Functional versus syndromal recovery in patients with major depression and bipolar disorder

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Abstract

Objectives: Many patients with major depressive disorder (MDD) or bipolar disorder (BD) experience impairments in daily life. We investigated whether patients with single episode MDD (MDD-s), recurrent MDD (MDD-r) and BD differ in functional impairments, whether time since last episode (syndromal state, in 4 categories) contributes to impairment, whether this association is moderated by diagnosis, and the role of depressive symptoms.

Method: Data were derived from 1664 participants of the NESDA study (MDD-s n=483; MDD-r n=1063; BD n=118), between 2006 and 2009. In additional analyses 530 healthy controls were included. Diagnosis and information about syndromal state were based on the Composite International Diagnostic Interview (CIDI). Psychosocial impairment was assessed with the World Health Organization Disabilities Assessment Schedule 2.0 (WHODAS 2.0). Adjusted associations between diagnosis, syndromal state, impairment and depression severity were investigated.

Results: Not taking syndromal state into account, patients with BD experienced more functional impairment than patients with MDD-s or with MDD-r, and in all diagnostic groups, impairments decreased with increasing time since last episode. However, impact of syndromal state on functioning showed a different course between diagnostic groups (WHODAS-score mean (sd): current: MDD-s 30.8 (2.8), MDD-r 32.7 (0.9), BD 37.7 (2.1), \( p = .7 \); recently remitted: MDD-s 21.7 (3.5), MDD-r 24.0 (1.2), BD 22.1(3.2), \( p = .7 \); remitted: MDD-s 10.6 (3.7), MDD-r 21.6 (1.4), BD 19.2 (4.4), \( p = .02 \); remitted>1year: MDD-s 13.3 (0.6), MDD-r 14.7 (0.5), BD 17.1 (2.2), \( p = .8 \). Depression severity accounted for these differences. Moreover, functioning in all remitted patients remained impaired when compared to healthy controls.

Conclusions: Functional recovery may take up to one year after syndromal remission in recurrent depressive and bipolar disorder, mainly due to residual depressive symptoms, emphasizing the need for prolonged continuation treatment.
Introduction

Mood disorders are highly prevalent and have a major impact on daily life of both patients and their partners and relatives. In the Dutch adult population, the lifetime prevalence rates are estimated at 18.7% for unipolar major depressive disorder (MDD) and 1.3% for bipolar I and II disorder (BD) (1). MDD now ranks as the first cause of years lived with impairment in Europe, whereas BD ranks 12th (2). Patients with major mood disorders may experience serious impairments in psychosocial functioning and quality of life (2-5), despite adequate treatment (2;3;6-8). Syndromal recovery (i.e., no longer fulfilling the formal criteria of a mood episode) does not necessarily lead to a level of functioning comparable to healthy persons (9), which may in part be due to persistent subsyndromal symptoms. Many studies have focused on clinical outcomes such as symptomatic remission and reduction of the number of mood episodes. Quality of life and level of functioning are increasingly valued as being important outcomes (10;11). Although it is obvious that acute mania and depression will impair psychosocial functioning, it is unclear to what extent functioning remains impaired after recovery of an episode and which factors determine functional recovery. Moreover, there is evidence that with each successive illness episode residual symptoms increase, and functional recovery further declines (12-14). Since BD is positioned at the more severe end of the mood disorder spectrum (15), it is of interest to explore whether functional recovery after remission of an illness episode differs between single episode or recurrent MDD and BD patients, and which factors are associated with persistent functional impairment. It has been hypothesized that recurrent depression shares more features with BD than single episode depression, sharing the core feature of cyclicity (16).

The aims of this study are: (1) to compare functional impairment in patients with single-episode MDD (MDD-s), recurrent MDD (MDD-r), and BD; (2) to investigate whether syndromal state (defined as currently in an episode, recently remitted, remitted or remitted>1year) is associated with level of functioning; (3) to investigate whether the association between syndromal state and functional impairment is moderated by type of mood disorder diagnosis; and (4) to investigate the impact of current depressive symptoms (either syndromal or subsyndromal) on functional recovery in these three diagnostic categories.

