Factors Influencing Depression Endpoints Research (FINDER) Results from the Belgian subgroup analysis

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Objectives: To investigate the quality-of-life of patients in Belgium from the prospective, observational FINDER study of adult outpatients with depression initiating antidepressant medication.

Method: Here we report the post-hoc subgroup analyses of patients enrolled at Belgian sites. Patients completed scales to assess quality of life, severity and chronicity of depression, anxiety and painful symptoms at baseline, 3 months, and 6 months.

Results: At baseline, 59.9% of 227 eligible Belgian patients had depression and 69.2% had anxiety. A higher HADS-A and SSI-Pain score and a lower SSI-Somatic score at baseline predicted lower odds of achieving remission. Higher baseline VAS scores were associated with the severity of nonpainful physical symptoms and previous depressive episodes. The mean mental health score (SF-36 MCS) increased during follow-up, while the mean physical health score (SF-36 PCS) remained stable.

Conclusions: Physicians may not differentiate between depressive and anxiety symptoms when initiating antidepressant treatment; anxiety may be a stronger predictor than depression for prescribing antidepressants. The presence of painful and nonpainful somatic symptoms may be predictors of treatment response in depression.

Key words: Depression – Anxiety - Observational study - Pain severity - Pain interference with functioning.

Introduction:

In psychiatry, a strong relationship is expected between diagnosis and prescription behaviour. However, this is not confirmed by the available literature. The ESEMeD study (The European Study on the Epidemiology of Mental Disorders) investigated the relationship between the diagnosis of depressive or anxiety disorders and the use of psychotropic medication (Demyttenaere et al. 2008a). The study revealed that less than one-third of the subjects with a 12-month prevalence of major depressive disorder (MDD) and a number of subjects without any lifetime diagnosis of a psychiatric disorder were taking antidepressants. The main predictors of the use of antidepressants were age and seeking help for emotional problems, rather than the presence of a formal Diagnostic and Statistical Manual, fourth edition (DSM-IV) diagnosis. This finding suggests that psychotropic medication is not always prescribed in accordance with the approved indications.

Physicians do not always comply with the guidelines for diagnosis and treatment (Linden et al. 1999). One reason for this could be the limited ecological validity of the findings in antidepressant randomised controlled trials (RCTs), which aim to achieve maximal homogeneity in the study population by using multiple inclusion and exclusion criteria. Strict inclusion criteria increase the likelihood that patients participating in RCTs are not representative of the heterogeneous patient samples seen in daily practice (Yastrubetskaya et al. 1997). This could serve as an alibi for physicians to develop their own prescription behaviour.

Only about 14% of patients with MDD in routine practice would be eligible for inclusion in an RCT, with comorbidity being the main reason for exclusion (Zimmerman et al. 2002; Zimmerman et al. 2005; Keitner et al. 2003). A second reason for noncompliance of clinicians with the guidelines is the large group of patients presenting with subthreshold conditions (eg, minor depressive episode, recurrent brief depressive episode, subsyndromal symptomatic depression, and adjustment disorder with depressed mood) (Bauer et al. 2002; Cuijpers et al. 2004). These conditions are highly prevalent and have a substantial impact on daily functioning (Judd et al. 2002). In view of the limited number of RCTs in these subthreshold depressive disorders, no evidence-based treatment recommendations can be given at present (Bauer et al. 2002). The WFSBP (World Federation of Societies of Biological Psychiatry) comments in its guidelines: “Close monitoring and problem solving therapy may be useful, and a treatment trial with one of the well-tolerated antidepressants is worth trying in more chronic and unremitting
cases” (Bauer et al. 2002). Logically, this may result in off-label prescriptions for antidepressants.

It has been shown that many patients do not present just 1 psychiatric condition but rather report depressed, anxious, and painful (somatic) symptoms concurrently that may or may not reach the threshold of comorbidity (Lowe et al. 2008).

Epidemiological studies show that the prevalence of chronic painful physical symptoms is increased in patients with a depressive disorder and in patients with anxiety disorders. This indicates that these pain symptoms are not specific to depressive disorders (Ohayon et al. 2003; Aaronsen et al. 1998; Demyttenaere et al. 2008b; Demyttenaere et al. 2006).

Comorbid chronic painful physical symptoms result in poorer recognition of depression, (Kirmayer et al. 1993) and in lower remission figures (Ohayon et al. 2003). This may be due to several factors, including less tendency to seek help, and longer delays before seeking help for depressive symptoms in combination with pain symptoms, (Demyttenaere et al. 2006) or a lower efficacy of antidepressants on painful physical symptoms.

