Manic symptoms in patients with depressive and/or anxiety disorders

Belinda van den Berg a, d,*, Brenda W.J.H. Penninx a, b, c, Frans G. Zitman b, Willem A. Nolen c

a Department of Psychiatry/EMGO Institute, VU University Medical Centre, Amsterdam, The Netherlands
b Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands
c Department of Psychiatry, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands
d Ánimo, Center for Psychotherapy and Psychiatry, Sitges, Spain

Article info

Article history:
Received 8 October 2009
Received in revised form 24 February 2010
Accepted 24 February 2010
Available online 24 March 2010

Keywords:
Bipolar depression
Manic symptoms
Depressive disorder
Anxiety disorders

Background: Previous studies found that patients with depressive disorders frequently have lifetime manic symptoms or even an unrecognized bipolar disorder and that these patients have more severe illness. In this study we investigated whether the presence of significant manic symptoms among patients presenting with depressive and/or anxiety disorders is associated with more severe illness, more comorbidity, more suicidality and more atypical symptoms.

Methods: In a large cohort (n = 2012) of persons with lifetime depressive and/or anxiety disorders (as confirmed with the Composite International Diagnostic interview (CIDI)) we used the 15-item Mood Disorder Questionnaire (MDQ) to assess the presence of lifetime manic symptoms. Patients with clinically recognized bipolar disorders were excluded from the study.

Results: Lifetime manic symptoms were present among 6.3% of the persons with depressive or anxiety disorders. Persons with lifetime manic symptoms more frequently had comorbid social phobia, generalized anxiety disorder and alcohol dependence, more frequently reported previous serious suicide attempts and their current depressive symptoms were more severe. Atypical depression symptoms were not more prevalent in persons with lifetime manic symptoms.

Limitations: The presence of a lifetime manic or hypomanic episode was not assessed with the CIDI.

Conclusions: Identifying lifetime manic symptoms with the MDQ in persons presenting with (unipolar) depressive or anxiety disorders, cannot only help the recognition of actual bipolar disorder (as described in previous studies), but also the identification of a subgroup of patients with more severe symptomatology, more comorbid anxiety and alcohol dependence disorders, and more suicidality.

1. Introduction

Many patients with bipolar disorder remain undetected or are initially misdiagnosed when seeking professional help (Hirschfeld et al., 2003a, b). The most frequent misdiagnosis is major depressive disorder (unipolar depression) (Hirschfeld et al., 2003a, b). An important reason for this misdiagnosis is that patients when in a depression, do not talk to their care provider spontaneously about their previous (hypo)manic symptoms. By carefully questioning for previous manic symptoms among patients presenting with a depression the number of patients diagnosed as actually having a bipolar disorder with a depressive episode (bipolar depression) nearly doubles (Akiskal et al., 2006; Hantouche et al., 1998).

A misdiagnosis of unipolar depression rather than bipolar depression can lead to inappropriate treatments, such as antidepressants as monotherapy (i.e. not combined with mood stabilizers) which in patients with bipolar depression not only may be less effective (Sachs et al., 2007) but also may have an increased risk of a manic switch or cycle acceleration (Bowden, 2005; Licht et al., 2008). In addition, it is important to distinguish bipolar depression from unipolar depression because social and occupational functioning is worse and risk...
of suicide is higher among patients with bipolar disorder (Bowden, 2005; Chen and Dilsaver, 1996). Furthermore, accurate and timely recognition of bipolar disorders is associated with lower medical costs and lower indirect costs due to work loss (Birnbaum et al., 2003; McCombs et al., 2006).

When seen in a depressive episode, bipolar depression and unipolar depression are difficult if not impossible to be discriminated from each other, as patients generally have similar complaints and symptoms. However, atypical symptoms like hypersomnia and increased appetite may be more frequent in bipolar depression (Angst et al., 2006; Benazzi, 2000; Bowden, 2005). Bipolar depression has also been associated with an earlier age at onset, more depressive episodes, fears and delusions and less insomnia (Perlis et al., 2006). Others have found bipolar II depression to be characterized by a symptom profile including more hypersomnia and psychomotor agitation than unipolar depression (Akiskal et al., 2006; Hantouche and Akiskal, 2005). In a study in primary care (Olsson et al., 2005), 53 depressed patients with a history of significant manic symptoms reported more hallucinations, more suicidal ideation and alcohol use and less disturbed appetite. In a Korean sample (n = 111) (Kim et al., 2008), bipolar individuals more frequently reported a family history of bipolar disorder, comorbid alcohol use disorders, a history of suicide attempts and an earlier age of onset than unipolar individuals, but no differences in the frequency of atypical symptoms was observed.