Method

Sample and procedure

Data were retrieved from the Netherlands Study of Depression and Anxiety (NESDA), a multi-site naturalistic cohort study aimed to describe the long-term course of depressive and anxiety disorders. Aims and design of this study are described in detail elsewhere (17). Subjects in NESDA are patients with a lifetime diagnosis of major depression, anxiety disorder, or both (n=2329, 78%) and healthy controls (n=652, 22%). Participants were recruited for baseline assessment between 2004 and 2007.
from the general population, 65 primary care practices and 17 mental health organization locations, reflecting various settings and stages of psychopathology. During a four-hour assessment, extensive information was gathered on health outcomes and demographic, psychosocial, clinical, biological and genetic determinants. Detailed follow-up assessments were repeated after two and four years, and further follow-up assessments are currently undertaken. Since NESDA was originally not aimed at bipolar disorder, patients with a previously clinically established diagnosis of BD had been excluded at baseline. Nevertheless, when at two-year follow-up (n=2049 patients and n=547 controls; data were gathered between 2006-2009) the DSM IV-TR (15) diagnosis was reassessed with the CIDI (18), now including a detailed history of hypomania and mania, 125 patients fulfilled criteria for a lifetime diagnosis of BD. The two-year follow-up sample was used for the current study, since these assessments gave detailed information about a lifetime DSM IV-TR diagnosis of single or recurrent MDD or BD, and about the course of illness in the previous year, as assessed with CIDI (18). For the main analyses we included data of 1664 patients (MDD-s, n=483; MDD-r, n=1063; BD, n=118) who had also completed the World Health Organization Disabilities Assessment Schedule 2.0 (WHODAS 2.0) (19). In additional analyses we also included 530 healthy controls.

**Diagnosis**

Psychiatric diagnoses were assessed by trained staff using the CIDI (18). The CIDI is being widely used in research in clinical practice, and has been shown to have high interrater reliability (18). Inclusion in the current study was based on the presence of a DSM IV-TR diagnosis of lifetime MDD or BD. We separately analyzed patients with MDD-s and MDD-r. The diagnoses BD I, BD II, or BD-NOS were combined into one group for BD, given the relatively small sample size. Syndromal state was defined and categorized at T2 as remitted>1year (having experienced an episode more than one year ago); remitted (having experienced an episode in the past year, but not in the past 6 months); recently remitted (having an episode in the past 6 months but not during the past month) and current (meeting DSM IV-TR criteria for an episode during the past month). The category ‘remitted >1year’ was used as reference group in the main analyses, and healthy controls were reference in the additional analyses.

**Severity of depressive symptoms**

Current severity of depressive symptoms was measured with the clinician rated version of the Inventory of depressive symptoms (IDS) (20) consisting of 30 items and assessing symptoms over the last seven days. The IDS-sr shows good psychometric properties, with high correlations with observer-rated scales, and sensitivity to change.
Functioning
The level of functional impairment was measured with the WHODAS 2.0, clinician-rated version. The WHODAS 2.0 (19) shows excellent psychometric properties in varying cultures, and consists of 36 items, each to be answered on a 5-point Likert scale (1=no problems; 5=extreme problems) (19). Overall standardized scores range from 0 to 100. Subscales and summary of the WHODAS 2.0 were coded according to the International Classification of Functioning levels (ICF) (18): No problems (0-4%), mild problems (5-24%), moderate problems (25-49%), severe problems (50-95%) and extreme problems (95-100%). The WHODAS covers impairment in six domains during the last 30 days: Cognition (understanding and communicating), Mobility (moving and getting around), Self-care (hygiene, dressing, eating and staying alone), Getting along (interacting with other people), Life activities (domestic responsibilities, leisure, work and school), and Participation (joining in community activities). Since 507 respondents in our sample did not have a paid job, nor attended school, the domain of Life activities had many missing values on WHODAS-36. Therefore, we will report only the standardized total score of the WHODAS-32 (i.e., without items work or school).

Covariates
Socio-demographic characteristics included age, gender, total years of education and marital status. Since co-morbidity of alcohol use disorders (AUD) and anxiety disorders is associated with poorer functioning in MDD and BD patients (21;22), these were included as covariates. The presence of AUD (alcohol dependence or abuse) and anxiety disorders (social phobia, panic disorder, agoraphobia, generalized anxiety disorder) over the past year was established with the CIDI.

Statistical analyses
Sample characteristics across MDD-S, MDD-R and BD patients were compared using univariate analyses of variance and $\chi^2$ statistics. To investigate whether diagnosis is associated with functioning, we conducted univariate analyses of variance with functioning as the dependent variable. All analyses were performed both unadjusted and adjusted for the covariates age, gender, educational level, marital status, alcohol disorders and anxiety disorders. In order to answer the research question whether syndromal state is associated with impaired functioning, we conducted univariate analysis of variance with WHODAS-32 total scores as outcome.