The effect size measured after 9 months of treatment with antidepressants is lower for painful (and nonpainful) depressive somatic symptoms, compared to nonsomatic depressive symptoms (Greco et al. 2004). During antidepressant treatment, responders (in remission or not) experienced significantly more change in both painful and nonpainful physical symptoms compared to nonresponders. This suggests that the changes in the nonpainful and painful physical symptoms occur in parallel with each other (Greco et al. 2004).

In addition, proof of the relevance of physical symptoms in depression and anxiety is, for example, the finding that in patients with myocardial infarction or chronic heart failure, the somatic symptoms which are associated with or which are part of depression not only influence the outcome of depression but also the somatic/affective symptoms of depression are even more predictive of mortality than the cognitive/affective symptoms of depression (deJonge et al. 2006; Schiffer et al. 2009).

Although recent literature is more focused on the “comorbidity” of depression and anxiety, and of depression and painful physical symptoms, the relationship between these clusters of symptoms (including the nonpainful physical symptoms) is not fully understood. Therefore, the specificity of the comorbidity between somatoform clusters and other mental disorders should be further investigated (Lieb et al. 2007).

Pain, like many somatic symptoms, is a subjective experience (from sensory to affective, cognitive, and behavioural aspects). Therefore, it is important to investigate not only the severity of pain but also the interference of pain with functioning in daily life in patients with a depressive episode.

The FINDER (Factors Influencing Depression Endpoints Research) study was a European, multicentre, prospective, observational study investigating health-related quality-of-life (HR-QoL) outcomes in an adult population with a clinical diagnosis of depressive disorder at baseline (untreated) and at 3 months and 6 months after commencing antidepressant medication (Bauer et al. 2008; Garcia-Cebrian et al. 2008; Reed et al. 2009).

This paper reports on the patients from the sites in Belgium enrolled in the FINDER study. First, we assessed the severity and prevalence of pain symptoms in this population. Second, we investigated the relationship between painful and nonpainful physical symptoms of depression and anxiety. Third, we examined the outcome in depression, anxiety, and pain following 3- and 6-month naturalistic follow-ups, and we investigated predictive factors of outcome.

METHOD:

Here we report the post-hoc subgroup analyses of patients enrolled at Belgian sites in the FINDER study - a 6-month, multicentre, prospective, observational study conducted in 12 European countries (Austria, Belgium, France, Germany, Ireland, Italy, The Netherlands, Norway, Portugal, Sweden, Switzerland, and the United Kingdom). The study was designed to provide more insight into the factors that may have an influence on HR-QoL in clinically depressed nonhospitalised patients, initiating antidepressant treatment, in primary or secondary care (Bauer et al. 2008; Garcia-Cebrian et al. 2008; Reed et al. 2009).

In order to keep the study as naturalistic as possible, no structured diagnostic criteria were required for establishing the diagnosis of depression. The aim of the study was non-interventional, which means that all treatment decisions were at the discretion of the participating physician.

Assessments were performed at baseline, at 3 months (±1 month), and at 6 months (±1 month) during the follow-up period. At baseline, data were collected on patient sociodemographics and psychiatric history. Investigators recorded whether there was a history of comorbid chronic medical or functional conditions, use of medication, and psychotherapeutic counseling.

The detailed study design and the methods have already been reported elsewhere (Garcia-Cebrian et al. 2008; Demyttenaere et al. 2010; Demyttenaere et al. 2009) and are only briefly described here. The study was approved in all countries according to local requirements for ethics and/or regulatory approvals for observational studies, and all patients provided written informed consent.

PSYCHOMETRIC INSTRUMENTS

Symptom scales collected at baseline, 3 months, and 6 months follow-up.

The symptom scales used in this study assessed both emotional and somatic symptoms.
The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (Zigmond et al. 1983; Spinhoven et al. 1997; Friedman et al. 2001) is a well-known and well-documented screening instrument for anxiety and depression. The HADS consists of 7 items for depression and 7 items for anxiety and evaluates how the patient felt during the week prior to completing the questionnaire. Each item is scored on a 4-point scale from 0 to 3, leading to scores on the subscales for anxiety and depression (respectively HADS-A and HADS-D) from 0 to 21. For both subscales, a score of 0 to 7 can be regarded as a noncase of anxiety (HADS-A) or depression (HADS-D); a score of ≥ 11 is indicative of a probable case, and scores between 8 and 10 indicate doubtful cases.

