See commentaries by Goodwin and Rush

Functional Versus Syndromal Recovery in Patients With Major Depressive Disorder and Bipolar Disorder

Trijntje Y. G. van der Voort, MScN; Adrie Seldenrijk, PhD; Berno van Meijel, PhD; Peter J. J. Goossens, PhD; Aartjan T. F. Beekman, MD, PHD; Brenda W. J. H. Penninx, PhD; and Ralph W. Kupka, MD, PhD

ABSTRACT

Objective: 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 1,664 participants in the Netherlands Study of Depression and Anxiety (MDD-s, n = 483; MDD-r, n = 1,063; BD, n = 118), from 2006 into 2009. In additional analyses, 530 healthy controls were included. *DSM-IV-TR* diagnosis and information about syndromal state were based on the Composite International Diagnostic Interview. Psychosocial impairment was assessed with the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). Adjusted associations between diagnosis, syndromal state, impairment, and depression severity were investigated.

Results: Syndromal state not being taken 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 (mean [SD] WHODAS score: current: MDD-s 30.8 [2.8], MDD-r 32.7 [0.9], BD 37.7 [2.1], $P = .07$; 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 > 1 year: 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 that in healthy controls.

Conclusion: Functional recovery may take up to 1 year after syndromal remission in recurrent depressive and bipolar disorder, mainly due to residual depressive symptoms, emphasizing the need for prolonged continuation treatment.

J Clin Psychiatry 2015;76(6):e809–e814

Submitted: *September 25, 2014; accepted December 19, 2014 (doi:10.4088/JCP.14m09548).*

Corresponding author: *T. van der Voort, MScN, GGZ inGeest, Department of Research, Postbus 74077, 1070 AB Amsterdam, The Netherlands (N.vanderVoort@ggzingeest.nl).*

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 first as the 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 (ie, no longer fulfilling the formal criteria of a mood episode) does not necessarily lead to a level of functioning comparable to that of 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 from 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 patients with single-episode or recurrent MDD and BD, and which factors are associated with persistent functional impairment. It has been hypothesized that recurrent depression shares more features with BD than with 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 > 1 year) 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 3 diagnostic categories.

METHOD

Sample and Procedure

Data were retrieved from the Netherlands Study of Depression and Anxiety (NESDA), a multisite 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]

Clinical Points

- Many patients with major mood disorders experience functional impairment and subsyndromal depressive symptoms, even after remission of a mood episode.
- Functional recovery takes longer in patients with recurrent mood disorders when compared to patients with single-episode depression.
- Continuation treatment after a major mood episode should last up to 1 year, especially in patients with recurrent mood disorders.

Subjects in NESDA are patients with a lifetime diagnosis of MDD, anxiety disorder, or both (n = 2,329, 78%) and healthy controls (n = 652, 22%). Participants were recruited for baseline assessment from 2004 into 2007 from the general population, 65 primary care practices, and 17 mental health organization locations, reflecting various settings and stages of psychopathology. During a 4-hour assessment, extensive information was gathered on health outcomes and demographic, psychosocial, clinical, biological, and genetic determinants. Detailed follow-up assessments were repeated after 2 and 4 years, and further follow-up assessments are currently undertaken. Since NESDA was originally not aimed at BD, patients with a previously clinically established diagnosis of BD had been excluded at baseline. Nevertheless, when, at 2-year follow-up (n = 2,049 patients and n = 547 controls; data were gathered from 2006 into 2009), the *DSM-IV-TR*[15] diagnosis was reassessed with the Composite International Diagnostic Interview (CIDI),[18] now including a detailed history of hypomania and mania, 125 patients fulfilled criteria for a lifetime diagnosis of BD. The 2-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 the CIDI.[18] For the main analyses, we included data for 1,664 patients (MDD-s, n = 483; MDD-r, n = 1,063; BD, n = 118) who had also completed the World Health Organization Disability 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 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 not otherwise specified (NOS) were combined into one group for BD, given the relatively small sample size. Syndromal state was defined and categorized at the NESDA 2-year follow-up measurement as remitted > 1 year (having experienced an episode more than 1 year ago, ie, recovered); 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 > 1 year" 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 Symptomatology (IDS)[20] consisting of 30 items and assessing symptoms over the last 7 days. The IDS 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, Disability, and Health (ICF)[18] levels: no problems (0%–4%), mild problems (5%–24%), moderate problems (25%–49%), severe problems (50%–94%), and extreme problems (95%–100%). The WHODAS covers impairment in 6 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 neither had a paid job nor attended school, the domain of life activities had many missing values on the WHODAS-36. Therefore, we will report only the standardized total score of the WHODAS-32 (ie, without items work or school).

