Prediction of Recurrence in Recurrent Depression and the Influence of Consecutive Episodes on Vulnerability for Depression: A 2-Year Prospective Study

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Objective: Depression is a recurring disease. Identifying risk factors for recurrence is essential. The purpose of this study was to identify factors predictive of recurrence and to examine whether previous depressive episodes influence vulnerability for subsequent depression in a sample of remitted recurrently depressed patients.

Method: Recurrence was examined prospectively using the Structured Clinical Interview for DSM-IV Axis I Disorders in 172 euthymic patients with recurrent depression (DSM-IV) recruited from February 2000 through September 2000. Illness-related characteristics, coping, and stress (life events and daily hassles) were examined as predictors.

Results: Risk factors for recurrence were a high number of previous episodes, more residual depressive symptomatology and psychopathology, and more daily hassles. Factors with both an increasing and decreasing pathogenic effect with increasing episode number were detected.

Conclusion: We found some support for dynamic vulnerability models that posit a change of vulnerability with consecutive episodes. Preventive interventions should be considered in patients with multiple recurrences, focusing on residual symptomatology and specific coping styles.

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Major depressive disorder (MDD) is a chronic disease, characterized by multiple episodes, so identifying risk factors for recurrences is of great clinical importance. Aside from illness-related characteristics, potential causal risk factors for recurrence are stressful life events, heightened cognitive reactivity, and maladaptive coping. (See Alford and Beck[1] and Lau et al.[2] for a review.) There is also evidence that the risk of new episodes increases with each consecutive episode. To provide an explanation for this latter finding, dynamic vulnerability models have been developed.[3–5] These models state that a new depressive episode might cause psychological and/or biological damage that results in a change or increase of vulnerability for the next episode. Although studies of these models in recurrent depression are sparse, some support for these models has been found.[6,7] Kendler et al.,[7] for instance, found an association between previous episodes and the pathogenic impact of exposure to stressful life events in the risk of major depression—both first-onset depression and recurrence—in female twin pairs (N = 2395) over a period of 9 years. They reported that, through approximately 9 episodes, the association between stressful life events and risk of major depression progressively declined but was largely unchanged with further episodes. This finding suggests a threshold at which the mind/brain is no longer additionally sensitized to the depressive state. In recurrently depressed patients, daily hassles, rather than life events, may act as risk factors for recurrence.[8]

Psychological interventions in the maintenance phase, such as brief cognitive-behavioral therapy (CBT) added either to regular care or medication and mindfulness-based cognitive therapy (MBCT), are helpful in preventing recurrence in a subpopulation of patients with recurrent depression.[9–17] Identification of potentially modifiable risk factors for recurrence, such as coping, in this specific group could provide us with the opportunity to develop tailored preventive interventions. Coping strategies seem

to play a key role in vulnerability to life stressors.[18] Empirical support has been found[19] for the idea, referred to as the *stress generation hypothesis*, that depressed individuals generate stressful conditions in part by their own actions, attitudes, and characteristics. Holahan et al.[20] integrated the stress generation and coping perspective to test a prospective model of depressive symptoms over a 10-year period. They found support for a stress-generating role of avoidant coping as a prospective link to future depressive symptoms.

Besides illness-related characteristics, our study focused on the effect of stress (daily hassles and life events) and coping on consecutive episodes in recurrent depression. They were assessed in a clinical trial comparing treatment as usual (TAU) with preventive CBT added to TAU. In results from our study reported previously,[9] differences in outcome of CBT versus TAU were dependent on the number of previous depressive episodes; patients with more previous episodes benefited more from preventive CBT. Our sample of 172 patients with recurrent depression who were remitted on various types of treatments was followed prospectively for 2 years with structured interviews based on DSM-IV. The present study has 2 aims: (1) to determine factors that predict time to recurrence and (2) to examine whether additional depressive episodes influence vulnerability to depression, as proposed by dynamic vulnerability models.

METHOD

Participants

All respondents participated in a clinical trial of patients with recurrent depression currently in remission, in which the effect of TAU (including no care at all) on recurrence was compared with TAU with additional preventive CBT.[9] To be eligible, subjects had to meet the following criteria: (1) at least 2 major depressive episodes (MDEs) in the last 5 years, as defined according to DSM-IV[21] and assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[22] by trained evaluators; (2) current remission status according to DSM-IV criteria, for longer than 10 weeks and no longer than 2 years ago; (3) a 17-item Hamilton Rating Scale for Depression (HAM-D)[23] (12) score of < 10. Exclusion criteria were current mania, hypomania, or a history of bipolar illness; any psychotic disorder (current and previous); organic brain damage; alcohol or drug misuse; predominant anxiety disorder; recent electroconvulsive therapy; recent cognitive treatment, receiving CBT at the start of the study, or current psychotherapy with a frequency of more than 2 times a month. There was no restriction on using pharmacotherapy.

