The association between the number of previous episodes and modifiable vulnerability factors in remitted patients with recurrent depression

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Abstract

Objective

Remitted patients with a history of several previous major depressive episodes have a higher risk of relapse/recurrence than patients with fewer previous episodes, and the probability of another episode increases progressively with each successive episode. This study examines the association between the number of previous episodes and modifiable vulnerability factors in remitted patients with recurrent depression.

Methods

Patients with recurrent depression (DSM-IV-diagnosed) who were in remission (N = 214) were recruited between September 2011 and July 2016. The association was examined between the number of previous episodes and the following factors: i.e. interpersonal functioning, daily stress, sense of mastery, coping and dysfunctional beliefs.

Results

A history of more previous episodes was associated with higher levels of interpersonal problems (P < .001), daily stress (P = .04) and a lower sense of mastery (P = .05). Interpersonal problems were most strongly associated with more previous episodes in a Generalized Linear Regression model. In the domain of interpersonal problems, the subscales that showed the strongest relationship were domineering/controlling, vindictive/self-centred, socially inhibited and self-sacrificing.

Conclusions

Patients with a history of more depressive episodes reported higher levels of interpersonal problems, daily stress and a lower sense of mastery. Future studies should examine these

factors in a longitudinal cohort and look at whether the effect of interventions to prevent relapse can be explained by targeting these psychological factors.

Trial registration

Netherlands Trial Register: 2599.

Introduction

The major contribution of Major Depressive Disorder (MDD) to disability and health care costs is largely due to its highly recurrent nature. Reported recurrence rates for high-risk groups, can be as high as 60–70% over two years [1, 2]. Known illness related factors that contribute to the risk of recurrence are age at onset, depression severity and residual symptoms after remission [3–8]. However, one of the most consistent predictors of recurrence is the number of previous major depressive episodes (MDEs). Remitted patients with more previous episodes have a higher risk of relapse/recurrence than remitted patients with fewer previous episodes, and the probability of another episode increases progressively with each successive episode [6, 9–11]. Explanations that have been given for the high relapse/recurrence risk in MDD are generally based on two hypotheses. First, high relapse/recurrence risk might be accounted for by individual differences in premorbid vulnerability [5, 6]. Second, an explanation for this finding may be found in vulnerability models such as the 'scarring' hypothesis, which states that a depressive episode may cause psychological and/or biological scarring that makes the patient more vulnerable to a subsequent episode [5, 6]. The very process of going through an MDE may therefore produce a change in the underlying vulnerability factors that make a new MDE more likely [6, 12]. A study of vulnerability factors (in other words, presumed vulnerability mechanisms where the scars are inflicted) in remitted patients with recurrent depression could therefore identify factors that can be targeted by interventions to prevent relapse.

Several modifiable vulnerability factors have been studied in relation to the recurrence of MDD [5, 6]. Interpersonal problems have been linked to the recurrence of MDD through the stress generation hypothesis [13–16] Several studies show that earlier recurrence can be predicted on the basis of the frequency of daily stress and a more avoidant coping strategy [15, 17, 18]. Furthermore, a cohort study has shown that a low sense of mastery was also a predictor of recurrent depression [19]. Finally, the cognitive model indicates that, activated dysfunctional beliefs are vulnerability factors for relapse/recurrence in depression [20, 21]. However, studies of this area have produced mixed results [22–25]. Even though the factors mentioned here are considered to be vulnerability factors for relapse/recurrence, this has been studied without taking into account the number of previous episodes. For example, we do not know if patients who have had more episodes have more dysfunctional beliefs than patients with less episodes. In other words, the association between these factors and the number of previous MDEs is not clear and the central aim of this study.

This study will explore the association between the number of previous episodes and several factors that previous research has identified as potentially modifiable vulnerability factors in recurrently depressed patients. We will examine whether chronicity in terms of the number of previous MDEs is related to interpersonal problems, daily stress, sense of mastery, coping and dysfunctional cognitions. The number of previous episodes will be the dependent variable and the different factors the independent variables. We expect that a history of more previous

MDEs will be associated with higher levels of interpersonal problems, higher levels of daily stress, more avoidant coping, more dysfunctional cognitions and lower levels of sense of mastery.