Covariates

Sociodemographic characteristics included age, gender, total years of education, and marital status. Since comorbidity 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 χ^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 of 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* × *diagnosis*. We performed regression analyses with both predictors in one model and added the interaction term. If interaction appears to exist, outcomes are 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 2-tailed, and α was set at .05, except for the interaction analyses, for which α was set at .1.

Table 1. Sample Characteristics[a]

Variable	MDD-s (N = 483)	MDD-r (N = 1,063)	BD (N = 118)	*P*
Covariates				
Sociodemographic characteristics				
Age, mean (SD), y	44.3 (13.5)	44.6 (12.2)	42.8 (11.7)	.33
Female	323 (66.9)	750 (70.6)	67 (56.8)	< .05
Education, mean (SD), y	12.2 (3.3)	12.4 (3.3)	11.5 (3.5)	< .05
Has marital partner	205 (42.4)	396 (37.3)	46 (39.0)	.15
Psychiatric comorbidities				
Anxiety disorder	139 (28.8)	423 (39.8)	69 (58.5)	< .001
Alcohol use disorder	37 (7.7)	96 (9.0)	17 (14.4)	.07
Clinical characteristics				
Family history of depression	377 (78.1)	922 (86.7)	110 (93.2)	< .001
Severity of symptoms,[b] mean (SD)	15.0 (10.4)	20.3 (12.1)	26.4 (14.8)	< .001
Age at onset, mean (SD), y	32.5 (13.3)	27.1 (12.1)	22.7 (10.5)	< .001
Duration of illness, mean (SD), y	12.0 (10.4)	17.5 (11.5)	20.0 (11.3)	< .001
Impairment (WHODAS score), mean (SD)	14.8 (16.2)	21.1 (16.2)	28.5 (18.3)	< .001
Syndromal state				
Remitted > 1 y[c]	421 (87.0)	542 (51.0)	33 (28.0)	
Remitted (6–12 mo)[d]	14 (2.9)	99 (9.3)	10 (8.5)	< .001
Recently remitted (< 6 mo)[e]	19 (3.9)	151 (14.2)	23 (19.5)	
Currently in an episode[f]	29 (6.0)	271 (25.5)	52 (44.1)	

[a]Values shown as n (%) unless otherwise noted. *P* values based on χ^2 statistics (for categorical variables) and analysis of variance (for continuous variables).
[b]Severity of symptoms as indicated by mean (SD) score on the Inventory of Depressive Symptomatology.
[c]Remitted > 1 y: no episode in last year.
[d]Remitted: last episode 6–12 months ago.
[e]Recently remitted: last episode 2–6 months ago.
[f]Current episode: current episode in past month.
Abbreviations: BD = lifetime bipolar disorder; MDD-r = major depressive disorder, recurrent episodes; MDD-s = major depressive disorder, single episode; WHODAS = World Health Organization Disability Assessment Schedule.

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 and more often had comorbid 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 their current depressive symptoms were more severe than those of MDD patients. Among patients with MDD, those with MDD-r more often suffered from comorbid anxiety, experienced a current episode, and reported 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.