Possible combinations of scores on the subscales (for anxiety: noncase [A-], doubtful case [A?], and probable case [A+]; for depression: noncase [D-], doubtful case [D?], probable case [D+]) were matched with the more commonly used DSM-IV diagnostic categories and defined according to the following 5 subgroups (Demyttenaere et al. 2009):

1. Noncaseness, no anxiety disorder, no depressive disorder: D-A-, D-A?, or D?/A-
2. Mixed anxiety-depression: D?/A? (subthreshold depressive and anxiety symptoms)
3. Caseness for depression: D+A- or D+A?
4. Caseness for anxiety: D-A+ or D?A+
5. Caseness for comorbid depression and anxiety: D+A+

All patients with complete HADS ratings at baseline, at 3 months, and at 6 months were classified according to these diagnostic categories.

Remission, traditionally defined as achieving a status with no significant symptomatology, was defined as D-A- at 3 months and 6 months (Demyttenaere et al. 2009) irrespective of the caseness status at baseline.

28-item Somatic Symptom Inventory

Somatic (painful and nonpainful) symptoms were scored with the 28-item Somatic Symptom Inventory (SSI-28) (Barsky et al. 1986). The SSI is a patient self-report questionnaire that assesses the extent to which different somatic symptoms are experienced as bothersome during the past week. Each complaint is rated on a defined scale from 1 (not at all) to 5 (very much). The pain subscale (SSI-Pain) is derived by calculating the mean score of 7 pain-related items. The somatic subscale (SSI-Somatic) consists of the remaining 21 items.

Visual Analogue Scale for Pain

The overall pain severity was represented on a visual analogue scale (VAS), rated from the extremes of experiencing ‘no pain’ (0 mm) to experiencing pain “as severe as I can imagine” (100 mm). A cutoff score of >30 mm was used to distinguish no or mild pain from moderate to severe pain (Kelly et al. 2001; Collins et al. 1997). The corresponding anchors for interference of pain in daily life according to VAS were “not at all” to “totally debilitating”. Moderate to severe interference of pain in daily life was defined as a score >30 mm.

Health-related quality of life at baseline, at 3 months, and at 6 months follow-up.

Health-related quality of life (HRQoL) was assessed by using the 36-item Short Form Health Survey (SF-36) (Ware et al. 1993). The SF-36 is a questionnaire, originally in English, validated in Dutch (Aaronsen et al. 1998) and French (Leplege et al. 1998), that consists of 36 questions generating scores across 8 health domains (4 mental and 4 physical subscales) and 2 summary scores (the Physical Component Score [PCS] and the Mental Component Score [MCS]). Within each subscale, the scores on the individual items are summed and transformed to a scale of 0 to 100. A higher score indicates a better quality of life. The SF-36 subscales were normalised to a mean of 50 (standard deviation [SD] 10) for the general United States adult population. Any score below 50 suggests a HRQoL below the average of the standardised population (Ware et al. 2001).

Sociodemographic variables and psychiatric history at baseline.

The following sociodemographic variables were collected: age, gender, education (none or mandatory compared to further education), marital status (married/domestic partner or other), occupational status (employed, unemployed, or other), number of dependants, body mass index (BMI), and smoking status. The following clinical variables were also collected: duration of the current depressive episode, number of previous depressive episodes, age at which the first depressive episode occurred, psychiatric comorbidity within the 2 years prior to inclusion, and the presence of a chronic medical condition.

Statistical method

All patients enrolled at a Belgian site, who were eligible for the FINDER study and who had completed the HADS at baseline, were included in this post-hoc analysis. Counts and percentages of patients falling within the defined diagnostic categories at baseline were calculated, and suitable summary statistics were applied to the different patient characteristics.

Differences between the diagnostic categories and within the 2 pain groups (none to mild/moderate to severe according to VAS for pain) are presented descriptively. For patients with follow-up data on the HADS, percentages of still caseness and of patients with remission, as defined above, were calculated.

For each of the 3 baseline categories (caseness for depression, caseness for anxiety, and caseness for comorbid depression and anxiety), logistic regression analyses were performed to model each of the log odds of still caseness and of remission, by using backward elimination methods.
The results are reported using Wald $c^2$ statistics, P-values, and odds ratios. The 95% confidence intervals are presented for all statistically significant ($p \leq 0.05$) independent variables in the model.

Multivariate regression analysis was performed to identify variables independently associated with severity of overall pain (overall pain VAS) at baseline (Demyttenaere et al. 2010).

More detailed information on the statistical methods is found in previous publications about the FINDER study (Bauer et al. 2008; Garcia-Cebrian et al. 2008; Reed et al. 2009; Demyttenaere et al. 2010).

**RESULTS**

**RESULTS AT BASELINE**

Patient recruitment started in May 2004 and completed in September 2005.

