Chapter 5

Predicting outcome of depression using the depressive symptom profile: the Leiden Routine Outcome Monitoring Study

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Abstract

Background: Being able to predict which patients are at risk for an unfavourable outcome is of high clinical importance. The aim of this study was to investigate the predictive value of items for individual depressive symptoms measured with the self-rated Beck Depression Inventory-Revised (BDI-II) self-report scale on outcome in a large naturalistic cohort of depressive outpatients.

Methods: We used a cohort of 1,489 adult patients aged 18-65 years with major depressive disorder or dysthymic disorder established with the MINI-Plus diagnostic interview. All patients had a Routine Outcome Monitoring (ROM) baseline measurement in 2004-2009, with a maximum of 2 years follow-up. We used multivariable Cox regression models to predict remission (MADRS<10; where MADRS stands for Montgomery-Åsberg Depression Rating Scale) and response (≥50% improvement), and adjusted for clinical and demographic characteristics (i.e., marital status, level of education, working status, comorbid anxiety, avoidant and borderline personality traits, and suicidality) that were identified as predictors in earlier studies.

Results: Of the 21 BDI-II items, the items 'pessimism' and 'loss of energy' independently predicted for both remission and response. For pessimism, the HR for remission was 0.81 (95% confidence interval [CI]: 0.73-0.89, p<0.001) and for loss of energy, the HR was 0.81 (0.72-0.92, p=0.001).

Conclusions: These findings of robust prediction of poor outcome by baseline items of 'pessimism' and 'loss of energy' in a naturalistic treatment setting may help clinicians to identify depressive patients in need for additional or alternative therapeutic approaches.

Introduction

Despite extensive therapeutic options roughly one third of the patients with depressive disorders do not achieve remission after several adequate treatment trials (Rush et al., 2006), which may result in chronic depression (Rush et al., 1995). Being able to predict which patients are at risk for an unfavourable outcome is of high clinical importance, because these patients who do not achieve remission despite treatment may suffer considerably, and result in a poor cost-effectiveness of psychiatric care (Thase, 2003; Wittchen et al., 2011). In prospective studies, several factors have been associated with a poor outcome in patients with major depression. Sociodemographic factors, including low education (Barkow et al., 2003; McKenzie et al., 2010), unemployment, (Barkow et al., 2003; Sherbourne et al., 2004; Fournier et al., 2009; Frank et al., 2010) and being unmarried (Fournier et al., 2009; Frank et al., 2010; Meyers et al., 2002; Weinberger et al., 2008) were found to be independent predictors of a poor outcome. Also, clinical characteristics including greater severity of depressive symptoms (Barkow et al., 2003; Enns et al., 2005; Frank et al., 2010; Melartin et al., 2004; Meyers et al., 2002; Moos et al., 1999; Sargeant et al., 1990; Souery et al., 2007; Vuorilehto et al., 2009), loss of interest, reduced activity (Uher et al., 2011), suicidality (Barkow et al., 2003; Sherbourne et al., 2004; Souery et al., 2007), melancholic features (Souery et al., 2007), comorbid anxiety disorders (Enns & Cox, 2005; Melartin et al., 2004; Penninx et al., 2011; Souery et al., 2007; Weinberger et al., 2008) and personality traits or disorders such as avoidant, low extraversion and borderline (Enns & Cox, 2005; Skodol et al., 2011; Souery et al., 2007; Vuorilehto et al., 2009; Wiersma et al., 2011) were predictors of poor outcome. However, various definitions and operationalisations of poor outcome have been used in these studies, and duration of follow-up differed largely. Also, these studies have been conducted in different settings, e.g. community (Sargeant et al., 1990; Skodol et al., 2011), primary care (Barkow et al., 2003; Vuorilehto et al., 2009), psychiatric specialty care inpatient (McKenzie et al., 2010; Souery et al., 2007) and outpatient settings (Enns & Cox, 2005; Fournier et al., 2009; Frank et al., 2010; Meyers et al., 2002; Penninx et al., 2011; Souery et al., 2007; Uher et al., 2011; Weinberger et al., 2008). Moreover, most studies used data obtained from clinical trials, that limits generalisability to everyday clinical practice because of the usually much more extensive and stringent in- and exclusion criteria (van der Lem et al., 2011).