Method

This study draws on data from a randomized controlled trial examining the effectiveness of Preventive Cognitive Therapy in the prevention of relapse in recurrent depression [26]. The study was conducted in the Netherlands from September 2011 to July 2016,the main objective being to compare preventive cognitive therapy (PCT) with treatment as usual in the prevention of recurrence in remitted patients with a history of recurrent depression who had received Cognitive Behavioural Therapy (CBT) during the acute phase of the depression. The protocol was approved by the Medical Ethics Committee, Stichting Medische-Ethische Toetsingscommissie Instellingen Geestelijke Gezondheidszorg (METiGG, NL 34721.097.10) and all patients provided informed consent prior to participation. The study was registered with the Netherlands Trial Register http://www.trialregister.nl/trialreg/index.asp (Identifier: 2599). A detailed description of the methods is available elsewhere [26].

Participants

Participants were recruited through secondary health care facilities and by generating publicity in a range of media. Inclusion criteria were , a) at least two previous MDEs, b) current remission according to DSM-IV criteria for at least 2 months as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [27], c) no, or mild depressive symptoms defined as a current score of <14 on the 17-item Hamilton Depression Rating Scale (HDRS) [28], d) a minimum of eight sessions of CBT during the acute phase of the depression, and e) a command of Dutch that was adequate for participation in the study. Exclusion criteria were a) mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), b) current alcohol or drugs abuse, and c) acute predominant anxiety disorder.

Measures

Following inclusion, patients completed a number of questionnaires. The questionnaires relevant for this study are described below.

Previous MDEs, illness-related characteristics. Number of previous MDEs, age of first onset and previous depression severity were determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [27]. Every past episode was assessed at symptom level, and methods from the Life Chart Interview were used to help patients recall the frequency and duration of lifetime MDEs. Personal landmarks and life anchors were used as memory cues to help assess the specifications of the MDEs.

Depressive symptomatology. The 30-item Inventory of Depressive Symptomatology–Self Report (IDS-SR) was used to assess levels of depressive symptomatology. The IDS-SR is a self-report measure which patients use to rate their symptoms on a scale of zero to three over the past 7 days. The IDS-SR rates all DSM-IV core symptom domains including mood, cognitive and psychomotor symptoms, but also commonly associated symptoms including anxiety. The IDS-SR has excellent psychometric properties [29, 30].

Interpersonal functioning. The Inventory of Interpersonal Problems (IIP-C) was used to measure interpersonal functioning. This is a self-report measure that consists of 64 items designed to measure interpersonal deficiencies and excesses. Patients are asked to rate two types of items: interpersonal behaviors that are "hard for me to do" (e.g., it is hard for me to be self-confident when I am with other people) and interpersonal behaviors that "I do too much"

(for example, I open up to people too much). Items are rated on a five-point response scale ranging from 0 (not at all) to 4 (extremely). The IIP-C has a total score and eight subscales: Domineering/Controlling, Vindictive/Self-centered, Cold/Distant, Socially Inhibited, Non-assertive, Overly Accommodating, Self-Sacrificing and Intrusive/Needy [31]. The Dutch version of the IIP-C has good psychometric properties [32, 33].

Daily stress. Daily stress was measured using the 114-item Everyday Problem Checklist (EPCL) [34]. The EPCL is a self-report measure that is designed to measure the frequency and the level of the subjective perception of daily stress over the past two months. It has good psychometric properties [34]. We used the manual to create two scores: the frequency and the intensity of daily stress. The frequency of daily stress was the sum of all items experienced, and it ranged from 0 to 114. The intensity of daily stress reflects the impact of stressors and was calculated by dividing the total intensity of all items by frequency, resulting in a score with a range of 0 ("no impact") to 3 ("major impact").

Sense of mastery. Mastery was measured using the abbreviated five-item version of the Pearlin Mastery Scale [35]. Mastery is the feeling to which a person perceives himself to be in control of events and ongoing situations around him. Items are rated on a five-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). The score is the sum of the recoded ratings and a higher score therefore indicates a higher sense of mastery.

Coping. Coping was measured using two subscales taken from the Dutch 'Utrechtse Coping Lijst' (UCL): avoidant coping (8 items) and active approach to problems (7 items). The UCL has good psychometric properties [36, 37]. In the general population, a score for active coping between 15 –and 20 and a score for avoidant coping between 12 and 17 would be considered average [36].

Dysfunctional cognitions. Dysfunctional cognitions were measured using the Dysfunctional Attitude Scale (DAS-17). The DAS-17 is the shorter 17-item version of a self-report scale DAS-A designed to measure patterns of negative thinking and beliefs in depressed patients. The DAS-A-17 has good psychometric properties in terms of reliability and convergent construct validity [38]. De Graaf et al. (2009) reported m = 46.3, SD = 14.7 in the general population and m = 68.1, SD = 18.5 in depressed patients.