Adult patients (Europe, n = 3468; Belgium n = 239) were eligible for inclusion if they were diagnosed as suffering from depression by their attending physician (psychiatrist) (Europe, n = 1818; Belgium, n = 104) or general practitioner (Europe, n = 1650; Belgium, n = 135) and if antidepressant treatment was about to be initiated for a first depressive episode or for a new episode of recurrent depression.

In total, 227 eligible Belgian patients with nonmissing scores for both HADS-A and HADS-D were included. Of these eligible patients, 67% were female and 33% were male. The mean age was 45.9 years old. The youngest patient was 18 years old; the oldest patient was 84 years old.

**Subgroups and diagnostic categories based on HADS at baseline.**

The distribution of the 227 patients based on the HADS for respectively each subgroup and each diagnostic category (status for depression: noncase, doubtful case, probable case; and status for anxiety disorder: noncase, doubtful case, probable case) is presented in Tables 1 and 2. Caseness for depression was present in 59.9% of the patients, irrespective of anxiety, and caseness for anxiety was present in 69.2% of the patients, irrespective of depression. In total, 15.4% did not meet the criteria of a depressive or anxiety disorder.

We noted different ratios in the subgroups according to the specialty of the investigator. For general practitioners, a probable case for depression was found in 56.2% of patients compared to 65% of the patients for psychiatrists. For comorbid depression and anxiety this was 50% of patients from general practitioners and 49.5% of patients from psychiatrists and for a probable case for anxiety this was 70% of patients from general practitioners and 68% of the patients, from psychiatrists. No depressive or anxiety disorder was found in 17.7% of the patients from general practitioners and in 12.4% of the patients from psychiatrists.

**Table 1: Distribution of all patients from Belgian sites included in the analysis according to HADS subgroups at baseline**

<table>
<thead>
<tr>
<th>% of all patients (n=227)</th>
<th>Non-case for depression D- (%)</th>
<th>Doubtful case for depression D? (%)</th>
<th>Probable case for depression D+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-case for anxiety A-(%)</td>
<td>6.2</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Doubtful case for anxiety A? (%)</td>
<td>6.6</td>
<td>5.3</td>
<td>7.5</td>
</tr>
<tr>
<td>Probable case for anxiety A+ (%)</td>
<td>7.5</td>
<td>11.9</td>
<td>49.8</td>
</tr>
</tbody>
</table>

HADS = Hospital Anxiety and Depression Scale. Overall caseness for depression (irrespective of anxiety) = 59.9%; Overall caseness for anxiety (irrespective of depression) = 69.2%.

**Table 2: Distribution of all patients from Belgian sites included in the analysis according to HADS diagnostic categories at baseline**

<table>
<thead>
<tr>
<th>HADS diagnostic category</th>
<th>Non-caseness for anxiety and depression D=A- D/A+</th>
<th>Mixed caseness anxiety D/A+</th>
<th>Caseness for depression D=A- D/A+</th>
<th>Caseness for anxiety disorder A=D- A=D+</th>
<th>Case- ness for comorbid depression disorder anxiety D=A+</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of all patients (n=227)</td>
<td>15.4</td>
<td>5.3</td>
<td>10.1</td>
<td>19.4</td>
<td>49.8</td>
</tr>
</tbody>
</table>

HADS = Hospital Anxiety and Depression Scale

**Severity of painful and nonpainful somatic symptoms at baseline according to diagnostic category.**

Moderate to severe clinically relevant pain scored on the VAS (VAS >30 mm), occurred in 57.5% of the patients. 50.0% of patients experienced a clinically relevant interference of their pain symptoms in daily life.

Clinically relevant pain (scored on both the VAS for pain severity measure and the SSI-Pain for bothersomeness) occurred most frequently in the comorbid depression and anxiety diagnostic category. On the VAS, 66.7% of the comorbid depression and anxiety diagnostic category had a score higher than 30 mm, accounting for moderate to severe pain. Likewise, this pattern is confirmed for the SSI-Pain, with the highest mean pain score found in the comorbid group (SSI-Pain mean score: 2.7). Therefore, painful somatic symptoms seem to increase with severity of the psychopathology. For nonpainful somatic symptoms (scored on the SSI-Somatic), we note a similar relationship with the severity of the psychopathology, with the greatest bothersomeness also in the comorbid group (SSI-Somatic mean score: 2.6). Table 3 shows the severity of the somatic symptoms according to HADS diagnostic categories at baseline.
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The regression analysis of the VAS overall pain score at baseline as the dependent variable demonstrates that the severity of the nonpainful physical symptoms (as measured by the SSI-Somatic score) was the variable most strongly associated with the baseline severity of pain, in addition to having a painful medical condition and having fewer previous depressive episodes being predictive of pain severity (Table 4).