To our knowledge, no previous study investigated whether specific baseline symptoms, reflected in individual items on depressive rating scales at baseline predict outcome in a naturalistic clinical outpatient setting. If the presence of specific depressive symptoms at baseline would be of value in predicting outcome of depression, assessment

of these symptoms using a self-report measure could help clinicians to identify patients at risk of a poor outcome in a relatively easy way. Since the standardised assessment of symptom presence is increasingly becoming part of the usual clinical process, identification of symptoms that predict outcome could be helpful for clinician and patient.

A recent study from Uher et al. including 811 major depressive disorder (MDD) patients tested whether baseline depression symptom *dimensions* predicted outcome upon a 12-week-treatment with escitalopram or nortriptyline. The authors found and replicated that higher scores on the interest-activity dimension (i.e. low interest, reduced activity, indecisiveness and lack of enjoyment) predicted poorer treatment outcome (Uher et al., 2011).

The aim of the present study was to investigate whether individual baseline depressive symptoms measured with the widely used Beck Depression Inventory-Revised (BDI-II) self-report scale (Beck et al., 1988) would predict outcome in a large naturalistic cohort of depressive outpatients in a psychiatry specialty care setting. Outcome was defined as response and remission measured on the Montgomery-Åsberg Depression Rating Scale (MADRS) according to generally accepted criteria during up to 2 years of follow-up.

Methods

Participants

We used an initial cohort of 8,021 adult outpatients aged 18-65 years who were referred for treatment of a mood, anxiety, or somatoform (MAS) disorder to the Regional Mental Health Provider Rivierduinen (RD) and Leiden University Medical Center (LUMC). All patients had a Routine Outcome Monitoring (ROM) baseline assessment between 2004 and 2009, during intake before the start of treatment (de Beurs et al., 2011). In ROM, data on diagnosis and complaint severity are collected systematically to assess treatment effectiveness in everyday clinical practice. In our setting, ROM is performed by well-trained and supervised psychiatric research nurses, who are not involved in treatment. A group-wise quality control and calibration among research nurses ensures quality maintenance during data collection (de Beurs et al., 2011). All questionnaires are completed on touch-screen computers, to prevent missing data within instruments. Patients with insufficient mastery of Dutch and patients unable to complete assessments are ineligible for ROM. On average, 80% of the referred patients were assessed with ROM in the study period. ROM data are primarily used for diagnosis and to inform clinicians and patients about treatment progress. The use of the anonymised data for research purposes has been approved by the Ethical Review Board of the LUMC.

Of these 8,021 patients, we selected all patients with a current MDD or dysthymic disorder according to the Mini International Neuropsychiatric Interview-Plus (MINI-Plus; n=3,632, 45.3%). The MINI-Plus is a standardised diagnostic interview that assesses current and lifetime Axis-I diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000). The inter-rater reliability ranges from 0.88 to 1.00, test-retest reliability from 0.76 to 0.93 and validity is adequate compared to the Composite International Diagnostic Interview (CIDI; Lecrubier, 1997; Sheehan et al., 1998; van Vliet et al., 2007). Patients with a lifetime bipolar disorder or primary psychotic illness were excluded, but a diagnosis of psychotic major depression according to the MINI-Plus was allowed. Of these 3,632 depressive patients, we selected all patients with a minimum of one follow-up ROM assessment (n=1,988, 54.7%). Patients who had only one ROM assessment were most likely not treated in the MAS outpatient clinics. Patients with a low baseline symptom severity (MADRS <10) were excluded (n=87, 2.4%) as well as patients with missing data on variables of interest (n=412, 11.3%). We thus included 1,489 patients in our analyses (41.0% of 3632 patients). There were no differences in age, gender, or level of education between included and excluded patients. Excluded patients had a lower MADRS baseline score than included patients (mean scores 21.9, standard deviation [SD] ± 9.7 vs. 24.1 ± 7.0; t= -4.6, p<0.001).