Participants were recruited at psychiatric centers and through media announcements from February 2000 through September 2000. They completed telephonic screening (N > 1000) and diagnostic interviews (N = 321) and provided informed consent to enter the protocol (N = 187). The protocol was approved by the relevant institutional ethics review committees. More detail about participants, recruitment, and inclusion and exclusion criteria is available in Bockting et al.[9]

Procedure

Participants were screened for inclusion and exclusion criteria via the telephone version of the SCID. The κ for interrater agreement between the interviewers (psychologists/research assistants), based on audiotaped interviews, for inclusion or exclusion was 0.77, which is indicative of good/excellent agreement.

Participants meeting the inclusion criteria were randomly allocated to:

(1) TAU: TAU involved "naturalistic" care, i.e., standard care (including no treatment), as typically provided by the referring agencies. There was no restriction on the use of pharmacotherapy during the period from entry through follow-up.
(2) TAU + 8 weekly 2-hour group CBT sessions: Randomization was performed using random permutated blocks and was stratified by study location and type of aftercare (family doctor/psychiatric center/no aftercare). Consecutively numbered, sealed envelopes contained computer-generated cards with concealed assignment codes. This procedure was organized and administered by an independent research associate.

Study Measures

Primary outcome measure. Recurrence was assessed with the SCID-I.[22] At baseline and at 3 follow-up assessments (3, 12, and 24 months), current and past depressive episodes (covering the prior 3, 12, and 24 months, respectively) were checked. (Cox regression analyses revealed no effect on time to recurrence when the duration of remission of the last episode was entered into the equation.) To maintain the blindness of assessors to treatment condition, we instructed participants not to reveal this information to the interviewers (psychologists/research assistants). All interviews were audiotaped. Two independent experienced psychiatrists who were blind to treatment condition evaluated all 108 occasions of participants meeting the DSM-IV criteria for major depression. In cases of disagreement, the ratings of the psychiatrists were used for further analyses. The κ for interrater agreement between the interviewers and psychiatrists on categorization of a recurrence versus no recurrence was 0.96, indicating high agreement.

Number of recurrences and severity. The severity of a recurrence was assessed by the SCID-I (light, < 6 symptoms; moderate, 6–7 symptoms; severe, 8–9 symptoms).

The number of recurrences was computed by adjusting for differences in follow-up time. The number of recurrences was converted to number of recurrences per 2 years at risk.

Prediction variables.

Severity of depressive residual symptoms. The 17-item HAM-D[23] was used to assess participants' baseline levels of depressive symptomatology. The HAM-D, administered by psychologists/research assistants who were blind to treatment condition, is a widely used, semistructured clinical interview that covers a range of affective, behavioral, and biological symptoms and has acceptable psychometric properties.[24] Scores can range from 0 to 52. Our 4 interviewers (psychologists/research assistants) second-rated 17 interviews. The intraclass correlation (ICC) was 0.94, indicating high agreement. Further, the 21-item self-report Beck Depression Inventory (BDI)[25] was used to assess baseline depression symptomatology in the past week. Scores can range from 0 to 63.

Level of psychopathology. The 90-item Symptom Checklist-90 (SCL-90)[26] was used to assess the total baseline level of psychopathology in the past week.

Dysfunctional attitudes. Dysfunctional attitudes (baseline) were assessed with the Dutch adaptation of the Dysfunctional Attitude Scale (DAS).[27] The DAS is a 40-item scale that assesses excessive and rigid beliefs, hypothesized by Beck[28] to be vulnerability factors for depression. Participants rate their agreement with each belief on a 7-point Likert scale ranging from "totally agree" to "totally disagree." Scores range from 40 to 280, with higher scores indicating greater levels of dysfunctional attitudes. Form A of the DAS (DAS-A), which has been shown to have good psychometric properties, was used.[29]

Stress: daily hassles. To measure baseline daily hassles, the 114-item Everyday Problem Checklist (EPCL)[30] was used. The items of the EPCL refer to stressors of daily living, particularly those in the domains of work, parenthood, relationship, and household activities. The EPCL assesses the frequency of daily hassles over the past 2 months and has good psychometric properties.[30]

Stress: life events. The experience of negative life events was measured with a 15-item checklist that covered adulthood (from age 16 years to the start of the study). The checklist was based on the Negative Life Events Questionnaire (NLEQ).[31] Events can involve the participant or significant others. In previous studies,[31–33] the predictive validity of the NLEQ proved to be good, as the number of negative life events predicted severity of depressive symptoms.

Behavioral coping. Information on behavioral coping with problems was obtained by using 2 subscales of the Utrecht Coping List (UCL)[34]; i.e., avoidant coping (8 items) and active approach to problems (7 items). Participants were asked how they reacted in general to the mentioned items (e.g., "Avoid difficult situations"). The UCL has good psychometric properties.[35]

Cognitive coping. Information on cognitive coping was gathered by using the self-report Cognitive Emotion Regulation Questionnaire (CERQ),[36] containing 36 items with 9 subscales such as rumination, self-blame, and refocus on other positive matters. Participants were asked how they think in general when confronted with stressful events (e.g., "I think about how I can change the situation").

Statistical Analysis

The effect of a specific predictor, say A, on recurrence was assessed with Cox regression; this procedure takes into account differences in time at risk and censoring (no recurrence during the study period).