Above findings are based on rather small studies and are somewhat conflicting as some studies found more atypical symptoms in bipolar depression while other studies did not find this difference.

The present study examined characteristics of the presence of significant lifetime manic symptoms in a large sample of patients with depressive and/or anxiety disorders. Based on the literature, we hypothesized a priori that respondents with a lifetime history of manic symptoms would have an earlier age of onset of first symptoms, more comorbid alcohol dependence and anxiety disorders, more severe depressive symptoms, more suicidality and a symptom profile with more atypical symptoms.

2. Methods

2.1. Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is a longitudinal naturalistic cohort study including 2981 persons aged 18–65 years. A complete description is given elsewhere (Penninx et al., 2008). The baseline sample consists of 1701 persons with a current (6 month-recency) diagnosis of depressive and/or anxiety disorder, 628 persons with a lifetime non-current diagnosis of depressive and/or anxiety disorder and 652 persons without a lifetime diagnosis. Recruitment of these respondents took place in the general population, in general practices, and in mental health care institutions in order to recruit persons reflecting various settings. In NESDA, patients with clinically recognized bipolar disorders were not included. However, as it is known that bipolar disorders frequently are not clinically recognized, we assumed that some subjects in our sample would have an unrecognized bipolar disorder (Hantouche et al., 1998).

Since the present study focuses on the presence of lifetime manic symptoms among persons with depressive and/or anxiety disorders, we excluded those subjects without a lifetime depression or anxiety disorder (n = 652). Information on manic symptoms (see below) was missing for 317 subjects who did not fill out the MDQ, leaving 2012 study subjects for the present analyses. Subjects with missing information on manic symptoms did not differ in terms of lifetime alcohol dependency (16.4% vs. 15.1%, p = .52) but were younger (37.9 vs. 42.4 years, p <.001), more frequently male (39.3% vs. 32.8%, p = .015), compared to those with available information.

3. Measurements

3.1. Sociodemographics

Age, gender, education (in years) and Dutch ancestry (yes/no) were determined at baseline and we explored whether these characteristics differed in patients with or without lifetime manic symptoms. In addition, we examined whether lifetime manic symptoms differed across recruitment settings (general population, primary care, and mental health care).

3.2. Depression and anxiety disorder characterization

Current and lifetime diagnoses as well as age of onset of depressive and anxiety disorders and alcohol related disorders (alcohol dependency and abuse) were established with the respective sections of the DSM-IV based CIDI interview (WHO version 2.1), while not applying other CIDI sections such as the psychosis and bipolar sections. Severity of depressive symptoms over the past week was measured with the 30-item Inventory of Depressive Symptoms self-report version (IDS-SR; Rush et al., 1996) including items specifically assessing melancholic and atypical features. A question asking whether a serious lifetime suicide attempt had ever occurred was added.

3.3. Assessment of manic symptoms

The Mood Disorder Questionnaire (MDQ), a self-report, 15-item questionnaire screening for a lifetime history of manic symptoms, was developed to help detect bipolar disorders (Hirschfeld et al., 2000). Its validity has been shown in various settings (Hirschfeld, 2002; Hirschfeld et al., 2003a,b, 2005; Miller et al., 2004; Das et al., 2005). We decided to define significant lifetime manic symptoms to be present when the MDQ was positive (Hirschfeld, 2002): 7 or more positive answers on 13 items, conditional on the respondents’ indication that the symptoms occurred at the same time and that they experienced at least moderate problems due to these symptoms. We decided on using the cut-off used by Hirschfeld, (Hirschfeld et al., 2000) as this is the most commonly used cut-off with a rather high specificity.
3.4. Statistical analyses

Sociodemographic as well as psychopathology characteristics were compared between subjects scoring MDQ-positive or not using chi-square and t-test statistics. Subsequently, multivariate logistic regression analysis was conducted that included the variables found to be statistically significant (p<.05) in bivariate analyses.

In order to test whether specific depressive symptoms, e.g., atypical symptoms, were associated with lifetime manic symptoms, we conducted multivariate logistic regression analyses examining whether specific (i.e., atypical) IDS items were associated with a MDQ-positive score, after adjustment for IDS total score. This analysis was conducted only among subjects with a past-month depression since IDS only reflects past week symptoms. First, we entered the IDS total score in the model in order to adjust for depression severity. Second, the atypical symptom scores (reactivity of mood, hypersomnia, increased appetite and increased weight, leaden paralysis and interpersonal sensitivity) were entered. Finally, we performed a stepwise regression analysis on the other IDS items to define whether specific additional depressive symptoms were associated with lifetime manic symptoms. All statistical analyses were done using SPSS version 13.0.