The Temporal Course of Functional Recovery

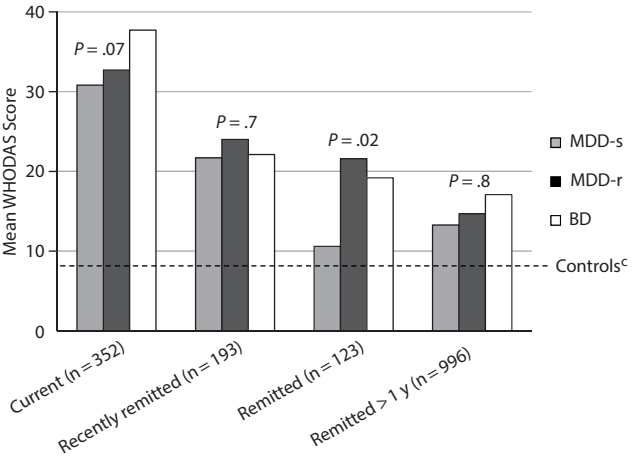
Since the interaction term syndromal state × diagnosis reached significance, our assumption that the association of syndromal state and functional impairment is moderated by diagnosis is correct. This means differences exist between diagnostic categories concerning the impact of syndromal state on impairment. Figure 1 shows the degree of functional impairment in the diagnostic groups for each category of syndromal state, ie, 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 = 24.0 [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, in which patients with MDD-s have less functional impairment than those with MDD-r and BD. This finding 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

Table 2. Associations Between Functional Impairment and Diagnosis or Syndromal State (N = 1,664)

Variable	WHODAS score,[a] mean (SE)	R^2	P[b]
Diagnosis			
Unadjusted		.05	
MDD-s (reference)	14.7 (0.7)		
MDD-r	21.1 (0.5)		< .001
BD	28.5 (1.5)		< .001
Adjusted[c]		.24	
MDD-s (reference)	15.9 (0.7)		
MDD-r	20.9 (0.4)		< .001
BD	25.4 (1.3)		< .001
Syndromal state			
Unadjusted		.22	
Currently in an episode (reference)[d]	33.3 (0.8)		
Recently remitted (< 6 mo)[e]	23.5 (1.0)		< .001*
Remitted (6–12 mo)[f]	20.2 (1.3)		< .001**
Remitted > 1 y (> 12 mo)[g]	14.2 (0.5)		< .001
Adjusted		.32	
Currently in an episode (reference)	30.3 (0.7)		
Recently remitted (< 6 mo)	22.0 (1.0)		< .001***
Remitted (6–12 mo)	19.4 (1.2)		< .001†
Remitted > 1 y	15.6 (0.4)		< .001

[a]WHODAS 2.0 scores, estimated marginal means.
[b]Statistical significance at $P < .05$.
[c]Adjusted for age, gender, educational level, marital status, alcohol disorders, and anxiety disorders.
[d]Currently in an episode: current episode in past month.
[e]Recently remitted: last episode 2–6 months ago.
[f]Remitted: last episode 6–12 months ago.
[g]Remitted > 1 y: no episode in last year.
*$P = .06$ for recently remitted versus remitted.
**$P \leq .001$ for remitted versus remitted > 1 y.
***$P = .1$ for recently remitted versus remitted.
†$P = .003$ for remitted versus remitted > 1 y.
Abbreviations: BD = lifetime bipolar disorder; MDD-r = major depressive disorder, recurrent episodes; MDD-s = major depressive disorder, single episode; WHODAS = World Health Organization Disability Assessment Schedule.

Figure 1. Associations Between Syndromal State[a] and Functional Impairment[b] in Patients With MDD-s, MDD-r, and BD



[a]Syndromal state defined as current (current episode in past month); recently remitted (last episode 2–6 months ago); remitted: last episode 6–12 months ago; remitted > 1 y: no episode in the past year.
[b]Functional impairment was measured with WHODAS 2.0; a higher mean score indicates more functional impairment.
[c]Dotted line: mean (SD) WHODAS score = 8.0 (0.5) in healthy controls.
Abbreviations: BD = lifetime bipolar disorder; MDD-r = major depressive disorder, recurrent episodes; MDD-s = major depressive disorder, single episode; WHODAS = World Health Organization Disability Assessment Schedule.

