

Brief report

# Prediction of the three-year course of recurrent depression in primary care patients: Different risk factors for different outcomes

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## Abstract

**Background:** The objectives of this study are: (1) identification of predictors for the three-year course of recurrent depression in the rarely studied, but relevant sample of primary care patients, and (2) investigation whether different outcome indicators, time to recurrence, proportion depression-free time and mean severity of depressive symptoms during follow-up, are associated with different risk factors.

**Methods:** Depression course was established by assessing 110 patients three-monthly with the Composite International Diagnostic Interview and the BDI, during a three-year period. Eight (groups of) predictors, assessed at baseline, were examined: socio-demographics, parental depression, history and severity of depression, anxiety, coping potential, social dysfunctioning and physical functioning.

**Results:** Time to recurrence was predicted by number of previous episodes (OR=1.91). Both proportion depressive disorder-free time and mean depression severity during follow-up were predicted by: severity of depression ( $B=-.19$  and  $.21$  respectively), anxiety ( $B=-.32$  and  $.33$ ), social dysfunctioning ( $B=-.21$  and  $.22$ ) and physical functioning ( $B=.24$  and  $-.39$ ). Mean severity was additionally predicted by: educational level ( $B=-.21$ ), duration of the longest prior episode ( $B=.32$ ), and coping potential ( $B=-.40$ ). Coping potential and number of previous episodes were marginally significant predictors for *all* three outcomes.

**Limitations:** Although substantial, sample size was restricted.

**Conclusion:** Different outcome variables are predicted by different risk factors. Restriction to one outcome may lead to missing important determinants of the depression course. Number of prior episodes and coping potential seem to warrant special attention from the GP.

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**Keywords:** Prediction; Multiple outcomes; 3-year course; Recurrent depression; Primary care

## 1. Introduction

The alarmingly unfavorable course of recurrent depression (Solomon et al., 2000) urges for a better

understanding of its determinants in order to improve treatment. However, there are considerable inconsistencies in findings across prediction studies of depression due to variability in: (1) samples, (2) range of predictors and (3) outcome indicators (Solomon et al., 2004). Taking into account these problems, we conducted a new study.

First, prediction studies usually apply mixed samples of first episode *and* recurrent depressed patients, or

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outpatients and primary care patients (c.f. Bockting et al., 2006; Simon, 2000; Ronalds et al., 1997; Katon et al., 1994; Keller et al., 1992). In order to enhance interpretability of findings we studied risk factors in a homogeneous sample of recurrent depressed primary care patients; a clinically very relevant but rarely investigated group. Second, we evaluated a fairly broad range of known potential predictors for depression, including: socio-demographic characteristics, parental depression, depression history, severity of depression, coping potential, anxiety, social functioning and physical functioning (c.f. Solomon et al., 2004; Ormel et al., 2001; Bockting et al., 2006; Brown and Moran, 1994; Brugha et al., 1997; Barkow et al., 2003). Third, usually studies are limited to time to recurrence as single outcome indicator. We studied two additional course characteristics, proportion depression-free time and mean severity of depression, in order to examine whether different outcome indicators are associated with different risk factors.

## 2. Methods

### 2.1. Participants and procedure

Patients participated in a randomized clinical trial evaluating the effects of four treatments (for details see Conradi et al., 2007). We included patients referred by GPs who had a diagnosis of depression, were between 18 to 70 years old, and were not suffering from: a life threatening medical condition, psychotic disorder, bipolar disorder, dementia or primary alcohol or drug dependency. For the present study we selected patients with a DSM-IV recurrent depression, who received usual care (UC) by the GP, or UC plus the low intensity Psycho-Educational Prevention Program (PEP) consisting of three face-to-face sessions and short three-monthly telephone contacts thereafter. These two groups were pooled for the present analyses because they did not differ on the outcome indicators. At baseline 81% of the patients used antidepressants.

### 2.2. Study measures

We quarterly administered an adapted depression section of the CIDI, a structured psychiatric interview with good reliability and validity (Andrews and Peters, 1998; Wittchen, 1994), measuring the presence of each of nine DSM-IV depressive symptoms per week in the previous three months. Thus we established whether or not patients were meeting DSM-IV criteria for major depression per week during the entire follow-up

period. Two of our outcome indicators, proportion of depressive disorder-free time and time from remission of the index-episode to recurrence, were derived from these data. Recurrence was defined as a depressive episode starting after a period of at least eight weeks without depression (Frank et al., 1991). To measure the third outcome, mean severity of depressive symptoms, we used the three-monthly administered Beck Depression Inventory (BDI; Dutch version Luteijn and Bouman, 1988). Mean severity was calculated on basis of at least five of the twelve measurements during follow-up.