4. Results

Of the 2012 respondents, a total of 126 (6.3%) had a positive MDQ score. Table 1 shows the characteristics of the MDQ-positives versus MDQ-negatives. The MDQ-positives were significantly more often male (OR = 1.69, p = .02), more often had a life time history of dysthymia (OR = 1.69, p = .009), more social phobia (OR = 1.54, p = .31) and generalized anxiety disorder (OR = 1.80, p = .003), more life time alcohol dependency (OR = 2.48, p < .001) and reported more often a history of a serious suicide attempt (OR = 2.67, p < .001) than MDQ-negatives.

4.1. Depressive symptoms profile

Subsequently, we conducted logistic regression analyses among persons with a past-month depression to examine whether certain depressive symptoms (IDS items) were related to a MDQ-positive score. MDQ-positives had a higher mean total IDS score (41.3 ± 10.5 vs. 34.8 ± 11.1, p = .001) than MDQ-negatives. After adjusting for IDS score, the atypical symptoms were entered. Finally, we performed a stepwise regression analysis on the additional depressive symptoms.

The final model is described in Table 2. MDQ-positives reported more interpersonal sensitivity and—contrary to our hypothesis—less increased appetite. There was no significant difference in the other atypical symptoms. Furthermore, MDQ-positives reported less difficulty falling asleep, less feeling anxious, less difficulty concentrating and making decisions, more aches and pains and less loss of interest in sex. This indicated that although some depressive symptoms differentiated between MDQ-positives and MDQ-negatives, the atypical symptoms were not consistently among them.

5. Discussion

Overall, our findings illustrate that significant lifetime manic symptoms in patients with depressive and/or anxiety disorders are associated with a more severe and complex form of illness. In line with previous studies (Hirschfeld et al., 2005; Hantouche et al., 1998) we found that manic symptoms are common in subjects with depressive and/or anxiety disorders: 6.3% of our sample scored MDQ-positive, even though patients with clinically recognized bipolar disorder

---

Table 1

<table>
<thead>
<tr>
<th>Psychopathology indicators</th>
<th>MDQ pos n = 126</th>
<th>MDQ neg n = 1886</th>
<th>Odds Ratio a</th>
<th>95% Confidence Interval a</th>
<th>p a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive episode (%)</td>
<td>87.3</td>
<td>81.8</td>
<td>.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent depressive disorder (%)</td>
<td>44.1</td>
<td>42.2</td>
<td>.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysthymia (%)</td>
<td>48.4</td>
<td>26.8</td>
<td>&lt;.001</td>
<td>1.69</td>
<td>1.14–2.52</td>
</tr>
<tr>
<td>Social phobia (%)</td>
<td>54.8</td>
<td>37.3</td>
<td>&lt;.001</td>
<td>1.54</td>
<td>1.04–2.29</td>
</tr>
<tr>
<td>Panic disorder (%)</td>
<td>58.3</td>
<td>48.3</td>
<td>.03</td>
<td>1.13</td>
<td>0.76–1.68</td>
</tr>
<tr>
<td>Generalized anxiety disorder (%)</td>
<td>52.4</td>
<td>31.4</td>
<td>&lt;.001</td>
<td>1.80</td>
<td>1.22–2.66</td>
</tr>
<tr>
<td>Alcohol dependence (%)</td>
<td>40.2</td>
<td>16.8</td>
<td>&lt;.001</td>
<td>2.48</td>
<td>1.67–3.70</td>
</tr>
<tr>
<td>Alcohol abuse (%)</td>
<td>6.3</td>
<td>10.9</td>
<td>.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early age at onset (&lt;21 years) (%)</td>
<td>51.2</td>
<td>43.5</td>
<td>.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious suicide attempt ever (%)</td>
<td>36.0</td>
<td>12.5</td>
<td>&lt;.001</td>
<td>2.67</td>
<td>1.76–4.04</td>
</tr>
</tbody>
</table>

a Based on multivariate logistic regression analyses.
were excluded from our sample. MDQ-positives were more often male, less educated, and reported more often (comorbid) dysthymia, social phobia, generalized anxiety disorder and alcohol dependence. Severity of depressive symptoms was higher in MDQ-positives and they had more often a history of serious suicide attempts. Contrary to our hypotheses, we did not find evidence that MDQ-positives had an earlier age of onset or a specific atypical symptom profile.