Procedure. The SCID-I was administered at randomization in telephone—or face-to-face interviews conducted by independent trained assessors who attended monthly consensus meetings to enhance inter-rater agreement. The SCID-I interviews were recorded and randomly sampled for rescoring by the other assessors under the supervision of the trainer. The assessors were master students in psychology at the university. The IDS-SR, IIP, EPCL, Mastery, UCL and DAS-17 were administered online, with patient access through a personalized hyperlink. The IDS-SR, IIP, EPCL and Mastery were administered at randomization. The UCL and DAS-17 were administered four weeks later.

Data analysis. In this cross-sectional study, the dependent variable (number of previous MDEs) was skewed to the right and it could not be transformed to fit a parametric distribution. To determine if there may be a relationship between the number of previous MDEs and the individual factors, a Spearman's Rho correlation was done. We then assessed which factor was most strongly associated with the number of previous MDEs. A backward-step Generalized Linear Regression(GLR) Model was used to generate a model for the factors most strongly associated with the number of previous MDEs. This analysis was used because the assumptions for a multiple linear regression model were not met owing to the nonparametric distribution of the dependent variable, the number of previous episodes. All the assumptions for the GLR were met. We calculated the variance inflation factor (VIF) for each subscale of the IIP and they ranged between VIF = 1.01–3.28, indicating no multicollinearity [39]. The first backward-step GLR model included all the measures that were significant in the first analysis as

independent variables: Interpersonal Problems, Daily stress frequency, Daily stress intensity and Sense of mastery. The second backward-step GLR model included the same independent variables again and also controlled for residual symptoms, age of onset and time since onset. The third backward-step GLR model was explorative and included all eight subscales of the IIP as independent variables.

Statistical analyses were conducted using SPSS Statistics for Microsoft Windows version 22 [40]. All analyses were two-tailed with a probability level of p < .05.

Results

A total of 2064 patients from five different treatment centres in the Netherlands were approached between January 2012 and August 2014. A range of media were used to generate awareness of the study. A total of 659 patients were assessed for eligibility: 214 met the inclusion criteria and consented to randomization. Eighty-eight per cent of the included patients were recruited through treatment centres and 12% through the media. An overview of the demographic and clinical characteristics of the participants is presented in Table 1. The average age of the included patients was 43, 32% were male -and the average number of previous episodes was 3.98. This sample profile is comparable with other studies. Scores on the DAS were higher than expected based on previous research (m = 77.9, SD = 17.8) [38].

A relationship was found between the number of previous MDEs and interpersonal problems, frequency and intensity of daily stress and sense of mastery. The results are presented in Table 2. No relationship was found between number of previous MDEs and coping and dysfunctional cognitions.

We then combined the factors for which a significant association had been found in the previous analysis to determine which factors or combination of factors are most strongly associated with more previous MDEs. The analysis showed that having more interpersonal problems was most strongly associated with a higher number of previous episodes. The results are presented in Table 3. We repeated the analysis, controlling for residual symptoms, age of onset and time since onset. Interpersonal problems remained most strongly associated (B = .004, S. E. = .0011, P = .002). Scores for interpersonal problems significantly correlated with the scores for all the other factors that we measured, as well as residual symptoms and age of onset (r ranging from .138 to .425).

Since we determined interpersonal problems with an instrument that consists of eight subscales, a backward-step generalized linear model was used to see which specific subscales contributed most to the model. This explorative analysis showed that subscales 1, 2, 4 and 7 were most strongly associated with the number of previous episodes. Subscale 1 is 'Domineering/ Controlling', which means that the subject has more difficulty in relinquishing control over others. Subscale 2 is 'Vindictive/Self-centred', which means problems with hostile dominance and the tendency to fight with others. Subscale 4 is 'Socially Inhibited', which means the tendency to feel anxious and avoidant in the presence of others. Subscale 7 is 'Self-Sacrificing', which means there is a tendency to affiliate excessively. A history of more MDEs was associated with a higher score for 'Domineering/Controlling', 'Socially Inhibited' and 'Self-Sacrificing' but a lower score for 'Vindictive/Self-centred'.

Discussion

The central aim of this cross-sectional study was to explore the association between the number of previous episodes and potentially modifiable vulnerability factors in remitted patients with recurrent depression. Our results showed that a history of more MDEs was associated with higher levels of interpersonal problems and daily stress, and a lower sense of mastery. The

Table 1. Participants' demographic and clinical characteristics.