In the analyses, we have to take into account the fact that half of our sample received an additional psychological intervention that prevented recurrence. The effect depended on the number of previous depressive episodes.[9] One way to take this fact into account is to restrict all analyses to the control group. However, this approach would mean that all analyses are performed on only half our sample, which would lower the power of these analyses considerably. An alternative approach is to assess whether the intervention had an effect on the relation between the predictor and recurrence or not. In the first case, the analyses should be restricted to the control group; in the latter case, the analysis could be performed on the total sample without loss of statistical power. We chose the latter option.

We used a 2-step procedure: In the first step, we tested, for each predictor, whether its effect on recurrence was modified by treatment condition (this is the case when, in the regression model, the coefficient of the 2-way treatment by predictor interaction term is statistically significant) and whether the strength or direction of this modification depended on the number of previous depressive episodes of the patient. (This is the case when, in the regression model, the coefficient of the 3-way treatment condition by predictor by number of previous episodes interaction term is statistically significant.) In the second step, we assessed the effect of predictors on recurrence. Depending on the results of the first step, these analyses were performed either in the total sample (N = 172) or (in case of a significant interaction with treatment condition) only in the TAU group (N = 84). In both cases, the treatment factor would not be incorporated into the statistical model, in the first case, since treatment had no effect, and in the latter case, since we restricted ourselves to one treatment condition (the control group). For 3 predictors (avoidant coping, number of previous episodes, and daily hassles), we had to restrict analyses to the TAU group (N = 84) because, for these predictors, the effect on recurrence was modified by treatment condition (effect modification).

In the second step, 2 models were tested to assess whether the effect of a predictor was modified by

the number of previous depressive episodes. Model 1, $Y = \beta_1 A + \beta_2 P + \beta_3 AP$, assessed whether the number of previous episodes (P) modified the effect of a specific predictor (A) on recurrence. (This was the case when the coefficient of the 2-way predictor by previous episodes term was statistically significant.) If the AP interaction term in this model was not statistically significant, model 2, $Y = \beta_1 A$, which states that recurrence is related to predictor A, applied.

To account for chance capitalization because of multiple testing, which affects type I error, we used a relatively conservative α level of .01 for all main effects tests. However, given the relatively lower power of the test for interaction compared with tests for main effects, we used an α level of .10 for all tests for interaction to guard against type II error. Since the distribution of number of previous episodes was skewed, and the minimum number of previous episodes was 2, we used the formula $P = LN(p - 1)$, with p the actual number of previous episodes and P the transformed variable used in the analysis.

Analyses revealed that the number of previous episodes moderated the relation between recurrent risk and, respectively, avoidant coping strategies (also moderated by treatment condition), duration of last episodes before entry, marital status, and dysfunctional attitudes.

Table 1. Demographic and Clinical Characteristics[a]

Characteristic	Completers (N = 172)
Sex, % female	73
White, %	98
Age, mean ± SD, y	44.7 ± 9.5
Years of education, mean ± SD (range)	14.2 ± 2.5 (8–18)
Marital status, %	
Single	24
Married/cohabiting	58
Divorced/widowed	18
Type of current treatment, %	
Family doctor	29
Psychiatric help	31
No treatment	40
Antidepressant medication, %	51
HAM-D score, mean ± SD	3.8 ± 2.8
Previous episodes	
Median previous episodes ± IQR	4 ± 3.8
> 2 previous episodes, %	82
Age at first onset, mean ± SD, y	28.5 ± 12.5
Coping strategies, mean ± SD	
Dysfunctional attitudes (DAS-A)	124.6 ± 33.5
Avoidant coping strategy (UCL)	17.1 ± 3.9
Coping—refocus on positive matters (CERQ)	8.7 ± 3.3

[a]All data represent baseline values.
Abbreviations: CERQ = Cognitive Emotion Regulation Questionnaire, DAS-A = form A of the Dutch adaptation of the Dysfunctional Attitude Scale, HAM-D = Hamilton Rating Scale for Depression, IQR = interquartile range, UCL = Utrecht Coping List.

RESULTS

Sample Characteristics

The sample consisted of 187 participants. We excluded 15 participants (9 from CBT; 6 from TAU) because they dropped out of the study immediately. Dropouts (N = 15) were slightly younger than completers (N = 172), t = –2.25, df = 170, p = .026 (dropouts: mean age = 38.9 years, SD = 10.6 years, completers: mean age = 44.7 years, SD = 9.5 years), but equivalent on all other characteristics. The analyses are based on the remaining 172 patients (84 TAU; 88 CBT). Demographic and clinical characteristics are summarized in Table 1. The CBT and TAU groups (N = 172) were comparable on each of the variables (all p values > .05), except for experience of negative life events before the 16th year ($\chi^2 = 6.74$, df = 1, p = .009). (In the CBT group, 84/88 patients experienced negative life events vs. 70/84 patients in the TAU group.) To examine whether this initial difference confounded the relation between recurrence and the interaction of treatment condition with the predictor, a model with and without childhood life events was compared. No confounding effect of childhood life events was detected.