Psychiatrists and clinical psychologists or psychotherapists in LUMC and RD provided outpatient treatment in accordance with the Dutch evidence based guidelines, consisting of pharmacotherapy, psychotherapy, or a combination of both. Treatment modalities were not taken into account in the analyses.

Measures

ROM assessments: We used the baseline ROM assessments and all successive ROM assessments with a maximum follow-up of 2 years. During the first ROM session the MINI-Plus was administered, as well as observer-rated and self-report scales, both generic and disorder-specific. In addition, demographic variables were collected (an overview of instruments is available at http://www.lumc.nl/psychiatry/ROM-instruments), as previously described in detail elsewhere (de Beurs et al., 2011; van Noorden et al., 2010).

Remission and response: Remission and response of depression were assessed using the MADRS. The MADRS is an observer-rated scale that assesses depression severity, and that is sensitive to change. The MADRS has an internal consistency (Cronbach's alpha) of 0.86, an inter-rater reliability coefficient of 0.65-0.97 (Montgomery, 1979). Remission was defined as the first follow-up ROM assessment at which the MADRS score of <10 had

been reached (Hawley et al., 2002; Zimmerman et al., 2004a; Zimmerman et al., 2004b) and response was defined as the first ROM assessment at which a reduction of ≥50% of the baseline MADRS score had been achieved. The MADRS was administered at baseline and at every follow-up ROM assessment.

Individual depressive symptoms as possible predictors: Baseline depressive symptoms were measured with the BDI-II (Beck et al., 1996; Beck et al., 1988). The BDI-II is a 21-item self-report questionnaire that assesses the presence and severity of a broad range of depressive symptoms on a 4-point Likert-scale (0-3), with good psychometric properties (Beck et al., 1988). Symptoms measured with the BDI-II that most closely would fit in the interest/activity dimension found by Uher et al. (2008) are loss of pleasure, loss of interest, indecisiveness, loss of energy, concentration difficulties, and loss of interest in sex. In the present study, the BDI-II was chosen because of the broad range of symptom coverage in 21 individual items, and because of the practicability of a self-report measure. Furthermore, with the MADRS as relatively objective and 'gold standard' outcome measure, the risk of circularity as the result of functional relatedness of dependent and independent variables was likely to be lower than when the MADRS would have been used both as predictor and outcome (Senn, 1994).

Additional measures: Demographic variables were obtained at baseline with a self-report questionnaire. A Dutch ethnic background was assumed when the patient and both parents were born in the Netherlands. Marital status was assessed, as well as housing situation, educational status and working situation. The Dimensional Assessment of Personality Pathology-Short Form (DAPP-SF) was administered at baseline to assess maladaptive personality traits (van Kampen et al., 2008) Additional scales in ROM that we used for this study were the observer-rated Brief Anxiety Scale (BAS; Tyrer et al., 1984), the patient-rated Brief Symptom Inventory (BSI; de Beurs et al., 2006; Derogatis et al., 1983), the observer-rated Clinical Global Impression (CGI; Guy, 1976) and the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000; Endicott et al., 1976).

Statistical analyses

Using descriptive statistics, baseline characteristics are described as number (percentage) or mean (SD, with interquartile range [IQR]), when appropriate. Univariable Hazard Ratios (HRs) of remission and response were computed according to baseline individual BDI-II items (predictor variables) using Cox regression on the time-to-remission and time-to-response endpoints. Possible collinearity of the individual BDI-II items was checked using Variance Inflation Factor (VIF) analysis. If the endpoint of remission or response was not reached within 2 years or the endpoint was not reached at the final follow-up