### Table 3: Severity of somatic symptoms according to HADS diagnostic categories at baseline

<table>
<thead>
<tr>
<th>All patients (N=227)</th>
<th>Non-caseness for depression and anxiety</th>
<th>Mixed anxiety-depression</th>
<th>Caseness for depression</th>
<th>Caseness for anxiety</th>
<th>Caseness for comorbid depression-anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI-Pain score, mean (SD)</td>
<td>2.1 (0.7)</td>
<td>1.7 (0.5)</td>
<td>2.2 (0.7)</td>
<td>2.4 (0.9)</td>
<td>2.7 (0.9)</td>
</tr>
<tr>
<td>SSI-Somatic score, mean (SD)</td>
<td>1.7 (0.4)</td>
<td>1.7 (0.4)</td>
<td>2.2 (0.5)</td>
<td>2.1 (0.6)</td>
<td>2.6 (0.7)</td>
</tr>
<tr>
<td>VAS-Pain score &gt;30 mm (moderate to severe pain) (%)</td>
<td>47.1</td>
<td>25.0</td>
<td>54.6</td>
<td>59.5</td>
<td>66.7</td>
</tr>
</tbody>
</table>

For SSI and VAS: higher figures indicate worse scores. HADS = Hospital anxiety and depression Scale; SD = standard deviation; SSI = Somatic Symptom Inventory; VAS = Visual Analogue Scale.

Figure 1 presents the distribution of the patients for VAS pain scores (a) and for interference of pain with functioning (b) at baseline and at 6 months.

### Table 4: Independent variables significantly associated with pain severity (VAS) at baseline

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Estimate</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain severity (VAS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSI-Somatic score</td>
<td>13.9</td>
<td>33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medical condition</td>
<td>11</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Painful</td>
<td>18.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-painful</td>
<td>9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of previous depressive episodes</td>
<td>-4.2</td>
<td>6.1</td>
<td>0.015</td>
</tr>
</tbody>
</table>

VAS = Visual Analogue Scale; SSI = Somatic Symptom Inventory.

Figure 1: Distribution of patients for VAS for a) overall pain severity, and b) interference of pain with functioning.
Results at Follow-up

Remission and still caseness (persistence of pathology) at 3 and 6 months follow-up.

Table 6 illustrates remission rates at 3 and 6 months follow-up. At 3 months, 213 patients were still in follow-up compared to 208 patients at 6 months. Remission rates at 6 months follow-up were clearly higher than at 3 months follow-up in the caseness for anxiety group (27% and 16.2%, respectively) and in the comorbid anxiety-depression group (34.7% and 11%, respectively). This correlation between longer duration and better outcome was not observed in the caseness for depression group, for which lower remission rates were found at 6 months compared to 3 months follow-up (31.6% and 42.1%, respectively).

In addition, it is noteworthy that, respectively, 36.8%, 40.5%, and 40% of the patients with caseness for anxiety, depression, and comorbid anxiety-depression at baseline still met the criteria for caseness after 6 months.

Baseline factors associated with remission at 6 months follow-up.

A logistic regression analysis was conducted of all patients for evaluating remission at 6 months follow-up including all baseline variables as possible predictors. A higher baseline HADS-A score, a higher SSI-Pain score, and a lower SSI-Somatic score predicted lower odds of achieving remission (Table 7).

Table 7: Logistic regression analysis for remission at 6 months with baseline variables as possible predictors

<table>
<thead>
<tr>
<th>Effect</th>
<th>Odds Ratio</th>
<th>95% Wald Confidence Limits</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS-A</td>
<td>0.884</td>
<td>0.81 0.965</td>
<td>0.006</td>
</tr>
<tr>
<td>SSI-Somatic</td>
<td>1.994</td>
<td>1.076 3.695</td>
<td>0.0284</td>
</tr>
<tr>
<td>SSI-Pain</td>
<td>0.587</td>
<td>0.366 0.941</td>
<td>0.0271</td>
</tr>
</tbody>
</table>
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Table 9: Health-related quality of life at baseline, 3 months, and 6 months (overall patient population).

<table>
<thead>
<tr>
<th>Health-related Quality of Life</th>
<th>Study Period</th>
<th>Mean (SD) of Standardized Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Health summary score</td>
<td>baseline</td>
<td>23.2 (10.0)</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>33.7 (11.7)</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>38.4 (12.2)</td>
</tr>
<tr>
<td>Physical Health summary score</td>
<td>baseline</td>
<td>45.1 (9.6)</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>46.8 (8.6)</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>48.7 (8.4)</td>
</tr>
</tbody>
</table>

Discussion

Within this naturalistic study of patients, a first interesting finding is that almost 60% of the patients enrolled at Belgian sites with a clinical diagnosis of depression, whose attending physician decided to initiate antidepressant treatment, were probable cases for depression, with the vast majority having a comorbid anxiety disorder. This does not imply that the other 40% did not have any psychiatric condition; half of these did show probable caseness for anxiety disorder. Remarkably, within the total group of patients included in this analysis, more patients had caseness for anxiety (69.2%) than for depression (59.9%) (Tables 1 and 2).