To assess whether the association between syndromal state and impairment is being influenced by diagnosis, we computed an interaction term syndromal state $\times$ diagnosis. We performed regression analyses with both predictors in one model and added the interaction term. If interaction appears to exist, outcomes will be reported stratified for syndromal state. Moreover, to investigate the proportion of the variance explained by depressive symptoms, we adjusted for depression severity in
the analyses of variance. In additional analyses, we investigated if there is a different association between functional impairment for the subgroup of recovered patients when compared to healthy controls, to be able to judge if ‘recovered’ is comparable to ‘healthy’. All statistical tests were two-tailed, and alpha was set at 0.05, except for the interaction analyses, where alpha was set at 0.1.

Results
Sample characteristics
Table 1 summarizes characteristics of patients with MDD-s, MDD-r and BD. In comparison to patients with MDD, those with BD were more often male and were less educated, had more often co-morbid alcohol and anxiety disorders, and a family history of depression. Patients with BD had an earlier age at onset and a longer duration of illness. More patients with BD were currently in an episode, and current depressive symptoms were more severe than in MDD patients. Among patients with MDD, those with MDD-r more often suffered of comorbid anxiety, experienced a current episode more often, reported more often having a family history of depression, and had a higher severity of depressive symptoms, an earlier age at onset and a longer duration of illness, when compared to MDD-s patients.

Diagnosis, syndromal state and functioning
Table 2 shows the associations between diagnostic categories and impairment scores, and between syndromal state and impairment scores. On average, patients with BD experienced more functional impairment than patients with MDD-r, who in turn were more functionally impaired than patients with MDD-s. As expected, patients who were currently in an episode had more functional impairment compared to patients who were recently remitted, remitted or recovered, and the level of functional impairment decreased significantly with increasing time since last episode.
Table 1. Sample characteristics

<table>
<thead>
<tr>
<th>Covariates</th>
<th>MDD-S¹</th>
<th>MDD-R²</th>
<th>BD³</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>N=483</td>
<td>N=1063</td>
<td>N=118</td>
<td></td>
<td></td>
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<tr>
<td><strong>Sociodemographic characteristics</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age, mean years (SD)</td>
<td>44.3 (13.5)</td>
<td>44.6 (12.2)</td>
<td>42.8 (11.7)</td>
<td>.33</td>
</tr>
<tr>
<td>Gender,% female</td>
<td>323 (66.9)</td>
<td>750 (70.6)</td>
<td>67 (56.8)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Education, years, mean (SD)</td>
<td>12.2 (3.3)</td>
<td>12.4 (3.3)</td>
<td>11.5 (3.5)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Marital state, partner, n (%)</td>
<td>205 (42.4)</td>
<td>396 (37.3)</td>
<td>46 (39.0)</td>
<td>.15</td>
</tr>
<tr>
<td><strong>Psychiatric comorbidities</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Anxiety disorder, n (%)</td>
<td>139 (28.8)</td>
<td>423 (39.8)</td>
<td>69 (58.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol use disorder, n (%)</td>
<td>37 (7.7)</td>
<td>96 (9.0)</td>
<td>17 (14.4)</td>
<td>.07</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Family history depression, n (%)</td>
<td>377 (78.1)</td>
<td>922 (86.7)</td>
<td>110 (93.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severity of symptoms⁴, mean (SD)</td>
<td>15.0 (10.4)</td>
<td>20.3 (12.1)</td>
<td>26.4 (14.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age of onset, mean (SD)</td>
<td>32.5 (13.3)</td>
<td>27.1 (12.1)</td>
<td>22.7 (10.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of illness, mean (SD)</td>
<td>12.0 (10.4)</td>
<td>17.5 (11.5)</td>
<td>20.0 (11.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Impairment, mean (SD)</td>
<td>14.8 (16.2)</td>
<td>21.1 (16.2)</td>
<td>28.5 (18.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Syndromal state, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remitted&gt;1year (&gt; 12 months)⁵</td>
<td>421 (87.0)</td>
<td>542 (51.0)</td>
<td>33 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Remitted (6-12 months)⁶</td>
<td>14 (2.9)</td>
<td>99 (9.3)</td>
<td>10 (8.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recently remitted (&lt; 6 months)⁷</td>
<td>19 (3.9)</td>
<td>151 (14.2)</td>
<td>23 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Currently in an episode⁸</td>
<td>29 (6.0)</td>
<td>271 (25.5)</td>
<td>52 (44.1)</td>
<td></td>
</tr>
</tbody>
</table>

1.MDD-S: Major Depression Disorder, single episode
2.MDD-R: lifetime Major Depression Disorder, recurrent episodes.
3.BD: lifetime Bipolar Disorder.
4.Severity of symptoms: based on IDS.
5.Remitted>1year: No episode in last year.
6.Remitted: Last episode 6 – 12 months ago.
7.Recently remitted: Last episode 2 - 6 months ago.