measurement, the case was censored at the last ROM assessment. All BDI-II items that predicted remission or response with HRs with p-values <0.10 in univariable analyses were subsequently selected for an initial forward stepwise multivariable Cox regression model, for both endpoints. We used criteria for selection and removal both of 0.10. In this multivariable model we adjusted for baseline MADRS score, age and gender. Furthermore, we repeated the multivariable model with adjustment for demographical factors (i.e., marital, educational and working status), comorbid anxiety (i.e., based on the MINI-Plus), avoidant and borderline personality traits (i.e., measured with the DAPP-SF), and current suicidal thoughts (i.e., based on the MINI-Plus) because these clinical characteristics had been associated with outcome in earlier studies (Barkow et al., 2003; Enns & Cox, 2005; Fournier et al., 2009; Frank et al., 2010; McKenzie et al., 2010; Melartin et al., 2004; Meyers et al., 2002; Moos & Cronkite, 1999; Penninx et al., 2011; Sargeant et al., 1990; Sherbourne et al., 2004; Skodol et al., 2011; Souery et al., 2007; Uher et al., 2011; Vuorilehto et al., 2009; Weinberger et al., 2008; Wiersma et al., 2011).

Based on the combined presence and or absence of the BDI-II symptoms 'pessimism' and 'loss of energy' four categories were constructed. In Kaplan-Meier analyses the cumulative incidence of remission is presented. Presence of a symptom was dichotomised as a score of 2 or 3 on the 4-point Likert scale.

We then performed sensitivity analyses in which we included only those patients with more severe complaints at baseline (MADRS ≥14), and additional analyses in which we excluded the patients with dysthymic disorder to include only patients with MDD.
We used SPSS version 17.0 for all statistical analyses (SPSS Inc., Chicago, Ill).

Results

Baseline Characteristics

In the study sample of 1,489 depressed adults 62.3% were female. The mean age at ROM baseline assessment was 40.1 years (SD ± 12.1). Table 5.1 summarises the baseline characteristics of the sample. A Dutch ethnic background was found in 80.9%. The majority of the patients were living with a partner, 40.5% of the patients were currently working, 93.3% were diagnosed with MDD, and 6.7% with a dysthymic disorder. The mean MADRS score at baseline was 24.1 (SD ±7.0), the mean BDI-II total score at baseline was 31.0 (SD ±9.6), and the mean CGI score was 4.3 (SD ±0.8).

Table 5.1. Baseline characteristics in 1,489 outpatients with MDD or Dysthymic Disorder

	n	%
Categorical baseline variables		
Female gender	928	62.3
Dutch ethnic background	1205	80.9
Marital status:		
Married	799	53.7
Divorced/ widowed	261	17.5
Never married	429	28.8
Housing situation:		
Living alone	329	22.1
Living with partner	819	55.0
Living with family	341	22.9
Educational status:		
Lower education	636	42.7
Higher education	853	57.3
Employment situation:		
Working full-time	294	19.7
Working part time	309	20.8
Retired/unemployed	372	25.0
On sick leave	514	34.5
DSM-IV-TR diagnostic categories:		
Major Depressive Disorder (MDD)	1389	93.3
Dysthymic Disorder (DD)	100	6.7
DSM-IV-TR comorbidity:		
Single Mood Disorder (MDD or DD)	705	47.3
Mood and Anxiety Disorder	577	38.8
Mood and Somatoform Disorder	122	8.2
Mood and Anxiety and Somatoform Disorder	85	5.7
Comorbidity of abuse or dependence :		
Alcohol abuse or dependence	96	6.4
Drug abuse or dependence	54	3.6
Continuous baseline variables	Mean (SD)	IQR
Age at interview (years)	40.1 (12.1)	30-50
MADRS score	24.1 (7.0)	19-28
BDI-II total score	31.0 (9.6)	24-38
BAS score	17.0 (6.1)	13-21
BSI total score	1.5 (0.7)	1.0-1.9
CGI score	4.3 (0.8)	4.0-5.0
GAF score	57.3 (6.8)	53-60

Abbreviations: SD: Standard Deviation; IQR: Interquartile Range; BSI: Brief Symptom Inventory; CGI: Clinical Global Impression: MADRS: Montgomery-Åsberg Depression Rating Scale; BDI-II: Beck Depression Inventory; BAS: Brief Anxiety Scale; GAF: Global Assessment of Functioning scale.