Our study confirms findings from other studies of a higher rate of comorbidity with anxiety disorders (Chen and Dilsaver, 1995; Freeman et al., 2002; Simon et al., 2004) or alcohol dependence (McElroy et al., 2001; Kim et al., 2008), and a greater depression severity and suicidality (Kim et al., 2008) among depressed persons with lifetime manic symptoms. Our findings also confirm known demographic differences between subjects with unipolar and bipolar depression, with a more equal gender distribution in bipolar depression than in unipolar depression (Weissman et al., 1996). Contrary to our hypothesis, we did not find atypical symptoms to be more prevalent among subjects with lifetime manic symptoms. In line with Perlis et al. (2006) we found that MDQ-positives more often had non-atypical symptoms like insomnia (indicated by less difficulty falling asleep) and more often reported aches and pains.

Possibly, some of our MDQ-positives not yet meeting criteria for a DSM-IV bipolar disorder, will develop a manic or hypomanic episode in the future. In studies investigating predictors for switch from unipolar depression to bipolar disorder (Holma et al., 2008; Angst et al., 2005; Goldberg et al., 2001) characteristics similar to our findings were found. Subjects who switched had more severe depression, more comorbid disorders and more lifetime suicide attempts.

The major strength of our study is, that we studied a well-characterized large sample collected in different settings (general population, primary care and secondary mental health care), so that its generalizability goes beyond the patients recruited in clinical settings.

Our study has also limitations. First, we did not assess whether our respondents actually had a bipolar disorder, as we did not apply a diagnostic interview for bipolar disorder. Consequently, the subjects with a positive result on the MDQ likely consisted of two subgroups: those with an unrecognized previous (hypo)manic episode, and those with previous subsyndromal manic symptoms. Moreover, some factors associated with bipolar disorder risk—such as psychotic symptoms and family history of bipolar disorder—as identified by others (Othmer et al., 2007; Phelps and Ghaemi, 2006; Zimmerman et al., 2004) were not systematically collected in our study. Finally, the validity of the MDQ has not yet formally been tested in subjects with anxiety disorders, either as pure disorder or comorbid with depression, which may be of relevance given the overlap in symptoms.

In conclusion, we showed that assessing lifetime manic symptoms with a short self-report questionnaire in persons presenting with depressive or anxiety disorders can help to identify a subgroup of patients with more severe symptomatology, more comorbid anxiety disorders and alcohol dependence, and more suicidality.

### Role of funding source

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Health Care (IQ Healthcare), Netherlands Institute for Health Services Research (NIVEL) and the Netherlands Institute of Mental Health and Addiction (Trimbos)). The funding source was not involved in data analysis nor preparation of this manuscript.

### Conflicts of interests

B. van den Berg: none
B.W.J.H. Penninx: none
F.G. Zitman: none
W.A. Nolen: has received grants from the Netherlands Organisation for Health Research and Development, the European Union, the Stanley Medical Research Institute, Astra Zeneca, Eli Lilly, GlaxoSmithKline and Wyeth; has received honoraria/speaker’s fees from Astra Zeneca, Eli Lilly, Pfizer, Servier and Wyeth; and has served in advisory boards for Astra Zeneca, Cyberonics, Pfizer and Servier.

---

Table 2

Logistic regression analyses associating severity of depression (IDS total score) and atypical as well as other depressive symptoms with significant manic symptoms (MDQ-positives) among persons with a 1-month prevalent major depressive disorder (n = 584, of whom 71 with a MDQ-positive score).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive MDQ score</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDS total score</td>
<td>1.09</td>
<td>1.03–1.16</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Atypical depression symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactivity of mood</td>
<td>1.14</td>
<td>0.77–1.69</td>
<td>.51</td>
<td></td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1.01</td>
<td>0.73–1.38</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>Increased appetite</td>
<td>0.71</td>
<td>0.51–1.00</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>1.02</td>
<td>0.72–1.46</td>
<td>.91</td>
<td></td>
</tr>
<tr>
<td>Leaden paralysis</td>
<td>1.29</td>
<td>0.87–1.92</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>1.36</td>
<td>1.00–1.86</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Other depression symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>0.74</td>
<td>0.57–0.97</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Feeling anxious</td>
<td>0.64</td>
<td>0.41–0.99</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Problems in concentration/decision making</td>
<td>0.65</td>
<td>0.44–0.98</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Aches and pains</td>
<td>1.55</td>
<td>1.07–2.25</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Loss of interest in sex</td>
<td>0.64</td>
<td>0.47–0.89</td>
<td>.01</td>
<td></td>
</tr>
</tbody>
</table>

Data in bold reached significance level (≤ .05).
Acknowledgements

We would like to thank the funding sources for their financial support.

References