These findings suggest that, in daily clinical practice, physicians do not always make a differential diagnosis between depressive and anxiety disorders when initiating antidepressant treatment, and that anxiety is present in a high proportion of patients receiving antidepressants. It has been shown previously that physicians use other methods to make prescription decisions instead of basing their decision on the formal DSM-IV or ICD-10 criteria (Linden et al. 1999).

In this post-hoc analysis of patients enrolled from Belgian sites, caseness for comorbid anxiety-depression was found in 49.8% of the patients. Previously published results reveal that depression and anxiety comorbidity varies between 39% (in an Australian national study evaluating mental health [Hunt et al. 2004]), and 59% (in a German national study [Carter et al. 2001]), and between 51% and 62% in depressed outpatient samples (Rush et al. 2005; Fava et al. 2000).

Nearly 21% of patients had no formal psychiatric diagnosis of anxiety or depressive disorder according to their self-reported symptomatology (Table 2). This does not exclude having any sign at all of a mental disorder. The accurate prescription of antidepressants has been discussed above (Demyttenaere et al. 2008a; Linden et al. 1999). A Finnish study (Joukamaa et al. 1995) in primary care revealed that psychotropic medication was prescribed in 70% of patients with symptoms of a mental disorder (a wider definition than a formal diagnosis) and in 13% of patients with no obvious sign of a mental disorder.

HADS-A = Hospital Anxiety and Depression Scale – Anxiety; SSI = Somatic Symptom Inventory.

Severity and interference in daily functioning of the painful somatic symptoms and associated variables.

Looking at pain severity, 72.8% of the patients scored below the cutoff for moderate to severe pain (VAS > 30 mm) at 6 months (as opposed to 41% at baseline). Considering interference of pain in daily life, 78.2% of the patients scored below the cutoff score (VAS > 30 mm) at 6 months (as opposed to 48.7% at baseline) (Figure 1).

A higher pain severity measurement at the 6 months follow-up was significantly associated with the presence of a higher pain severity measurement at baseline, a higher baseline severity score of the nonpainful physical symptoms, by the class of administered analgesics between baseline and the 3-month assessment, by a lower severity of depression at baseline, and by the presence or nonpresence of a painful medical condition at baseline (Table 8).

Health-related quality of life (SF-36) at baseline, at 3 months, and at 6 months follow-up.

The mean mental health score (SF-36 MCS) increased during follow-up. The mean score for the whole patient group was 23.2 at baseline, 33.7 at 3 months, and 38.4 at 6 months. The mean physical health score (SF-36 PCS) remained rather stable over the whole follow-up period, with a mean score of 45.1 at baseline and 48.7 at 6 months. See Table 9 for HRQoL (SF-6) at baseline, 3 months, and 6 months.

Table 8: Independent variables at baseline significantly associated with the severity of overall pain at 6 months

<table>
<thead>
<tr>
<th>Severity of overall pain (VAS)</th>
<th>Independent variable</th>
<th>Estimate</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain severity (VAS)</td>
<td>0.3</td>
<td>26</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SSI-Somatic score</td>
<td>9.3</td>
<td>17</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Class of analgesics</td>
<td>8</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>12.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>20.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS-D</td>
<td>-1.2</td>
<td>15</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Medical condition</td>
<td>5</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful</td>
<td>11.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Painful</td>
<td>3.9</td>
<td>(NS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analgesics used during the observation period from baseline to 3 months. VAS = Visual Analogue Scale; HADS-D = Hospital Anxiety and Depression Scale - Depression; NSAID = nonsteroidal anti-inflammatory drug; SSI = Somatic Symptom Inventory; NS = Non Significant.
The percentage of patients not meeting the criteria of a depressive or anxiety disorder and who are prescribed antidepressant medication, nevertheless, is greater in the group treated by the general practitioner compared to the group treated by the psychiatrist. The findings are consistent with previously published data (Mojtabai 1999).

A second important finding in this naturalistic study is the presence of moderate to severe pain in more than half of the patients within our population seeking help and of interference of pain in daily life in about half the patients (Fig. 1). This is consistent with previously published data regarding the relationship between depression or anxiety and more chronic pain (Ohayon et al. 2003; Demyttenaere et al. 2006; Bair et al. 2003; Bair et al. 2004). Both pain and interference of pain decreased during follow-up.