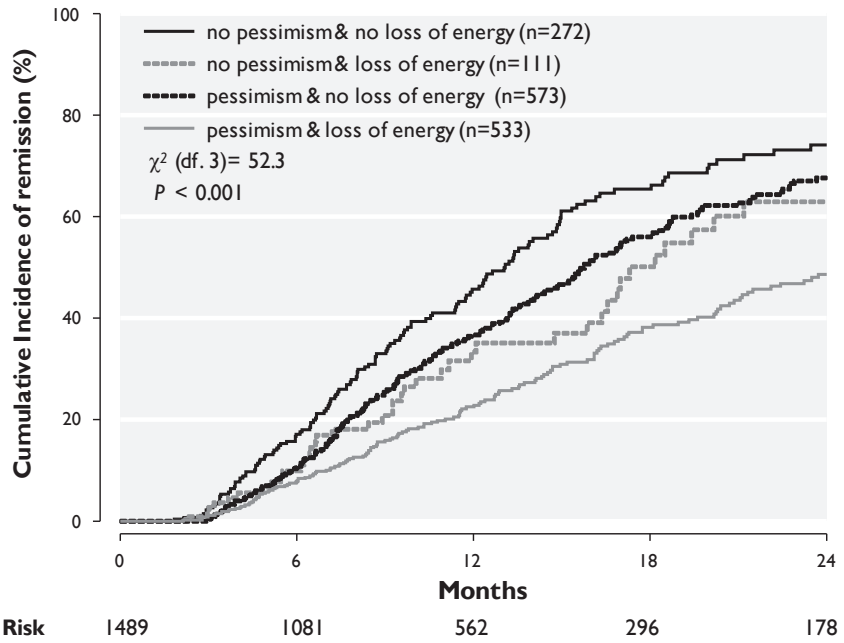

Figure 5.1. Cumulative incidence of percentage of patients that reached remission according to baseline presence and/or absence of the BDI-II symptoms pessimism and loss of energy. Presence of a symptom was defined as a score of 2 or 3 on a four-point Likert scale (0-3).

Predictors of remission

Within the follow-up time of 2 years, 562 patients (37.7%) achieved remission on the MADRS, defined as the first ROM assessment with a MADRS score <10. In univariable Cox regression analyses 16 of 21 BDI items were associated with remission (Table 5.2). Among other symptoms, both 'core symptoms of depression', i.e. sadness and loss of interest, negatively predicted remission (HRs 0.76, 95% CI 0.68-0.86; p<0.001 and 0.81, 95% CI 0.74-0.89; p<0.001, respectively). In the first multivariable model, adjusted for age, gender and baseline MADRS score, only the BDI-II symptoms pessimism and loss of energy were independently associated with a lower chance of remission (HRs 0.81, 95% CI 0.73-0.89; p<0.001 and 0.81, 95% CI 0.72-0.92; p=0.001, respectively), and the core symptoms sadness and loss of interest were not. The additional multivariable model, adjusted for previously established clinical variables, yielded the same predictors (data not shown). Figure 5.1 shows the cumulative incidence of remission in Kaplan-Meier curves according to the combined items of pessimism and loss of energy. Presence of both pessimism and loss of energy predicted a 72.2% chance of

remission in 2 years, and absence of both symptoms predicted a 49.1% chance of remission in 2 years (HR 0.78, 95% CI 0.73-0.84; χ^2 52.3 (3); p<0.001).