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 [SE] WHODAS score: Controls [reference] = 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] $P < .001$).

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 1 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 suggest not only 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 patients with recurrent MDD and BD 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 bidirectional.[33] Various mechanisms have been suggested as explanation for functional recovery's 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 to 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 fewer 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 3 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 unable 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-episode major depressive disorder 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 finding 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 area is one of controversy.[16,38] Our results suggest that an 8-week 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.

Author affiliations: Department of Psychiatry and EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam (Ms van der Voort and Drs Seldenrijk, van Meijel, Beekman, Penninx, and Kupka); Research Group Mental Health Nursing, Department of Health, Sports & Welfare/Cluster Nursing, Inholland University of Applied Sciences, Amsterdam (Dr van Meijel and Ms van der Voort); Dimence, Deventer (Dr Goossens and Ms van der Voort); Parnassia Psychiatric Institute, Parnassia Academy, The Hague (Dr van Meijel); and Scientific Institute for Quality of Healthcare, Radboud University Nijmegen Medical Center, Nijmegen, and GGZ-VS, Institute for the Education of Clinical Nurse Specialists in Mental Health, Utrecht (Dr Goossens), The Netherlands.

Potential conflicts of interest: The authors of this manuscript have read the journal's policy and have the following competing interests: **Dr Beekman** reports personal fees (as a speaker) from Lundbeck, outside the submitted work. **Ms van der Voort** and **Drs Seldenrijk**, **van Meijel**, **Goossens**, **Penninx**, and **Kupka** have no potential conflicts to report.
Funding/support: The Netherlands Study of Depression and Anxiety (NESDA; 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]).
Role of the sponsor: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. De Graaf R, ten Have M, van Dorsselaer S. *De psychische gezondheid van de Nederlandse bevolking. NEMESIS-2: Opzet en eerste resultaten*. Utrecht, Netherlands: Trimbos-Instituut; 2010.
2. Michalak EE, Yatham LN, Lam RW. Quality of life in bipolar disorder: a review of the literature. *Health Qual Life Outcomes*. 2005;3(1):72.
3. Ishak W, Balayan K, Bresee C, et al. A descriptive analysis of quality of life using patient-reported measures in major depressive disorder in a naturalistic outpatient setting. *Qual Life Res*. 2013;22(3):585–596.
4. Goossens PJJ, Hartong EG, Knoppert-van der Klein EAM, et al. Self-reported psychopathological symptoms and quality of life in outpatients with bipolar disorder. *Perspect Psychiatr Care*. 2008;44(4):275–284.
5. Moreno C, Hasin DS, Arango C, et al. Depression in bipolar disorder versus major depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Bipolar Disord*. 2012;14(3):271–282.
6. Angermeyer MC, Holzinger A, Matschinger H, et al. Depression and quality of life: results of a follow-up study. *Int J Soc Psychiatry*. 2002;48(3):189–199.
7. Rosa AR, Reinares M, Amann B, et al. Six-month functional outcome of a bipolar disorder cohort in the context of a specialized-care program. *Bipolar Disord*. 2011;13(7-8):679–686.
8. Rosa AR, Reinares M, Michalak EE, et al. Functional impairment and disability across mood states in bipolar disorder. *Value Health*. 2010;13(8): 984–988.
9. Rubio JM, Olfson M, Villegas L, et al. Quality of life following remission of mental disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2013;74(5):e445–e450.
10. Daly EJ, Trivedi MH, Wisniewski SR, et al. Health-related quality of life in depression: a STAR*D report. *Ann Clin Psychiatry*. 2010;22(1):43–55.
11. IsHak WW, Greenberg JM, Balayan K, et al. Quality of life: the ultimate outcome measure of interventions in major depressive disorder. *Harv Rev Psychiatry*. 2011;19(5):229–239.
12. Solomon DA, Fiedorowicz JG, Leon AC, et al. Recovery from multiple episodes of bipolar I depression. *J Clin Psychiatry*. 2013;74(3):e205–e211.
13. Bockting CLH, Spinhoven P, Koeter MWJ, et al; Depression Evaluation Longitudinal Therapy Assessment Study Group. Prediction of recurrence in recurrent depression and the influence of consecutive episodes on vulnerability for depression: a 2-year prospective study. *J Clin Psychiatry*. 2006;67(5):747–755.
14. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med*. 2011;41(6):1165–1174.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
16. Goodwin F, Jamison K. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. New York, NY: Oxford University Press; 2007.
17. Penninx BWJH, Beekman ATF, Smit JH, et al; NESDA Research Consortium. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res*. 2008;17(3):121–140.
18. Wittchen HU. Reliability and validity studies of the WHO—Composite