The finding that pain symptoms and severity of pain (onSSI-Pain and on VAS-Pain) increase with the severity of the psychopathology confirms that patients with a depressive disorder or with an anxiety disorder experience more painful somatic symptoms (Demyttenaere et al. 2008b; Demyttenaere et al. 2006; McWilliams et al. 2004; Sartorius et al. 1993).

A third interesting finding is that the nonpainful somatic symptoms (SSI-Somatic) follow the same pattern (Table 3). This suggests that their relationship with depression and anxiety is similar to the relationship of pain symptoms with depression and anxiety. These findings support recently published data claiming that scores on the SSI-Pain (headache, low back pain, muscle stiffness, neck pain, and joint pain), as well as scores on the nonpainful SSI items (SSI-Somatic: fatigue, the feeling of not being in good general health, not feeling well, feeling weak, a feeling of heaviness in arms and legs, cold hands and feet) increase significantly in patients with major depression (Vaccarino et al. 2008). Previous studies have demonstrated that the presence of pain symptoms compromises the outcome of antidepressant treatment (Ohayon et al. 2003; Bair et al. 2003; Bair et al. 2004). The present findings suggest that nonpainful physical symptoms should probably also be taken into account as possible predictors of treatment response in depression (Reed et al. 2009).

The association between painful physical symptoms and nonpainful physical symptoms may suggest that they are better understood as 1 group of somatoform or somatic symptoms instead of focusing separately on the 1 (painful) or the other (nonpainful) subgroup. Standardised rating scales for somatic symptoms (like the SSI, Patient Health Questionnaire-somatization subscore, or the Symptom Check List-somatization subscore) currently cluster both painful and nonpainful symptoms into 1 group of symptoms.

A fourth interesting finding is that a higher score on the HADS-D at baseline is associated with a lower severity of the pain symptoms at 6 months. This seems a rather counterintuitive result (Table 8). It has been documented that the reported pain severity is partly determined by the severity of depression (Shelton et al. 2007). This explains why patients with a higher HADS-D score at baseline could have lower pain severity at 6 months, since a great part of the pain severity at baseline was probably associated with the severity of the depressive psychopathology at baseline. In addition, it has been shown that effective pain reduction with antidepressant treatment is partly due to a direct effect and partly via an improvement of depressive symptomatology (Dworkin et al. 2007; McClean 2008).

The mean mental health score (SF-36) at baseline was much lower compared to the standard population norm, in contrast to the more stable physical health score. It is noticeable that the lower mean mental health score was observed at baseline even in the group of patients where no diagnosis was established (D-A-, D-A?, D-A-) (Table 5). This suggests that these help-seeking patients really do present with a substantial loss of emotional quality of life, even though they do not meet the caseness criteria for depression or anxiety disorder. The finding that the lowest mental health score of the SF-36 was observed in the comorbid depression-anxiety group at baseline confirms previously published results of functional limitation within this subgroup (Boulenger et al. 1997; Judd et al. 1998) and of a lower mental health score in this subgroup compared to a pure generalised anxiety disorder or a pure depression (Carter et al. 2001). In addition, the fact that the mean mental health score increases at 3 months and 6 months follow-up evaluations indicates an increase in mental HRQoL when depressive and anxiety symptoms decrease. For the whole patient sample, the mental health score at 6 months was still 1 SD below the standard population norm.

Within the 3 diagnostic categories (caseness for depression, caseness for anxiety, and caseness for comorbid depression and anxiety) remission rates of approximately 30% were noted at 6 months follow-up. These rather low remission rates can be due to the presence of residual depressive symptoms leading to continued impairment. For patients with caseness for anxiety and those with caseness for comorbid depression-anxiety, a better symptomatic outcome was reported with more long-term treatment (6 months compared to 3 months) (Table 6). This correlation was not present in the caseness for the depression group, considering the greater remission rates at 3 months compared to 6 months. This finding is in contrast to the one from the European data (Demyttenaere et al. 2009) demonstrating a positive correlation between treatment outcome and treatment duration for all 3 diagnostic categories. At 3 months, the remission rates for the depression caseness group were higher than those of the caseness for anxiety group or of the comorbid group. At 6 months, this difference among the groups seems smaller (Table 6). Therefore, in this analysis, there was no large difference in remission rates after 6 months between patients with caseness for depression (rate of 31.6%) and those with caseness for comorbid depression and anxiety (rate of 34.7%), unlike the European FINDING data which demonstrated a difference in outcome between the diagnostic categories, with 10% lower remission rates for the comorbid group. These results should be seen in light of an ongoing debate on the question of whether remission rates in patients with depression and
additional anxiety symptoms are lower compared to patients with depression without anxiety symptoms (Nelson 2008). Part of the discussion is probably to be understood in view of the use of different definitions of anxious depression within different studies, albeit not explaining it entirely. In STAR*D (Sequenced Treatment Alternatives to Relieve Depression), remission rates in nonanxious depression compared to anxious depression were 33.4% and 22.2%; respectively; remission rates in patients without or with generalised anxiety disorder were 29.5% and 21.2%, respectively (Fava et al. 2008; Trivedi et al. 2006). This 10% difference in remission rates corresponds with the European data of the FINDER study (Demyttenaere et al. 2009).