Predictor variables, assessed at baseline were: (1) socio-demographics (gender, educational level, income of the household, (un-)employment and living with(-out) a partner), (2) parental depression (considered to be present if patients reported one or both of the biological parents ever been diagnosed as being depressed or treated because of depression), (3) depression history (number of episodes prior to the index-episode, and duration of the longest depressive

Table 1  
Demographic and clinical characteristics at baseline

	<i>n</i> = 123
Mean age (SD)	43.7 (10.9)
Female	68.3%
Marital status	
Married/cohabiting	71.5%
Not married	13.0%
Divorced	11.4%
Widowed	4.1%
Primary occupation	
Employed	58.5%
Homemaker	22.0%
Other	19.5%
Educational attainment	
Low	42.3%
Medium	39.8%
High	17.9%
Severity depression	
Mild	30.9%
Moderate	29.3%
Severe	39.8%
Mean age first onset (SD)	28.9 (11.7)
Suicide attempt ever	12.2%
Previous episodes	
Median	4.0
≥ 3 episodes	65.0%
AD usage	81.3%

episode ever), and (4) severity of anxiety (established with the Anxiety scale of the SCL-90; Dutch version: Arrindell and Ettema, 1986). To measure the other four predictors, we used factor scores obtained by means of a Principal Component Analysis on scales we expected to mirror the intended constructs (results available upon request). The resulting predictors were: (5) severity of depression (chiefly composed of the Depression scale of the SCL-90, the BDI and the Mental Health and Vitality subscales of the MOS-SF-36 (Dutch version: Van der Zee et al., 1993), (6) physical functioning (predominantly the Physical Functioning, Perception of General Health and Pain scales of the MOS-SF-36), (7) coping potential (composed of the Rosenberg Self-Esteem scale (Rosenberg, 1965) and the Mastery scale (Pearlin and Schooler, 1978) which points at locus of control), and (8) social dysfunctioning (a combination of the Groningse List Protracted Difficulties (Hendriks et al., 1990) and the Hostility scale of the SCL-90).

### 2.3. Statistical analyses

We first controlled for potential interactions between predictors and treatment modality. Per outcome vari-

able, therefore, the predictor, the PEP treatment condition dummy, along with the interaction term of PEP\*predictor were entered simultaneously in the regression model. Thus we could establish whether intervention had an effect on the relation between predictor and dependent variables. In case of a significant interaction, Betas, odds ratios and *p*'s were computed for the two treatment groups separately and for both groups together.

Second, we entered the predictor variables in simple regression analyses; Cox regression for time to recurrence, and linear regression for proportion depression-free time and mean severity of depressive symptoms during follow-up. Finally, significant predictor variables were entered simultaneously in the multiple analyses. Significance level for all analyses was set at 5% (two-sided).

## 3. Results

### 3.1. Patient characteristics and non-response at assessments

Socio-demographical and clinical characteristics of the sample are displayed in Table 1. There were no

Table 2

Predictors at baseline of time from remission to recurrence, depression-free time, and mean severity during follow-up in recurrent depressed (UC and PEP) patients

Predictor	Time to recurrence				Depression-free time				Mean severity			
	simple ( <i>n</i> =108)		multiple ( <i>n</i> =104)		simple ( <i>n</i> =108)		multiple ( <i>n</i> =104)		simple ( <i>n</i> =108)		multiple ( <i>n</i> =104)	
	OR	<i>p</i>	OR	<i>p</i>	<i>B</i>	<i>p</i>	<i>B</i>	<i>p</i>	<i>B</i>	<i>p</i>	<i>B</i>	<i>p</i>
Socio-demographic												
Gender	1.365	.287			-.030	.757			-.069	.477		
Education	1.127	.472 <sup>a</sup>			.038	.693			-.214	<b>.027</b>	-.107	.200
Unemployment	1.218	.456			-.059	.543			-.124	.205		
Income household	.990	.918			.114	.241			.019	.846		
Living with(-out) a partner	1.117	.698			-.087	.370			.066	.497		
Parental depression	.913	.852			-.035	.723			-.012	.901		
Depression history												
Duration longest episode	1.000	.841			-.124	.203			.318	<b>.001</b>	.139	.115
>3 episodes	1.908	<b>.013</b>	1.908	<b>.013</b>	-.158	.100			.183	.059		
Depression severity	1.026	.861			-.193	<b>.047</b>	.111	.314	.201	<b>.040</b>	.283	<b>.005</b>
Anxiety	1.130	.459			-.324	<b>.001</b>	-.154	.219	.325	<b>.001</b>	-.212	.080
Coping potential	.816	.093			.184	.061			-.395	< <b>.001</b> <sup>d</sup>	-.416	< <b>.001</b>
Social dysfunctioning	1.202	.199 <sup>b</sup>			-.213	<b>.028</b> <sup>c</sup>	-.171	.075	.221	<b>.023</b>	.239	<b>.005</b>
Physical functioning	.892	.387			.274	<b>.004</b>	.215	<b>.041</b>	-.387	< <b>.001</b>	-.348	<b>.001</b>

Data rendered in bold are significant *p* values (<.05), in italics marginally significant *p* values (≤.10) and in regular font non-significant *p* values.