Characteristic	N	Descriptive
Age, mean (SD)	214	43.41 (11.26)
Gender, no (%)	214	
Male		68 (31.8)
Female		146 (68.2)
Cohabitating, no (%)	210	107 (51.0)
Education, no (%)	210	
Lower		21 (10)
Intermediate		67 (31.9)
Higher		122 (58.1)
Previous MDEs, median (IQR)	214	3 (2)
Previous MDEs, mean (SD)	214	3.98 (3.25)
Previous MDEs, no (%)	214	
2 episodes		75 (35.0)
3 episodes		52 (24.3)
4 episodes		35 (16.4)
5 episodes		18 (8.4)
6 episodes		10 (4.7)
7 episodes		8 (3.7)
8+ episodes		16 (7.5)
Severity last MDE, no (%)	213	
Mild		23 (10.8)
Moderate		105 (49.3)
Severe		85 (39.9)
Age of first onset, mean (SD)	214	24.57 (11.38)
Patients on antidepressants, no (%)	200	57 (28.5)
Inclusion HDRS, mean (SD)	214	4.35 (3.68)
Residual symptoms IDS-SR, mean (SD)	205	16.98 (9.38)
Interpersonal Problems, mean (SD)	202	86.09 (32.47)
Daily Stress frequency, mean (SD)	187	35.98 (17.65)
Daily Stress intensity, mean (SD)	187	1.08 (0.50)
Sense of Mastery, mean (SD)	200	16.70 (3.83)
Active Coping, mean (SD)	186	18.30 (3.57)
Avoidant Coping, mean (SD)	184	16.80 (3.55)
Dysfunctional Cognitions, mean (SD)	188	77.86 (17.79)

Note. MDE = Major Depressive Episode, IQR = Interquartile range, Severity last MDE as assessed by Structured Clinical Interview for DSM-IV Axis I Disorders, Mild = 5 symptoms, Moderate = 6–7 symptoms, Severe = 8–9 symptoms, HDRS = 17-item Hamilton Depressive Rating Scale, Residual symptoms IDS-SR = Inventory Depressive Symptomatology- Self Report, Interpersonal Problems = Inventory of Interpersonal Problems total score, Daily Stress = Everyday Problem Check List, Sense of Mastery = Pearlin Mastery Scale, Coping = Utrechtse Coping Lijst, Dysfunctional Cognitions = Dysfunctional Attitude Scale-17.

presence of interpersonal problems was most strongly associated with the number of previous MDEs in a Generalized Linear Regression model. Contrary to our expectations, we found no association between the number of previous MDEs and coping or dysfunctional cognitions.

Our results linking interpersonal problems, daily stress, and sense of mastery to chronicity in terms of the number of previous MDEs are in line with previous research linking these factors to the recurrence of MDD [14, 16, 41–43]. These factors were all individually associated

Table 2. Spearman's rho correlation between previous MDEs and Interpersonal problems, daily stress, mastery, coping and cognitions.

	MDEs		
	N	r	p
Interpersonal Problems	202	.266	**.000**
Daily Stress frequency	187	.150	**.040**
Daily Stress intensity	187	.231	**.001**
Sense of Mastery	200	.141	**.046**
Active Coping	186	-.009	.902
Avoidant Coping	184	.058	.438
Dysfunctional cognitions	188	-.006	.336

Note: MDE = Major Depressive Episodes, Interpersonal Problems = Inventory of Interpersonal Problems total score, Daily Stress = Everyday Problem Check List, Sense of Mastery = Pearlin Mastery Scale, Coping = Utrechtse Coping Lijst, Dysfunctional cognitions = Dysfunctional Attitude Scale-17.

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with the number of previous MDEs, indicating that patients with more MDEs have more severe interpersonal problems, more frequent and intense daily stress, and less sense of mastery over their problems. These factors are also associated with each other, as shown by the correlation between them (r ranging from .32 to .41).

When we examined the factors in a Generalized Linear Regression model that included interpersonal problems, daily stress and sense of mastery, the presence of interpersonal problems was most strongly associated with chronicity (also after controlling for residual symptoms, age of onset and time since onset). Nevertheless, the association between the IIP and the number of previous episodes was modest as expressed in Exp(B) = 1.005. A previous study has shown that, even though interpersonal functioning improves during treatment for MDE, it does not improve as much as depressive symptoms [44]. Furthermore, a recent study has shown that a deterioration in social-interpersonal functioning preceded and predicted

Table 3. Results of generalized linear regression model analyses for factors significantly associated with the number of previous MDEs.