Recurrence

In the total sample (N = 172), 102 participants (59%) were diagnosed with a new depressive episode over a period of 2 years (mode = 25 months, in the TAU sample 52/84; 62%, in the CBT sample 50/88; 57%). Mean time to recurrence in the TAU sample was 15.5 months (SE = 1.3) with a median of 14.0 months (range: 9.3–18.7 months), and in the CBT sample a mean time of 17.9 months (SE = 1.1 months) with a median of 22.0 months (range: 15.6–28.4 months) was observed. In the CBT sample, the addition of a CBT program reduced cumulative recurrence rates significantly (p = .01) in patients with 5 or more previous episodes, from 72% to 46%.[9] In the 2-year follow-up period, over one quarter of the participants (N = 83, 1 missing) experienced 1 recurrence (27.7%, N = 23), 18% experienced 2 recurrences (18.1%, N = 15), and 16% experienced 3 recurrences or more (15.7%, N = 13). The severity of the recurrences was, like the last depression before study entry, mostly moderate (54%, 28/52) to severe (42%, 22/52).

Predictors of Time to Recurrence

As shown in Table 2, the following baseline variables were examined on their relation with time to recurrence in the total sample (N = 172): demographic characteristics (sex, marital status, age, education level); historic illness-related characteristics (age at onset, severity of last depression, duration of last episode, duration of remission since last episode, percentage of time illness free since first episode); recent illness-related characteristics (level of psychopathology and level of residual depressive symptoms); familial psychiatric disease; coping; and stress (daily hassles and life events).

Table 2. Predictors of Time to Recurrence (N = 172)[a]

Predictor	Predictor	Number of Episodes	Predictor*Episodes
Avoidant coping[b]			
β	0.202	0.587	–0.080
SE(β)	0.060	0.170	0.033
p	.001	.001	.015
Duration of last depression			
β	–0.525	0.008	0.515
SE(β)	0.402	0.135	0.226
p	.192	.950	.023
Coping—refocus on positive matters			
β	–0.148	0.162	0.076
SE(β)	0.054	0.108	0.035
p	.006	.135	.031
Number of previous episodes[b]			
β	0.471		
SE(β)	0.146		
p	.001		
Daily hassles[b]			
β	0.529		
SE(β)	0.216		
p	.014		
Marital status (single/widowed/divorced vs married/cohabiting)			
β	1.111	0.386	–0.401
SE(β)	0.340	0.147	0.220
p	.001	.008	.069
Residual depressive symptomatology (HAM-D)			
β	0.097		
SE(β)	0.034		
p	.004		
Residual depressive symptomatology (BDI)			
β	0.565		
SE(β)	0.166		
p	.001		
Psychopathology (SCL-90)			
β	1.807		
SE(β)	0.358		
p	< .001		
Dysfunctional attitudes (DAS)			
β	0.016	0.186	–0.006
SE(β)	0.005	0.110	0.003
p	.001	.089	.052

[a]No significant relation for the following variables: age, education level, gender, age at onset, severity of last depression, duration of remission of last episode, percentage of time illness-free since first episode, other types of emotional coping, familial psychiatric disease, and life events between 16th year and the start of the study.
Reference values for predictors are:
Duration of last depression = 0 (0 = > 2 months).
Number of previous episodes [transformed as P = LN(ndeps – 1), where ndeps equals the raw number] = 0 (= 2 previous episodes).
LN(daily hassles score) = 0 (EPCL score = 1).
Marital status = 0 (married/cohabitating).
HAM-D = 0 (Hamilton score 0).
LN(BDI + 1) = 0 (BDI = 0).
LN(SCL-90) = 0 (SCL-90 = 1).
Other continuous variables were centralized around their mean; avoidant coping (16), coping—refocus positive matters (8), DAS-A (119).
[b]N = 84, modification by treatment condition.
Abbreviations: BDI = Beck Depression Inventory, DAS-A = form A of the Dutch adaptation of the Dysfunctional Attitude Scale, EPCL = Everyday Problem Checklist, HAM-D = Hamilton Rating Scale for Depression, LN = natural logarithm, ndeps = raw number of previous episodes, P = number of previous episodes, SCL-90 = Symptom Checklist-90.

Only variables that were significant predictors will be described here. In case of effect modification (significant interaction) with treatment condition, analyses were based on the TAU cohort only; in all other cases, analyses were based on the total sample. Table 2 also shows apparent effect modification (significant interaction) or confounding by the number of previous depressive episodes. Table 3 presents the hazard rate ratios (HRRs). Predictors with HRRs smaller than 1 indicate protective factors, i.e., relatively longer time to recurrence; those with HRRs exceeding 1 indicate risk factors, i.e., a relatively short time to recurrence. In case of effect modification by the number of previous episodes, the HRR depends on this number. Significant predictors follow (see Table 2 for p values):

