suggest to cluster the broad symptom presentation of many patients into 'depressive,' 'anxious' and 'somatoform' (painful and non-painful) symptom clusters. This supports the recent proposal that 'a potential consideration for future diagnostic classification would be to describe basic diagnostic criteria for a single overarching disorder (general neurotic syndrome or negative affect syndrome) and to optionally code additional diagnostic features that allow a more detailed classification into specific depressive, anxious and somatoform subtype' (Löwe et al., 2008).

The presence of a painful medical condition is a logical predictor of pain at baseline as well as over 6 months. Although treatment with antidepressants may be effective in reducing some forms of pain (e.g. those linked to depression or neuropathy) independent of a mood-enhancing effect (Dworkin et al., 2007; McCleane, 2008), the additional use of opioids by a subgroup of patients requiring this level of pain control in conjunction with antidepressant treatment indicates that such

Table 3
Linear regression: independent baseline[a] variables significantly associated with overall pain severity (VAS) over 6 months ($n=2436$).

Independent variable	Estimate	*F* value	*p* value
Severity of overall pain (VAS)	0.4	489	<0.001
SSI-somatic score	5.4	64	<0.001
Class of analgesic[a]		30	<0.001
(ref: no analgesic treatment)			
Simple	4.4		
NSAIDs	5.2		
Opioids	16.4		
HADS-D	−0.5	29	<0.001
Medical conditions (reference: none)		15	<0.001
Painful	5.5		
Non-painful	3.7		
Age	0.1	13	<0.001
Duration of current depressive episode	0.1	11	<0.001
Number of previous episodes of depression	0.9	10	0.001
Further education	−2.6	9	0.002
(reference: none/mandatory)			
Occupational status (reference: paid work)		5	0.007
Unemployed	3.7		
Other	ns		
AD group[a] (reference: no treatment)	–	2	0.043
Country (reference: UK)	–	4	<0.001

Independent variables are sorted in order of the strength of the association with the outcome.
Note: individual classes of AD taken between baseline and 3 months were not significant compared to no treatment, but the term was retained in the model because there were significant differences between other pairs of AD groups: combinations and SSRI (adjusted means 34.8 and 31.6, respectively; $p=0.010$), combinations and other drugs (34.8 and 31.0; $p=0.037$).
AD, antidepressant; HADS-D, Hospital Anxiety and Depression Scale depression score; ns, not significant; NSAIDs, non-steroidal anti-inflammatory drugs; SSI, Somatic Symptom Inventory; VAS, visual analogue scale.
[a] AD and analgesic taken were those for the observation period between baseline and month 3.

Table 4
Linear regression: independent baseline [a] variables significantly associated with interference of pain with ability to perform daily activities over 6 months ($n=2303$).

Independent variable	Estimate	*F* value	*p* value
Interference of pain	0.2	133	<0.0001
Class of analgesic [a]		32	<0.0001
(ref: no analgesic treatment)			
Simple	4.1		
NSAIDs	5.5		
Opioids	18.8		
SSI-somatic score	5.2	50	<0.0001
Severity of overall pain (VAS)	0.1	21	<0.0001
Further education (ref: none/mandatory)	−3.1	12	<0.001
Duration of current depressive episode	0.1	11	<0.001
Medical conditions (ref: none)		6	0.002
Painful	4.1		
Non-painful	ns		
Age	0.1	9	0.002
HADS-D	−0.3	9	0.003
Number of previous episodes of depression	0.9	9	0.003
Occupational status (ref: paid work)		3	0.038
Unemployed	3.1		
Other	ns		
BMI	0.2	4	0.039
Marital status (ref: other)			
Married/domestic partner	−1.7	4	0.043
AD group [a] (ref: no treatment)	–	6	<0.001
Country (ref: UK)	–	2	0.006

Independent variables are sorted in order of the strength of the association with the outcome.
Note: AD group taken between baseline and 3 months was not significant compared to no treatment, but was retained in the model because there were significant differences between other pairs of AD groups: combinations and SSRIs (adjusted means 33.6 and 26.8, respectively; $p<0.001$); combinations and SNRIs (33.6 and 29.8; $p=0.028$); combinations and TCAs (33.6 and 29.6; $p=0.036$), SNRIs and SSRIs (29.8 and 26.8; $p=0.024$).
AD, antidepressant; BMI, body mass index; HADS-D, Hospital Anxiety and Depression Scale depression score; ns, not significant; NSAIDs, non-steroidal anti-inflammatory drugs; SSI, Somatic Symptom Inventory; VAS, visual analogue scale.
[a] AD and analgesic taken were those for the observation period between baseline and month 3.

patients are the most likely to have enduring pain. The finding that the presence of a non-painful medical condition is also significantly associated with overall pain severity at baseline and during 6 months of AD treatment is interesting. We hypothesise that this could be due to the fact that patients do not make a distinction between the importance of painful versus non-painful symptoms when they are asked to assess the severity of pain, i.e. they take into account the somatic sensations of symptoms when evaluating pain.