One could expect a higher baseline HADS-A score and a higher baseline SSI-Pain score to predict lower odds of obtaining remission (Demyttenaere et al. 2009; Trivedi et al. 2006) (Table 7). Consequently, given the strong correlation between SSI-Somatic and SSI-Pain, it was a rather unexpected finding that a lower SSI-Somatic score was predictive of lower remission rates.

This study has a number of important limitations that affect the interpretation and generalisability of the study results. First, the study population is small (n = 227). Although most findings correspond with those found in the larger European database (Demyttenaere et al. 2009), some were contradictory.

Second, several variables (length of depressive episode, history of past episodes, somatic comorbidity, etc.) were collected via medical records, patient reports, and a clinical interview, rather than via a standardised diagnostic interview.

Third, the HADS-based diagnostic categories were constructed in order to approach more standardised diagnostic categories. However, the European study (Demyttenaere et al. 2009) reveals that the results closely reflect those of other studies that used more standardised diagnostic categories.

Fourth, the data on intensity and interference of pain are limited to the past week. Pain is a complex matter, and more detailed information on the duration of pain, or its location, could be of added value in the study. However, the total pain experience can never be completely understood via questionnaires.

Fifth, the observation period was limited to 6 months. At 6 months, about one-third of the patients reported persistence of moderate to severe pain. A longer follow-up period could have revealed a subgroup with refractory pain and depression.

Finally, in analogy to the VAS for pain, a VAS for interference of pain in daily life was used, and no significant cutoff score for this instrument has been reported so far in literature. It was used only descriptively in the analyses of this study and has a good face validity.

We conclude that physicians do not always differentiate between depressive and anxiety disorder symptoms when initiating antidepressant medication and that anxiety seems a stronger predictor than depression for prescribing antidepressants. Second, we conclude that there is a high correlation between nonpainful somatic symptoms, painful somatic symptoms, depression, and anxiety disorder. These findings may contribute to the discussion on the future classification of somatic (painful and nonpainful) symptoms in patients with a depressive and/or anxiety disorder. Third, we conclude that the majority of patients with a depressive and/or anxiety disorder only have partial or no response to a treatment with antidepressants.

Acknowledgement

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Références


Ware JE, Kosinski M, Gandek B. SF-36 Health Survey Manual and Interpretation Guide (New England Medical Center, Health Institute, Boston, MA, 1993).


Objectifs: 
Examiner la qualité de vie des patients belges dans l’étude prospective et observationnelle de FINDER, dans laquelle des patients adultes et ambulatoires souffrant de dépression prennent un traitement d’antidépresseurs.

Méthode: 
Dans cet article, nous rapportons l’analyse du sous-groupe post-hoc de patients inclus en Belgique. Les patients ont rempli des questionnaires à fin d’évaluer la qualité de vie ainsi que la gravité et la chronicité de la dépression, de l’anxiété et des symptômes de douleur, ceci au point de départ, à 3 mois et à 6 mois.

Résultats: 
Au départ, 59.9% des 227 patients souffraient de dépression et 69.2% d’anxiété. Un score élevé pour le HADS-A et pour le SSI-Pain et un faible score pour le SSI-somatique au départ prédisaient moins de chance de rémission. Un score élevé pour le VAS au point de départ était associé à la gravité des symptômes physiques de non-douleur et des épisodes dépressifs précédents. Le score de santé mentale moyen (SF-36 MCS) a augmenté au cours du suivi, alors que le score de santé physique moyen (SF-36 PCS) est resté stable.

Conclusions: 
Les médecins ne font pas de distinction entre les symptômes de dépression et d’anxiété lorsqu’ils initient un traitement par antidépresseurs. L’anxiété se révèle être un facteur prédictif plus puissant que la dépression pour la prescription d’antidépresseurs. La présence de symptômes somatiques de douleur et de non douleur permet de prédire la réponse aux antidépresseurs dans la dépression.


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