(1) Demographic characteristics: The association between marital status and recurrence was dependent on the number of previous episodes; time to recurrence was shorter for single, widowed, or divorced patients. The importance of this risk factor diminished with an increasing number of previous episodes.
(2) Historic and recent illness-related predictors: A higher level of depressive residual symptoms (HAM-D and BDI) and psychopathology (SCL-90) predicted earlier recurrence. The number of previous episodes was a risk factor for recurrence, in which an increasing number of episodes predicted earlier recurrence. The effect of the duration of the last depressive episode before the start of the study on recurrence was dependent on the number of previous episodes. A short last episode (≤ 2 months) became a risk factor (i.e., shorter time to recurrence) in patients with more than approximately 4 previous episodes (HRR > 1). This effect became stronger with an increasing number of previous episodes.
(3) Coping: Higher levels of dysfunctional attitudes and avoidant coping strategies, as well as lower levels of coping by refocusing on positive matters, predicted earlier recurrence. However, this effect was dependent on the number of previous episodes, implicating a diminishing influence with an increasing numbers of previous episodes.
(4) Stress: Higher levels of daily hassles predicted earlier recurrence.

No confounding effects of treatment and/or number of previous episodes were found.

DISCUSSION

In this study, 172 participants who were remitted from recurrent depression were followed for up to 2 years. Over this period, 59% (102/172) were diagnosed with a

Table 3. Hazard Rate Ratios (HRRs), Standard Errors (SEs) of the Natural Logarithm of the HRR, and Confidence Intervals (CIs) for the HRR for Predictors of Recurrence

Predictor	HRR	SE	CI[a]	Previous Episodes[b]
Avoidant coping[c,f]	1.224	0.060	1.109 to 1.351	2
	1.047	0.037	0.985 to 1.113	8
Duration of last depression[d]	0.592	0.402	0.305 to 1.146	2
	1.611	0.257	1.057 to 2.457	8
Coping—refocus on positive matters[c]	0.862	0.054	0.789 to 0.943	2
	1.000	0.039	0.937 to 1.067	8
Number of previous episodes[c§,f]	1.601	0.146	1.259 to 2.035	
Daily hassles[c†,f]	1.698	0.216	1.190 to 2.422	
Marital status[e]	3.037	0.340	1.736 to 5.314	2
	1.392	0.257	0.912 to 2.124	8
Residual depressive symptomatology (HAM-D)[c]	1.102	0.034	1.009 to 1.202 (99% CI)	
Residual depressive symptomatology (BDI)[c‡]	1.759	0.166	1.146 to 2.699 (99% CI)	
Psychopathology (SCL-90) [c†]	6.092	0.358	2.425 to 15.300 (99% CI)	
Dysfunctional attitudes[c]	1.016	0.005	1.008 to 1.025	2
	1.004	0.003	0.999 to 1.010	8

[a]90% Confidence intervals are reported, unless otherwise specified (99%).
Limits of the 90% confidence interval for HRR are given by $HRR/exp(SE)^{1.645}$ and $HRR*exp(SE).^{1.645}$
Those for the 99% confidence interval by $HRR/exp(SE)^{2.576}$ and $HRR*exp(SE).^{2.576}$
[b]For avoidant coping, duration of last depression, coping—refocus on positive matters, marital status, and dysfunctional attitudes, values are dependent on number of previous episodes; values are given for 2 and 8 episodes.
Formulas allowing other numbers of previous episodes are:
Avoidant coping: $HRR = 1.223848*0.923116^{P}$ and $SE = \sqrt{(0.0036 + 0.001089*P^2 - 0.003259*P)}$.
Duration of last depression: $HRR = 0.591555*(1.673639)^{P}$ and $SE = \sqrt{(0.161604 + 0.051076*P^2 - 0.148634*P)}$.
Coping—refocus on positive matters: $HRR = 0.862431*(1.07896)^{P}$ and $SE = \sqrt{(0.002916 + 0.001225*P^2 - 0.003092*P)}$.
Single: $HRR = 3.037394*(0.669650)^{P}$ and $SE = \sqrt{(0.115600 + 0.048400*P^2 - 0.119680*P)}$.
Dysfunctional attitudes: $HRR = 1.016129*(0.994018)^{P}$ and $SE = \sqrt{(0.000025 + 0.000009*P^2 - 0.000025*P)}$.
[c]Continuous scores [1 = raw score].
[†][1a = LN(raw score)].
[‡][1b = LN(raw score + 1)].
[§][1c = LN(raw score – 1)].
[d]Categorized: 0 = 3 months or more, 1 = 2 months or less.
[e]Dichotomized: single/widowed/divorced vs. married/cohabitation.
[f]N = 84, modification by treatment condition.
Abbreviations: BDI = Beck Depression Inventory, exp = exponent, HAM-D = Hamilton Rating Scale for Depression, LN = natural logarithm, P = number of previous episodes, SCL-90 = Symptom Checklist-90.

depressive recurrence according to DSM-IV. This high recurrence rate is consistent with the study of Teasdale et al.,[16] which found a recurrence rate of 70% to 80% in patients with 3 or more previous episodes over 1 year and reported a previously recurrence rate of 79% over a period of 3 years.[37,38]

Aim 1: Prediction of Time to Recurrence

In summary, we found in our sample (N = 172) characterized by multiple recurrences that an earlier time to recurrence was predicted by higher numbers of previous episode, higher levels of general psychopathology and residual depressive symptoms, and more daily hassles. We found little impact of other sociodemographic variables on time to recurrence. Previous studies reported inconsistent results with respect to age, age at onset, and gender.[39–41] However, as Kessing et al.[5] point out, these factors initially act as risk factors for further recurrence, whereas later, as in this recurrent sample, the illness itself seems to follow its own rhythm regardless of these predictors.