Several socio-demographic characteristics (gender, age, BMI, educational level, occupational status) were associated with pain and related interference with functioning in this sample of clinically depressed outpatients, both at baseline and over the 6-month follow-up period. At baseline, increasing age and female gender were significantly associated with less pain-related interference with functioning but not with overall pain severity. However, increasing age was significantly associated with higher pain scores and greater interference with functioning over 6 months. These latter findings are consistent with previous studies that older age is associated with increased pain severity (Bair et al., 2004; Demyttenaere et al., 2006).

A higher education level was consistently associated with lower pain severity and lower interference of pain with functioning at both baseline and during the observation period. These confirm previous findings of an inverse relationship between educational attainment and pain (Demyttenaere et al., 2006).

There are high rates of unemployment and impairments in social functioning among patients with depression and pain (Bair et al., 2003). In the present study, patients not in paid work had greater pain-related interference with functioning at baseline and over 6 months of treatment than patients in paid work. Unemployed patients also had greater pain severity over the 6-month follow-up period than patients in paid work. This suggests that reporting of pain and interference of pain with functioning is also moderated by socio-demographic variables again underlining the 'subjective experience' of pain.

When comparing the mean baseline depression severity scores (HADS) between the patients with no/mild pain and those with moderate to severe pain, it appears that patients with more pain have higher depression severity. This relationship is not statistically significant in the multivariate model on baseline pain severity but it is significant in the model on baseline pain interference. In other words, severity of baseline depression is not significantly associated with severity of pain at baseline once all other variables are taken into account although it is positively associated with pain interference at this time.

For the 6-month outcomes, there was a somewhat counter-intuitive result that higher depression severity at baseline predicts lower pain severity over the observation period. It has been documented that the reporting of pain severity is partly determined by depression severity (Shelton et al., 2007). Therefore, patients with a higher baseline depression severity could have lower pain severity at endpoint because a larger part of the baseline pain intensity was depression severity-associated. In this analysis, we have not investigated the change in HADS-D scores as a time-dependent variable in the models to investigate this further.

Two depression-related factors were significantly associated with greater pain severity and pain-related interference of functioning over 6 months: a longer duration of the current depressive episode and a higher number of previous depressive episodes, whereas age at first depressive episode was not maintained in the models. Previous studies report that the duration of depressive episodes is longer in patients with pain than in those without pain (Ohayon and Schatzberg, 2003), and that patients with co-existing depression and pain tend to delay seeking help (Demyttenaere et al., 2006).

Combinations of AD treatments were associated with poorer pain outcomes over 6 months but may represent a patient group who are harder to treat.

The loss to follow-up analysis showed that patients discontinuing from the study between months 3 and 6 responded similarly during the first 3 months of observation compared with patients who completed the study, suggesting that these losses did not result in systematic under- or overestimates of changes in pain ratings over time.

This study has several limitations that affect the interpretation and generalisability of the results.

First, the pain measures are limited to 'overall pain severity during the past week' and to 'interference of pain with functioning during the past week.' The pain experience is known

to be complex and more detailed information on duration of pain, and on location of pain symptoms could have had added value. Anyhow, the 'complete pain experience' can never be fully captured with questionnaires.

Second, several variables (length of episode, previous episodes of depression, somatic comorbidity, ...) were gathered via medical records, patient report and clinical interview rather than form standardized diagnostic interviews. However, the most important variables (depressive, anxious, non-painful and painful physical symptoms) were all gathered with standard and well validated questionnaires and all covered the same duration (past week).

Third, the observation period was limited to 6 months, during which approximately one-third of patients reported enduring moderate to severe pain. Thus, a longer follow-up period may have identified the presence of a specific patient subgroup with 'refractory' pain and depression.

Fourth, analagous to the well-documented 30 mm cut-off threshold on the VAS to define moderate to severe pain, we used this value also to determine interference with functioning due to pain. Although not previously reported in the literature as a significant cut-off for this measure, it does have some face validity, and was used only descriptively in this analysis.

In conclusion, this longitudinal exploratory study has shown the presence of moderate/severe pain and pain-related interference with functioning among more than half of clinically depressed outpatients, which persisted in about one-third of patients after 6 months. A higher score for non-painful somatic symptoms at baseline was consistently strongly associated with greater pain severity and pain-related interference with functioning over 6 months suggesting their close association. These findings potentially add to the discussion on future diagnostic classification of (non-painful and painful) somatic symptoms in patients with mood or anxiety disorders. Certain socio-demographic factors (increasing age, being unemployed) and depression-related variables (more previous episodes, longer duration of current episode) were also significantly associated with greater pain severity and interference with functioning, while a higher score for depression (HADS-D) and further education were associated with less severe pain or pain-related interference with functioning over 6 months.

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Conflict of interest

Catherine Reed, David Perahia and Deborah Quail are Lilly employees and Brigitta Monz is a Boehringer Ingelheim employee. Michael Bauer, Nicolas Danchev, Koen Demyttenaere, Luigi Grassi, Angel Luis Montejo and Andre Tylee have received economic compensation for participation in the FINDER Advisory Board.

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