Abbreviations: SD: standard deviation.
P-values based on X² statistics (for categorical variables) and Analysis of Variance (for continuous variables).
Table 2. Associations between functional impairment and diagnosis or syndromal state (N=1664).

<table>
<thead>
<tr>
<th></th>
<th>WHODAS(^1)</th>
<th>(R^2)</th>
<th>(p)</th>
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</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>MDD-s (ref.)(^2)</td>
<td>14.7 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD-R(^3)</td>
<td>21.1 (0.5)</td>
<td>&lt;.001</td>
<td></td>
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<tr>
<td>BD(^4)</td>
<td>28.5 (1.5)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Adjusted(^5)</td>
<td></td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>MDD-s (ref.)</td>
<td>15.9 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD-R</td>
<td>20.9 (0.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>BD</td>
<td>25.4 (1.3)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td><strong>Syndromal state</strong></td>
<td></td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently in an episode (ref.)(^6)</td>
<td>33.3 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recently remitted (&lt; 6 months)(^7)</td>
<td>23.5 (1.0)</td>
<td>&lt;.001</td>
<td>(P**=.06)</td>
</tr>
<tr>
<td>Remitted (6-12 months)(^8)</td>
<td>20.2 (1.3)</td>
<td>&lt;.001</td>
<td>(P*=&lt;.001)</td>
</tr>
<tr>
<td>Remitted&gt;1year (&gt; 12 months)(^9)</td>
<td>14.2 (0.5)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>Currently in an episode (ref.)</td>
<td>30.3 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recently remitted (&lt; 6 months)</td>
<td>22.0 (1.0)</td>
<td>&lt;.001</td>
<td>(P**=.1)</td>
</tr>
<tr>
<td>Remitted (6-12 months)</td>
<td>19.4 (1.2)</td>
<td>&lt;.001</td>
<td>(P*=.003)</td>
</tr>
<tr>
<td>Remitted&gt;1year (&gt; 12 months)</td>
<td>15.6 (0.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

1. WHODAS 2.0 scores, Estimated Marginal Means.
2. MDD-S: Major Depression Disorder, single episode
3. MDD-R: lifetime Major Depression Disorder, recurrent episodes.
4. BD: lifetime Bipolar Disorder.
5. Adjusted: adjusted for age, gender, educational level, marital status, alcohol disorders, anxiety disorders.
7. Recently remitted: Last episode 2 - 6 months ago.
8. Remitted: Last episode 6 – 12 months ago.
9. Remitted>1year: No episode in last year.

\(P^*\) p-value remitted versus remitted>1year.

\(P**\) p-value recently remitted versus remitted.

Level of significance: \(p<.05\).
The temporal course of functional recovery

Since the interaction term diagnosis *syndromal state reached significance, our assumption that the association of syndromal state and functional impairment is moderated by diagnosis is correct. This means differences exist between diagnostic categories concerning the impact of syndromal state on impairment. Figure 1 shows the degree of functional impairment in the diagnostic groups, for each category of syndromal state, i.e., time since the last mood episode. Impairment in recovered patients shows no significant differences between diagnoses (mean (SE): MDD-s=13.3 (0.6); MDD-r=14.7 (0.5); BD=17.1 (2.2); p=.8). In remitted patients we found significant differences between diagnoses (mean (SE): MDD-s=10.6 (3.7); MDD-r=21.6 (1.4); BD=19.2 (4.4); p=.02). In recently remitted patients no significant differences were found between diagnoses (mean (SE): MDD-s=21.7 (3.5); MDD-r=4.0 (1.2); BD=22.1 (3.2); p=.7). In patients currently in an episode, functional impairments did not differ between diagnoses (mean (SE): MDD-s=30.8 (2.8); MDD-r=32.7 (0.9); BD=37.7 (2.1); p=.07). Thus, the degree of functional recovery over time is similar among MDD-s, MDD-r, and BD, except for the 'remitted' state, where patients with MDD-s have less functional impairments than those with MDD-r and BD. This suggests that patients with recurrent unipolar depression or bipolar disorder have a slower functional recovery than patients with single-episode depressive disorder. When current depression severity was added to the model, diagnoses no longer differed regarding impairment in the period 6 to 12 months after the last episode (remitted patients). This suggests that subsyndromal depression symptoms account for these differences between diagnostic groups.