In contrast to other studies,[39–42] with the exception of the number of previous episodes and residual symptoms, we have found little impact of other illness-related characteristics (like duration of remission from index episode, severity of index episode, and family history). However, consistent with several other studies,[41–43] we found that the number of previous episodes and residual symptoms were strong risk factors for recurrence. The difference in results can possibly be explained by sample differences. Most previous studies included patients with first episodes as well as recurrent episodes, and the number of previous episodes has not always been adequately accounted for. Moreover, in contrast to other studies, not all patients in our study sought treatment for the last depression before entry, and patients received diverse care after remission, including no care at all.

Interestingly, we found that major life events during adulthood had little impact on recurrence. Our finding that, instead of life events, daily hassles predicted time to recurrence (even after correction for the influence of prior episodes) concurs with findings of several previous studies[3,7,44] that, with repeated experiences of episodes of major depression, less environmental stress is required to provoke recurrence. A revised cognitive model of Teasdale,[45] referred to as the *differential activation hypothesis*, posits the activation of negative information-

processing biases when an individual experiences dysphoric mood. Depressive thinking results from repeated associations between the depressed state and negative thinking patterns. The strengthening of these associations with repeated episodes is assumed to contribute to an increased risk of recurrence following each subsequent episode. It is conceivable either that, in recurrent depression, depressogenic thinking patterns are directly reactivated by daily hassles or that daily hassles provoke dysphoria and thereby reactivate depressogenic thinking patterns. As mentioned before, there is some empirical evidence for this presumed heightened cognitive reactivity as a potential causal risk factor for recurrence. (See Lau et al.[2] for a review.) As reported elsewhere,[46] we did find that major life events during adulthood predicted time to recurrence in our CBT sample. Preventive CBT seemed ineffective in patients with life events.

Aim 2: Influence of Consecutive Episodes on Vulnerability for Depression

Examination of whether the association between predictors and recurrence changes with previous episodes number, as proposed by dynamic vulnerability models,[3–5] revealed that the number of previous episodes moderated the relation between recurrence risk and some predictors. Thus, to a certain extent these findings support dynamic vulnerability models that posit a change of vulnerability with consecutive episodes. We identified both predictors with a decreasing pathogenic effect (decreasing risk factor) with increasing episode number and predictors with an increasing pathogenic effect (increasing risk factor) with increasing episode number. Both groups of predictors will be described below.

A decreasing pathogenic effect. Predictors with a decreasing pathogenic effect with increasing episode number were predominantly coping-related factors and potentially open to therapeutic intervention: higher levels of an avoidant way of dealing with problems, higher levels of dysfunctional attitudes, and lower levels of coping by refocusing on positive matters.

How is this change in association between predictors and recurrence with episode numbers to be explained? Holahan et al.[20] found support for a stress-generating role of avoidant coping as a prospective link to future depressive symptoms. An avoidant way of dealing with problems resulted in a higher number of daily hassles and life events, which are linked to depressive symptoms. Although we did not find any evidence for increased stress generation with increasing episode number in this recurrent subpopulation, we cannot rule out that our test had insufficient power to detect the increased stress generation in patients with avoidant coping strategies.

Hammen[47] speculated that vulnerability for depression consists of maladaptive cognitions about attachment and dysfunctional interpersonal skills that contribute to interpersonal stress generation. A higher number of daily hassles and life events or an increasing impact of these kinds of events could result in the activation of dysfunctional attitudes that are thought to determine vulnerability to recurrence (diathesis stress).[28] To some extent, we found support for the role of cognitive processes in recurrence. Higher levels of dysfunctional attitudes, higher levels of an avoidant way of dealing with problems, and lower levels of refocusing on positive matters are risk factors for recurrence. However, sample sizes were too small to explore the relation between the combination of an avoidant coping strategy, stress, and dysfunctional attitudes with recurrence. The substantial decline of a relation between time to recurrence and, respectively, dysfunctional attitudes, an avoidant coping strategy, and refocusing on positive matters in participants with higher episode numbers could indicate that these types of coping influence recurrences up to a certain threshold value. We speculate that above this threshold (of a certain number of prior episodes) either more daily hassles will be generated that cannot be prevented by an adequate coping style (stress generation hypothesis) or the amount of stress required to provoke a recurrence will have become so small that an adequate coping style cannot influence it (kindling model).[48] Another explanation is that there might be different types of depression.[9,17] One type of depression may be closely associated with reaction to life events, such that an adequate coping style (response to stress) may prevent recurrence. It is possible that the group of patients with fewer previous episodes in our study reflects this type of depression. The other type of depression may be brought about by rumination, reflecting the group of patients with a high number of episodes. Even so, vulnerability in participants with very high numbers of previous episodes is, to a lesser extent, determined by coping-related factors.