Table 5.2. Univariable and multivariable hazard ratios of remission on the MADRS according to baseline BDI -II scores in 1,489 outpatients with MDD or Dysthymic Disorder

	Remission MADRS Univariable model		Remission MADRS Multivariable model [a]	
BDI-II item	HR (95% CI)	p-value	HR (95% CI)	p-value
1 Sadness	0.76 (0.68-0.86)	<0.001		
2 Pessimism	0.73 (0.66-0.80)	<0.001	0.81 (0.73-0.89)	<0.001
3 Past failure	0.91 (0.84-0.99)	0.02		
4 Loss of pleasure	0.76 (0.68-0.85)	<0.001		
5 Feelings of guilt	0.90 (0.82-0.98)	0.02		
6 Punishment feelings	0.98 (0.91-1.05)	0.53		
7 Self dislike	0.95 (0.86-1.05)	0.29		
8 Self criticism	0.98 (0.90-1.06)	0.59		
9 Suicidal thoughts or wishes	0.81 (0.72-0.91)	<0.001		
10 Crying	0.98 (0.91-1.06)	0.64		
11 Agitation	0.97 (0.87-1.09)	0.61		
12 Loss of interest	0.81 (0.74-0.89)	<0.001		
13 Indecisiveness	0.84 (0.77-0.92)	<0.001		
14 Worthlessness	0.87 (0.80-0.95)	0.003		
15 Loss of energy	0.72 (0.64-0.80)	<0.001	0.81 (0.72-0.92)	0.001
16 Change of sleeping pattern	0.91 (0.83-1.00)	0.06		
17 Irritability	0.87 (0.79-0.95)	0.002		
18 Change of appetite	0.87 (0.80-0.95)	0.001		
19 Concentration difficulties	0.79 (0.71-0.88)	<0.001		
20 Tiredness or fatigue	0.80 (0.73-0.87)	<0.001		
21 Loss of interest in sex	0.86 (0.79-0.92)	<0.001		

Abbreviations: MADRS = Montgomery Åsberg Depression Rating Scale, BDI-II = Beck Depression Inventory, HR = Hazard Ratio, CI = Confidence Interval. Remission on the MADRS was defined as a score of < 10, response on the MADRS was defined as at least 50% reduction of the baseline score.

[a] Multivariable models were adjusted for age, gender and baseline MADRS score.

Predictors of response

According to the criterion of at least 50% improvement on the MADRS score compared to baseline MADRS score, 650 patients (43.7%) were responder within 2 years. 10 of 21 BDI-II items were associated with treatment response in univariable analyses (Table 5.3). In the multivariable Cox regression model adjusted for age, gender and baseline MADRS score, again, only the BDI-II items pessimism and loss of energy independently predicted non-response with HRs of 0.86 (95% CI 0.78-0.94; p=0.001) and 0.84 (95% CI 0.75-0.95; p=0.003), respectively. Presence of both symptoms pessimism and loss of energy predicted a 61.1% chance of response in 2 years, and absence of both symptoms predicted a 49.4% chance of response in2 years (HR 0.84, 95% CI 0.81-0.93); χ^2 20.2 (3); p<0.001).

Sensitivity analyses

In the sensitivity analyses we first excluded patients with dysthymic disorder (n=100), leaving 1389 MDD patients. In the multivariable Cox regression model adjusted for age, gender and baseline MADRS score, results remained unchanged. Also, when we elevated the threshold for inclusion in analysis to a baseline MADRS score ≥14 the multivariable model in the 1410 remaining patients yielded the same results (data not shown).

Finally, the VIFs in a regression analysis were all <2, indicating that no multicollinearity existed between any of the BDI-II items.

Table 5.3. Univariable and multivariable hazard ratios of response on the MADRS according to baseline BDI -II scores in 1,489 outpatients with MDD or Dysthymic Disorder