Additional analysis

In an additional analysis, we compared the level of functioning between the subgroups of recovered patients (MDD-s, n=421; MDD-r, n=542; BD, n=33), and healthy controls (n=530). Functioning was more impaired in all groups of recovered patients than in healthy controls (mean WHODAS score (SE): Controls (ref.)=8.0 (0.5); MDD-s=12.3 (0.5) p <.001; MDD-r=13.6 (0.5) p <.001; BD=16.1 (1.9) p <.001).
Figure 1. Associations between syndromal state¹ and functional impairment², in patients with MDD-s³, MDD-r⁴ and BD⁵, and healthy controls⁶ for comparison

2. Functional impairment was measured with WHODAS 2.0; a higher mean score indicates more functional impairment.
3. MDD-s: Major depressive disorder, single episode.
4. MDD-r: Major depressive disorder recurrent episodes.
5. BD: Bipolar disorder.
6. Line: mean WHODAS score 8.0 (SD= 0.5) in healthy controls
Discussion

We investigated the degree of functional impairment among patients with MDD-s, MDD-r, or BD, and its temporal relationship to syndromal recovery. Patients with BD experienced more functional impairment than patients with MDD-r, who in turn had more functional impairment than patients with MDD-s. Obviously, all patients were most severely impaired during a current episode and least when the last episode occurred more than one year ago. Several studies reported differences in functioning between patients with MDD and those with BD, and confirm our finding that BD causes more severe functional disabilities than MDD (23-26). These studies however did not differentiate between single and recurrent MDD. Our data not only suggest that functional recovery lags behind syndromal recovery, but that this is especially true in patients with recurrent mood disorders, be it unipolar or bipolar. Most patients with single episode MDD recovered functionally during the first 6 months after the end of the episode, while recurrent MDD and BD patients needed more time for functional recovery.

It is of importance that even a year after syndromal recovery patients with MDD-s, MDD-r, or BD still experienced more functional impairments than healthy controls. We found that depressive symptoms accounted for most of the functional impairment in all diagnostic groups, and for all syndromal states. Several other studies also found that subthreshold depressive symptoms account for functional impairment (24,27-32), although the association between depressive symptoms and functioning may be bi-directional (33). Various mechanisms have been suggested as explanation for functional recovery lagging behind symptomatic recovery, such as cognitive dysfunction, even after controlling for subthreshold symptoms (32), and having experienced multiple mood episodes (34). Moreover, it has been suggested that patients with bipolar disorder are more vulnerable for the psychosocial consequences of mood episodes than patients with MDD, as is evident from receiving reduced social support, not being able to find or keep a job, and having less financial resources (23).

It has been hypothesized that recurrent mood disorders reflect a process of neuroprogression, in which cognitive dysfunction, treatment resistance, medical comorbidities, and neurobiological abnormalities increase with the number of prior illness episodes (35).

Strengths and limitations

This study has several strengths. To our knowledge this is the first study to examine the associations between functional impairment and syndromal state in patients with MDD-s, MDD-r, or BD. The overall large sample gave us the opportunity to compare these three groups of patients with regard to functioning. Data were collected from various treatment settings, which increases their generalizability. Several limitations have to be mentioned. The subgroup of patients with BD was relatively small, which might have decreased statistical power. Since patients with clinically
diagnosed BD were originally excluded from NESDA, those BD patients included in our study may not be fully representative and may be at the less severe end of the bipolar spectrum. Furthermore, we were not able to identify the precise nature of the last episode experienced in BD patients, since manic symptoms were not assessed in detail in NESDA. Although one can expect that depressive episodes largely prevail over (hypo-)manias (36) this would have provided us with valuable insights into the contribution of (hypo-)manic and depressive episodes to functional impairment.

**Conclusion and implications.**

Our study confirms that there is a considerable gap between syndromal and functional recovery in patients with unipolar and bipolar mood disorder. We found significant temporal differences in functional recovery between single major depression on the one hand and recurrent major depressive disorder and bipolar disorder on the other. Our findings add to the hypothesis that resilience in patients with unipolar and bipolar mood disorder becomes less with repeated mood episodes (37). This may have consequences for the duration of continuation treatment after syndromal recovery. In DSM IV-TR and elsewhere (16) the point of recovery is defined as 8 weeks after syndromal remission of a major mood episode, although especially in bipolar disorder this is an area of controversy (16;38). Our results suggest that an 8-weeks period may be far too short in patients with recurrent mood disorder, who on average seem to need up to 12 months to recover functionally. Even after a year, complete functional recovery may not be achievable for many patients. Residual subsyndromal symptoms and related functional impairment not only worsen quality of life but also increase the risk for a new episode. Given these findings, clinicians as well as patients should be aware that continuation treatment should remain rigorous for the first year after a major mood episode.

**Additional information**

The NESDA study (www.NESDA.nl) is funded through the Geestkracht program of The Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is further 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, Institute for Quality of Healthcare (IQ Healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos)). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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