International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res*. 1994;28(1):57–84.
19. Chwastiak LA, Von Korff M. Disability in depression and back pain: evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. *J Clin Epidemiol*. 2003;56(6):507–514.
20. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477–486.
21. Do EK, Mezuk B. Comorbidity between hypomania and substance use disorders. *J Affect Disord*. 2013;150(3):974–980.
22. Rakofsky JJ, Dunlop BW. Do alcohol use disorders destabilize the course of bipolar disorder? *J Affect Disord*. 2013;145(1):1–10.
23. Shippee ND, Shah ND, Williams MD, et al. Differences in demographic composition and in work, social, and functional limitations among the populations with unipolar depression and bipolar disorder: results from a nationally representative sample. *Health Qual Life Outcomes*. 2011;9(1):90.
24. Goldberg JF, Harrow M. Subjective life satisfaction and objective functional outcome in bipolar and unipolar mood disorders: a longitudinal analysis. *J Affect Disord*. 2005;89(1-3):79–89.
25. Judd LL, Schettler PJ, Solomon DA, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. *J Affect Disord*. 2008; 108(1–2):49–58.
26. Goldberg JF, Harrow M. A 15-year prospective follow-up of bipolar affective disorders: comparisons with unipolar nonpsychotic depression. *Bipolar Disord*. 2011;13(2):155–163.
27. Judd LL, Akiskal HS, Schettler PJ, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry*. 2005;62(12):1322–1330.
28. Altshuler LL, Post RM, Black DO, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. *J Clin Psychiatry*. 2006;67(10):1551–1560.
29. Strejilevich SA, Martino DJ, Murru A, et al. Mood instability and functional recovery in bipolar disorders. *Acta Psychiatr Scand*. 2013;128(3):194–202.
30. Marangell LB, Dennehy EB, Miyahara S, et al. The functional impact of subsyndromal depressive symptoms in bipolar disorder: data from STEP-BD. *J Affect Disord*. 2009;114(1–3):58–67.
31. Vieta E, Sánchez-Moreno J, Lahuerta J, et al; EDHIPO Group (Hypomania Detection Study Group). Subsyndromal depressive symptoms in patients with bipolar and unipolar disorder during clinical remission. *J Affect Disord*. 2008;107(1–3):169–174.
32. Bonnín CM, Sánchez-Moreno J, Martínez-Arán A, et al. Subthreshold symptoms in bipolar disorder: impact on neurocognition, quality of life and disability. *J Affect Disord*. 2012;136(3):650–659.
33. Weinstock LM, Miller IW. Functional impairment as a predictor of short-term symptom course in bipolar I disorder. *Bipolar Disord*. 2008;10(3):437–442.
34. Rosa AR, González-Ortega I, González-Pinto A, et al. One-year psychosocial functioning in patients in the early vs late stage of bipolar disorder. *Acta Psychiatr Scand*. 2012;125(4):335–341.
35. Post RM, Fleming J, Kapczinski F. Neurobiological correlates of illness progression in the recurrent affective disorders. *J Psychiatr Res*. 2012; 46(5):561–573.
36. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9(5):531–535.
37. Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neurosci Biobehav Rev*. 2008;32(4):675–692.
38. Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009;11(5):453–473.