	Response MADRS Univariable model		Response MADRS Multivariable model [a]	
BDI-II item	HR (95% CI)	p-value	HR (95% CI)	p-value
1 Sadness	0.88 (0.79-0.98)	0.02		
2 Pessimism	0.83 (0.76-0.90)	<0.001	0.86 (0.78-0.94)	0.001
3 Past failure	0.97 (0.90-1.05)	0.50		
4 Loss of pleasure	0.86 (0.77-0.95)	0.004		
5 Feelings of guilt	0.96 (0.89-1.05)	0.39		
6 Punishment feelings	1.02 (0.96-1.09)	0.25		
7 Self dislike	1.02 (0.93-1.12)	0.68		
8 Self criticism	1.04 (0.96-1.12)	0.39		
9 Suicidal thoughts or wishes	0.92 (0.82-1.02)	0.11		
10 Crying	0.99 (0.92-1.07)	0.85		
11 Agitation	1.05 (0.95-1.16)	0.38		
12 Loss of interest	0.90 (0.83-0.97)	0.007		
13 Indecisiveness	0.88 (0.82-0.95)	0.002		
14 Worthlessness	0.92 (0.85-1.00)	0.06		
15 Loss of energy	0.81 (0.73-0.90)	<0.001	0.84 (0.75-0.95)	0.003
16 Change of sleeping pattern	0.99 (0.91-1.08)	0.81		
17 Irritability	0.91 (0.84-0.99)	0.04		
18 Change of appetite	0.95 (0.88-1.03)	0.19		
19 Concentration difficulties	0.89 (0.80-0.98)	0.02		
20 Tiredness or fatigue	0.87 (0.79-0.94)	0.001		
21 Loss of interest in sex	0.91 (0.85-0.98)	0.009		

Abbreviations: MADRS: Montgomery-Åsberg Depression Rating Scale; BDI-II: Beck Depression Inventory-revised; HR: Hazard Ratio; CI: Confidence Interval. Remission on the MADRS was defined as a score of <10, response on the MADRS was defined as at least 50% reduction of the baseline score.

[a] Multivariable models were adjusted for age, gender and baseline MADRS score.

Discussion

In this large naturalistic cohort of 1,489 depressive outpatients, of all 21 BDI-II items measured at baseline, pessimism and loss of energy independently predicted poor remission and response. These poor remission and response rates were found independently from characteristics that had been identified as outcome predictors in earlier studies (Barkow et al., 2003; Enns & Cox, 2005; Fournier et al., 2009; Frank et al., 2010; McKenzie et al., 2010; Melartin et al., 2004; Meyers et al. 2002; Moos & Cronkite, 1999; Penninx et al., 2011; Sargeant et al., 1990; Sherbourne et al., 2004; Skodol et al., 2011; Souery et al., 2007; Uher et al., 2011; Vuorilehto et al., 2009; Weinberger et al., 2008; Wiersma et al., 2011).

To our knowledge, this is the first large scale prospective study that investigated whether baseline individual depressive symptoms could predict outcome in a naturalistic sample of MDD patients. Our findings may facilitate early identification of patients at risk of poor outcome, in a relatively easy way by application of a self-report measure at baseline. This may have clinical consequences, since there is large consensus about remission of depression being the goal of treatment (Thase, 2003; Wade et al., 2009).

Our findings are mostly in line with the recent findings of Uher et al. (2011), who tested baseline symptom dimensions rather than items as predictors of treatment outcome. Based on a previous study of the same group (Uher et al., 2008), in which a factor analysis of the MADRS, BDI and the 17-item Hamilton Depression Rating Scale (HDRS) revealed three higher order factors (i.e. observed mood, cognitive and neurovegetative) that further split in six dimensions (i.e. mood and anxiety, pessimism and interest-activity, and sleep and appetite, respectively), the predictive value of those 9 symptom dimensions was tested. The interest-activity dimension was found to be the strongest predictor of treatment outcome. The individual symptoms 'pessimism' and 'lack of energy' are both symptoms within the 'cognitive' higher order factor as described by Uher et al. (2008), but our results suggest that in addition to the loss of energy/low interest/low activity factor, pessimism may be an important factor in predicting treatment outcome.