An increasing pathogenic effect. On the other hand, having a last depressive episode of relatively short duration before study entry was a predictor of a depressogenic effect (risk factor) that increased as the number of previous episodes grew. This identified increasing pathogenic risk factor in more than approximately 4 episodes could reflect a group of patients with multiple short episodes accompanied by higher recurrence rates over time. In contrast to the decreasing depressogenic predictors, this factor possibly reflects autonomous characteristics of recurrent depression. Unfortunately, retrospective data on duration of all past episodes were less accurate and often missing; therefore, this interpretation could not be further analyzed and has to be treated with caution.

Limitations

These include the relatively small sample size, reducing power to detect weaker associations between recurrence and prediction factors. Although we used an α level of .10 for interaction with treatment condition (N = 172)

to account for a lower power, we cannot completely rule out that CBT did not influence the relation between the predictor and recurrence in case of nonsignificant interaction terms with treatment condition. Further, this study did not include patients with only 1 previous depressive episode. A further limitation concerns the retrospective nature of the information on the number of previous episodes before the start of the study as collected with a structured interview. However, Wells and Horwood[49] found in their study that lifetime prevalence rates based on retrospective recall were markedly underestimated but that the identification of major risk factors might be relatively little impaired. Another limitation concerns the self-report measures. They are subject to social desirability, and, therefore, further research is needed with interview-based stress and coping measures. Strengths of the study included the fact that our cohort included exclusively patients with at least 2 previous episodes and was followed prospectively for 2 years with structured interviews based on DSM-IV. Further, we included patients with recurrent depression remitted on medication and/or psychological therapy or no treatment at all, without restrictions on medication status at entry to the study. As such, this study was designed to maximize external validity, which suggests good generalizability of the findings.

CONCLUSIONS

These results suggest that some factors that predict recurrence in patients with 2 previous episodes are not the same for patients with 5 episodes or even 10 episodes. Researchers should not only differentiate between first-onset and subsequent depression but also consider both the increasing and decreasing pathogenic influence of lifetime history of depressive disorder. Specific attention should be paid to identify vulnerability factors in recurrent depression (such as coping-related factors) modifiable by therapeutic interventions. This focus will provide us with the opportunity to develop tailored preventive interventions.

For now, preventive interventions should focus on reducing residual symptomatology and enhancing coping (including coping to prevent daily hassles or to decrease the impact of daily hassles). Psychological preventive interventions with cognitive elements, such as brief CT or MBCT and well-being therapy, focus on these risk factors. Possibly, preventive CBT, rather than acting on changing dysfunctional attitudes or reducing residual symptoms, acts on promoting coping strategies, which result in distancing from stress. Moreover, Fava et al.[11–13] point out that the additional ingredients added to their preventive CBT, i.e., lifestyle modification (working on minor life stress, interpersonal friction, and excessive work) and psychotherapeutic strategies that enhance well-being, besides acting on residual symptoms, may be main ingredients of preventive CBT. Especially in patients with high numbers of previous episodes, preventive cognitive interventions in the maintenance phase are effective and should be considered.[9,13,16,17]

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REFERENCES

1. Alford B, Beck AT. The Integrative Power of Cognitive Therapy. New York, NY: Guilford Press; 1997
2. Lau MA, Segal ZV, Williams JM. Teasdale's differential activation hypothesis: implications for mechanisms of depressive recurrence and suicidal behaviour. Behav Res Ther 2004;42:1001–1017
3. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149:999–1010
4. Segal ZV, Williams JMG, Teasdale JD, et al. Cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. Psychol Med 1996;26:371–380
5. Kessing LV, Andersen PK, Mortensen PB. Predictors of recurrence in affective disorder: a case register study. J Affect Disord 1998;49:101–108
6. Brown GW, Harris F, Hepworth C. Life events and endogenous depression. Arch Gen Psychiatry 1994;51:525–534
7. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the 'kindling' hypothesis. Am J Psychiatry 2000;157:1243–1251
8. Ormel J, Oldehinkel AJ, Brilman EI. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. Am J Psychiatry 2001;158:885–891
9. Bockting CL, Schene AH, Spinhoven P, et al. Preventing relapse/recurrence in recurrent depression with cognitive therapy: a randomized controlled trial. J Consult Clin Psychol 2005;73:647–657
10. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in outpatients with recurrent depression. Br J Psychiatry 1997;171:328–334
11. Fava GA, Grandi S, Zielezny M, et al. Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. Am J Psychiatry 1996;153:945–947
12. Fava G, Rafanelli C, Grandi S, et al. Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. Arch Gen Psychiatry 1998;55:816–820
13. Fava GA, Ruini C, Rafanelli C, et al. Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. Am J Psychiatry 2004;161:1872–1876
14. Jarrett RB, Kraft D, Doyle J, et al. Preventing recurrent depression using cognitive therapy with and without a continuation phase. Arch Gen Psychiatry 2001;58:381–388
15. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Arch Gen Psychiatry 1999;56:829–835
16. Teasdale JD, Segal ZV, Williams JMG, et al. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. J Consult Clin Psychol 2000;68:615–623
17. Ma SH, Teasdale JD. Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. J Consult Clin Psychol 2004;72:31–40
18. Holahan CJ, Moos RH, Bonin L. Social context and depression: an integrative stress and coping framework. In: Joiner T, Coyne J, eds.