	B	S.E.	P	Exp(B)	95% CI for Exp(B)	
					Lower	Upper
Included in model: **Interpersonal Problems, Daily Stress frequency, Daily Stress intensity, Sense of Mastery[1]**						
Interpersonal Problems	.005	.0011	.000	1.005	1.003	1.007
Intercept	.582	.1784	.001	1.789	1.261	2.538
Included in model: **Interpersonal Problems subscales[2]**						
Subscale 1: Domineering/Controlling	.032	.0110	.004	1.032	1.010	1.054
Subscale 2: Vindictive/Self-centered	-.031	.0115	.008	.970	.948	.992
Subscale 4: Socially Inhibited	.023	.0080	.005	1.023	1.007	1.039
Subscale 7: Self-sacrificing	.016	.0073	.029	1.016	1.002	1.031
Intercept	.548	.1815	.003	1.729	1.212	2.468

Note. MDE = Major Depressive Episodes, Interpersonal Problems = Inventory of Interpersonal Problems, Daily Stress = Everyday Problem Check List, Sense of Mastery = Pearlin Mastery Scale.

[1]Omnibus test; *P* = .000

[2]Omnibus test; *P* = .000.

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depressive symptoms and even relapse/recurrence [45]. One of the explanations for the effect of interventions to prevent relapse (in other words, MBCT, PCT and Wellbeing CT) could be that they influence interpersonal functioning and therefore reduce daily stress and enhance a sense of mastery. Alternatively, sense of mastery could be improved, resulting in better interpersonal functioning and a reduction in daily stress. Future studies should examine these factors in a longitudinal cohort and determine whether the effect of interventions to prevent relapse can be explained by targeting these psychological factors.

Specific interpersonal problems associated with chronicity were: 'more difficulty with relinquishing control over others', 'feeling more anxious and avoidant in the presence of others', 'a tendency to affiliate excessively' and 'less hostile dominance'. Given the exploratory nature of these analyses and our cross-sectional study design we are cautious in our interpretation of these results and wish to encourage additional research in this area.

We found no relationship between the number of previous MDEs, active or avoidant coping, and dysfunctional cognitions in this group of remitted patients with recurrent depression. Nevertheless, previous research has provided evidence that higher levels of dysfunctional cognitions and specific types of coping (such as avoidant coping) are risk factors for recurrence [5, 22, 23]. The fact that we found no relationship in this study could be explained by the fact that coping and dysfunctional cognitions are premorbid vulnerability factors that make some patients prone to relapse/recurrence, or that the first MDE may have already caused the change in this specific vulnerability [6]. Another explanation for coping and dysfunctional cognitions not being linked to the number of previous MDEs could be that the effect of coping on recurrence diminishes with an increasing number of previous episodes, as suggested by previous research [17, 46]. Alternatively, coping and dysfunctional cognitions may have been addressed adequately during the CBT in the acute phase of the depression. Another alternative, that applies specifically to dysfunctional beliefs, is that scarring effects on dysfunctional beliefs may only be measurable when the dysfunctional beliefs are activated through negative mood states [22, 47].

This study has several limitations. It included only patients with two or more previous MDEs. It is not known whether the associations found were scarring effects or premorbid characteristics, or the result of the first episodes. Longitudinal studies are needed that study a cohort before the onset of the first episode [6, 12]. Furthermore, we could not examine whether the factors found predicted future relapse and recurrence. In addition, we could not address differences between depressive subtypes. Depression is a heterogeneous disorder and different subtypes may run a different course with regard to relapse/recurrence. Finally, the number of previous MDEs was assessed retrospectively at the start of the study, and recall bias is therefore a possibility. However, research based on retrospective recall has shown that recall bias plays only a minor role [48].

Despite these limitations, this study also has several strengths. We included only recurrently depressed patients who were not depressed upon inclusion. There is a high risk of relapse/recurrence in these patients, but measurements are not affected by current MDEs. We assessed the number of previous episodes with the Structured Clinical Interview for DSM-IV Axis I Disorders, which is considered the 'gold standard' for diagnosing MDD. Furthermore, we compared multiple factors that previous studies have shown to be potentially modifiable vulnerability factors. Finally, our results are relevant to clinical practice and they can be used to further improve and evaluate current interventions to prevent relapse.

The present study highlights the association between interpersonal functioning, daily stress and sense of mastery by linking them to chronicity in terms of the number of previous MDEs. However, methodological issues, associated with the cross-sectional nature of this study, preclude the drawing of conclusions about the direction of causality. Current effective

interventions for preventing the recurrence of depression could already target these factors directly or indirectly. Studies in the future should therefore examine whether the preventive effects of current interventions can be explained by targeting these factors.

Author Contributions

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