In earlier studies, pessimism was found to be a predictor of depression in the general population (Giltay et al., 2006), patients with breast cancer (Schou et al., 2004), and patients with urogenital cancer (Zenger et al., 2010), but these studies mainly studied low optimism or pessimism as dispositional traits, and patients were not diagnosed with MDD at baseline. Although dispositional optimism is not simply the reverse of pessimism, optimism and depression were investigated as predictors of physical and mental health functioning in a cohort of 659 veterans. Optimism was inversely correlated with depressive

symptoms, and depressive symptomatology was associated with reduced levels of psychosocial functioning. In this study, participants were not diagnosed with MDD either (Achat et al., 2000). Also, low dispositional optimism was associated with depression and a higher likelihood of starting psychotherapy in a large Finnish community study (Karlsson et al., 2011). In yet another study, pessimism was one of the predictors of suicide acts in 308 depressive patients that had been followed for2 years (Oquendo et al., 2004). The strongest predictors of future suicidal acts were prior suicide attempt, severity of episode and cigarette smoking. In this study, however, treatment outcome was not the focus.

Loss of energy and fatigue, together with loss of interest or pleasure in usual activities were found to be predictors of chronicity in a study in 371 MDD patients that had been re-evaluated at 1, 4 and 10 years after initial screening and treatment (Moos and Cronkite, 1999). In this study by Moos et al. three symptom domains were constructed from a set of risk factors: severity of specific depressive symptoms, lack of self-confidence plus social isolation, and avoidance coping. However, all analyses were univariable and the authors stated that no follow-up diagnostic interviews had been conducted. Still, loss of energy was identified as a predictor of chronicity in this study as well. The authors hypothesise that loss of energy may be more persistent during treatment than depressed mood and therefore may have been a more robust predictor for outcome.

Our findings find support in the cognitive theory of depression (see for example Newman & Beck, 2009), in which dysfunctional thoughts and viewpoints are thought to be maintained by cognitive distortive processes and biases. Depressed patients may for example think of themselves as failures, and selectively absorb information that points in that direction, neglecting the evidence for the contrary. This mechanism is believed to result in deepening of pessimism and worsening of mood, resulting in a vicious circle of withdrawal from social interactions (Newman & Beck, 2009). One could hypothesise that pessimism leads to social withdrawal, and that increasing isolation results in loneliness (Rius-Ottenheim et al., 2011) and lowering of physical activities leading to and loss of energy. Another mechanism could be that pessimism/low optimism and loss of energy both negatively influence the motivation for treatment resulting in lower adherence to treatment protocols (Leedham et al., 1995). Since the BDI-II measures state rather than trait symptoms, interpretations with respect to dispositional optimism/pessimism are not possible with the present results.

Our study has several strengths. First, this study was conducted in a large naturalistic sample of depressive patients increasing the generalisability of findings. Second, the extensive standard battery of our ROM assessments included a structured clinical interview, the BDI-II and the observer-rated scale (MADRS). Third, outcome

predictors identified in earlier studies were taken into account in our multivariable analyses. Fourth, assessments were done by well-trained research nurses who were not involved in treatment.

Possible limitations of our study include the absence of information regarding treatment in ROM. We assume that patients were mostly treated according to evidence-based guidelines; however, as our study represents a 'real world' setting, guideline concordance is often less strict than in a controlled setting (van der Lem et al., 2011). Second, no information on psychiatric history, family history and somatic comorbidity of the patients was available for our analyses. These parameters are assessed by clinicians and are not part of ROM. Third, the large proportion of patients lost to follow up at each ROM assessment is a limitation of our study. However, we believe that this large attrition rate is inherent to the design of the study that solely relies on ROM data collected as part of naturalistic treatment. A considerable loss to follow-up is common in cohort studies and trials with a 'real world' approach. In step II of the STAR*D multicenter trial for example, a study that aimed to be represent an everyday treatment setting, the loss to follow-up was 30% (Rush et al., 2006). Finally, the use of Cox regression analyses implies that subjects are censored upon reaching the defined endpoint of treatment response; therefore, the information about a possible relapse after an initial response could not be taken into account.

In conclusion, we found that the presence of baseline symptoms pessimism and lack of energy measured with the BDI-II strongly predicted naturalistic outcome in MDD outpatients. Systematic assessment of these depressive symptoms using validated rating scales is relatively easy to implement and often already form an invaluable part of clinical practice. Besides the goal to more objectively inform clinicians and patients about treatment progress, it may help the clinician in risk assessment of MDD patients already during the initial assessment of the intake phase.

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