The Interactional Nature of Depression: Advances in Interpersonal Approaches. Washington, DC: American Psychological Association; 1999:39–63
19. Hammen C. The emergence of an interpersonal approach to depression. In: Joiner T, Coyne J, eds. The Interactional Nature of Depression: Advances in Interpersonal Approaches. Washington, DC: American Psychological Association; 1999:21–36
20. Holahan CJ, Moos RH, Holahan CK, et al. Stress generation, avoidance coping, and depressive symptoms: a 10-year model. Consult Clin Psychol 2005;73:658–66
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
22. First MB, Gibbon M, Spitzer RL, et al. User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders. Washington, DC: American Psychiatric Association; 1996
23. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
24. Rabkin JG, Klein DF. The clinical measurement of depressive disorders. In: Marsella A, Hirschfeld R, Katz M, eds. The Measurement of Depression. New York, NY: Guilford Press; 1987:30–83
25. Beck AT, Rush AJ, Shaw BF, et al. Cognitive Therapy of Depression: A Treatment Manual. New York, NY: Guilford Press; 1979
26. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale. Psychopharmacol Bull 1973;9:13–28
27. Weissman AN. The Dysfunctional Attitude Scale: A Validation Study. PhD diss., Univ. of Pennsylvania, 1979. Abstract in Dissertation Abstracts International, publ. nr. AAT 7919533, DAI-B 40/03 (Sept 1979):1389–1390
28. Beck AT. Cognitive models of depression. J Cogn Psychother 1987;1: 5–37
29. Dozois DJ, Covin R, Brinker JK. Normative data on cognitive measures of depression. J Cons Clin Psychology 2003;71:71–80
30. Vingerhoets AJJM, van Tilburg MAL. Everyday Problem Checklist (EPCL). Lisse, the Netherlands: Swets & Zeitlinger BV; 1994
31. Kraaij V, de Wilde EJ. Negative life events and depressive symptoms in the elderly: a life span perspective. Aging Ment Health 2001;5:84–91
32. Garnefski N, Kraaij V, Spinhoven Ph. Negative life events, cognitive emotion regulation and emotional problems. Pers Individ Diff 2001; 30:1311–1327
33. Kraaij V, Garnefski N, de Wilde EJ, et al. Negative life events and depressive symptoms in late adolescence: bonding and cognitive coping as vulnerability factors? J Youth Adolescence 2003;32:185–193
34. Schreurs PJG, van de Willige G, Brosschot JF, et al. The Utrecht Coping List: UCL. Lisse, the Netherlands: Swets & Zeitlinger; 1988
35. Sanderman R, Ormel J. The Utrecht Coping List (UCL). Validity and reliability. Gedrag Gezond 1992;20:32–37
36. Garnefski N, Kraaij V, Spinhoven Ph. Manual for the Cognitive Emotion Regulation Questionnaire (CERQ). Leiderdorp, the Netherlands: Datec; 2002
37. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47: 1093–1099
38. Kupfer DJ, Frank E, Perel JM, et al. Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1992:49:769–773
39. Coryell W, Endicott J, Keller MB. Predictors of relapse into major depressive disorder in a nonclinical population. Am J Psychiatry 1991;148: 1353–1358
40. Surtees PG, Barkley C. Future imperfect: the long-term outcome of depression. Br J Psychiatry 1994;164:327–341
41. Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 1999;156:1000–1006
42. Kessing LV, Andersen PK, Mortensen PB, et al. Recurrence in affective disorder, 1: case register study. Br J Psychiatry 1998;172:23–28
43. Kessing LV, Hansen MG, Andersen PK, et al. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders: a life-long perspective. Acta Psychiatr Scand 2004;109:339–344
44. Lewinsohn PM, Rohde P, Seeley JR, et al. Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. Am J Psychiatry 2000;157:1584–1591
45. Teasdale JD. Cognitive vulnerability to persistent depression. Cogn Emotion 1988;2:247–274
46. Bockting CLH, Spinhoven Ph, Koeter MWJ, et al, and the DELTA study group. Differential predictors of response to preventive cognitive therapy in recurrent depression: a 2-year prospective study. Psychother Psychosom. In press
47. Hammen C. Generation of stress in the course of unipolar depression. J Abnorm Psychology 1991;100:555–561
48. Post RM, Weiss SRB. The neurobiology of treatment-resistant mood disorders. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1155–1170
49. Wells JE, Horwood LJ. How accurate is recall of key symptoms of depression? a comparison of recall and longitudinal reports. Psychol Med 2004;34:1001–1011