<sup>a</sup>UC (OR=.69; *p*=.21) and PEP (OR=1.547; *p*=.040).

<sup>b</sup>UC (OR=2.048; *p*=.005) and PEP (OR=.923; *p*=.67).

<sup>c</sup>UC (*B*=-.550; *p*<.001) and PEP (*B*=-.035; *p*=.785).

<sup>d</sup>UC (*B*=-.561; *p*<.001) and PEP (*B*=-.272; *p*=.033).

differences between the two treatment groups on these characteristics, neither on any of the predictor variables at baseline. Non-response for the twelve three-monthly telephone interviews ranged from approximately 8% to 20%. Loss to follow-up was not associated with characteristics at baseline.

### 3.2. Prediction of primary outcomes

Correlations between outcome indicators were as follows: proportion depression-free time correlated .63 with time to recurrence and  $-.62$  with mean severity, while the latter two correlated  $-.35$ ; all  $p < .01$  (two-sided). Of the 39 possible interactions of treatment with predictor, four were statistically significant (Table 2, notes 1–4).

Table 2 shows the results of the regression analyses per outcome indicator. Shorter time to recurrence was predicted by more than three previous episodes, and marginally significant by coping potential. For UC patients less social dysfunctioning, and for PEP patients lower educational level, had protective effects.

Shorter depression-free time was predicted by: higher depression severity, higher anxiety, more social dysfunctioning, and worse physical functioning. Coping potential reached marginal significance. For UC patients less social dysfunctioning had protective effects. In the multiple regression analysis only physical functioning remained statistically significant, with a  $R^2$  of 17.1% (adjusted 13.7%).

Higher mean severity of depressive symptomatology during follow-up was predicted by: low educational level, longer duration of the longest prior episode, higher depression severity, higher anxiety, limited coping potential, more social dysfunctioning, and worse physical functioning; and marginally by number of prior episodes. PEP patients with limited coping potential reported somewhat lower on mean severity compared to UC patients. In the multiple regression analysis depression severity, coping potential, social dysfunctioning and decreased physical functioning maintained significance, while educational level, duration of the longest episode ever and anxiety did not. The  $R^2$  was 40.7% (adjusted 36.4%).

## 4. Discussion

We can draw two conclusions: different outcomes are associated with different predictors, however coping potential and number of previous episodes are marginally significant predictors for *all* outcomes.

### 4.1. Limitations and strengths

A limitation of this study is that although a substantial part of the variance in the outcome measures is explained by the predictors, most of it remains unexplained. This may be due to: the rather long follow-up period which makes prediction intrinsically difficult, and the fact that we did not study several potential predictors, like life events and daily hassles, and comorbid psychiatric disorders like dysthymia, panic disorder and social phobia. A final restraint of this study may be restricted power; the number of patients available was substantial but limited.

This study has clear surplus value from both a clinical *and* a methodological point of view. First, as one of the first studies ever we examined risk factors in the clinically very relevant group of primary care patients with recurrent depression. Second, we were able to shed some light on the inconsistencies of findings across prediction studies by restricting sample variability, studying a fairly broad range of predictors and by including three instead of the commonly applied sole outcome indicator. Third, our outcome indicators reflect the *three-year course* of depression and were assessed quarterly both by interview and self-report.

### 4.2. The importance of studying different outcomes

Our findings clearly indicate that different outcome indicators were associated with different predictors, implying that restriction to one outcome leads to incomplete understanding. The three outcome indicators differ in clinically important respects. Although delay of recurrence is of interest, the value of time to recurrence as outcome indicator is overrated since it solely informs on the duration of depressive disorder-free time till recurrence, but tells nothing about the level of (residual) symptoms during that disorder-free interlude, nor about the duration or degree of severity of the recurrent episode. Proportion of depression-free time yields information on the mean duration of depression-free episodes (and its inverse: depressive episodes) within a *certain time frame*, but offers no insight in the severity of (sub-)syndromal symptomatology. Only mean severity of depressive symptomatology during a certain time frame yields this detailed information. This might account for the fact that the percentage of explained variance is substantially higher in the case of mean severity during follow-up than in the case of proportion depression-free time.

### 4.3. Clinical implications

It is important to notice that number of prior depressive episodes and coping potential were not only (marginally) significant predictors for *all* three outcome indicators, but also the strongest predictors for time to recurrence and mean severity respectively. Therefore, number of prior episodes and limited coping potential, characterized by low general self-worth and insecurity about one's capacity to solve problems or proactively manage one's life, are important warning signs of an unfavorable future course of recurrent depression for GPs to bear in mind.

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