Improving long-term outcome of major depression in primary care

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Chapter 5

Enhanced treatment for depression in primary care: Long-term outcomes of a psychoeducational prevention program alone and enriched with psychiatric consultation or cognitive behavioral therapy

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Abstract

Background: The long-term outcome of major depression is often unfavorable, and since most depressions are managed by general practitioners (GPs), this stresses the need to improve treatment in primary care. This study evaluated the long-term effects of enhancing the GP's usual care with three experimental interventions.

Methods: Randomized controlled trial, conducted from 1998 through 2003. Main inclusion criterion was receiving GP treatment for a depressive episode. We compared: (1) usual care (UC; n=72), with UC enhanced with: (2) a psychoeducational prevention program (PEP; n=112); (3) psychiatrist-enhanced PEP (n=37); and (4) brief CBT-enhanced PEP (n=44). We assessed depression status quarterly during a three-year follow-up.

Results: Pooled across groups, depressive disorder-free time and symptom-free time during follow-up were 83% and 17%. Almost 64% of the patients had a relapse or recurrence, median time to recurrence was 96 weeks, and the mean BDI score over twelve follow-up assessments was 9.6. Unexpectedly, PEP patients had no better outcomes than UC patients. However, psychiatrist-enhanced PEP and CBT-enhanced PEP patients reported lower BDI severity during follow-up than UC patients (mean difference 2.07 (95% CI 1.13 – 3.00) and 1.62 (.70 – 2.55) resp.), and PEP patients (2.37 (1.35 – 3.39) and 1.93 (.92 – 2.94) resp.).

Conclusion: The psychoeducational prevention program had no excess benefit compared to usual care and may even worsen outcome in severely depressed patients. Enhancing depression treatment in primary care with psychiatric consultation or brief CBT seems to improve long-term outcome, but findings need replication as the interventions were combined with the ineffective psychoeducational prevention program.

Introduction

Major depression is a highly prevalent mental disorder that frequently runs a chronic, intermittent lifelong course, with incomplete remission from episodes (Simon, 2000; ESEMeD/MHEDEA 2000 consortium, 2004a). The disorder is associated with significant social, emotional and physical dysfunction (e.g. Ormel *et al*. 1994; Buist-Bouwman *et al.* 2006). Approximately 50% of all first ever episodes is followed by one or more recurrences and with each recurrence the risk of a subsequent recurrence increases (Solomon *et al*. 2000). Residual symptoms, disability and vulnerability are not uncommon after an episode of major depression, and may constitute a risk for recurrence (Paykel *et al.* 1995; Mueller *et al.* 1999; Ormel *et al*. 2004a,b).

These observations underline the necessity to improve the long-term outcome of depression. Since general practitioners (GPs) treat the majority of depressed patients (Tiemens *et al.* 1996; ESEMeD/MHEDEA 2000 consortium, 2004b) and patients generally do not like to be referred to mental health specialty settings, we carried out a randomized controlled trial in primary care. We compared: (1) usual care provided by the GP (UC), with UC enhanced by: (2) a psychoeducation prevention program alone (PEP); (3) psychiatric consultation followed by PEP (psychiatrist-enhanced PEP); and (4) brief cognitive behavioral therapy followed by PEP (CBT-enhanced PEP).

The PEP-program included in this study was inspired by relapse prevention programs for addicts (Marlatt & Gordon, 1985), self-management programs for chronically diseased (Lorig *et al.* 1993), and more directly by the psychoeducational program developed by Katon and colleagues (Katon *et al.* 1996; Ludman *et al.* 2000). The latter intervention mainly targeted medication adherence. We broadened its focus to include the enhancement of patients' self-efficacy by stressing the importance of the patient's (social) reactivation. A systematic review in various, mainly primary care settings (Badamgarav *et al.* 2003) reveals a small effect of disease management programs for depression on symptoms, but contains no information on recurrence rates.

We supplemented PEP by psychiatric consultation and brief CBT. Psychiatric consultation was added mainly to improve pharmacotherapy by the GP (Katon & Gonzales, 1994). A recent meta-analysis on randomized controlled trials on pharmacotherapy showed that maintenance treatment with antidepressants may have beneficial effects on long-term outcomes (Geddes *et al.* 2003). Ten to twelve sessions of CBT was added because CBT is effective in the acute phase treatment (Emmelkamp, 2004; Hollon & Beck, 2004), but also may improve outcomes in the longer term by reducing recurrence risk in outpatients as reanalyses of several studies by Hensley and colleagues (2004) show. However, none of these studies targeted primary care patients, and the few studies in which this was the case, reported contradictory outcomes or lack information on the long-term outcome (Scott *et al.* 1997; Ward *et al.* 2000; Simon *et al.* 2004).

In a previous article we reported the short-term depression outcomes of our study (Smit *et al.* 2006). At six-month follow-up, the three experimental interventions were no more effective than usual care concerning remission and recovery. In the present article we evaluate the long-term effects. We hypothesized that the PEP group would have better long-term outcomes than the UC group, and that the psychiatrist-enhanced PEP group and the CBT-enhanced PEP group would report better outcomes than both the PEP and the UC groups. Main outcome measures included: time from remission of the index-episode to recurrence; severity of depression during the three-year follow-up; proportions of time free from depressive disorder and free from depressive symptoms during follow-up, and relapse/recurrence rate. In the short-term outcome paper (Smit *et al.* 2006) the PEP-program was labeled the Depression Recurrence Prevention (DRP) program. Because this label inadvertently emphasized too strongly recurrence in comparison to other aspects of long-term outcome, we changed the name.

Method

Design and randomization

The study was designed as a randomized controlled effectiveness trial in primary care practices with usual care as the reference group and was conducted from January 1998 till June 2003. Most patients were followed up to three years, a minority for 24 to 33 months. Patients were stratified with regard to antidepressant usage at baseline. They were randomly allocated to one of four conditions by means of a computer-generated random allocation list, organized in blocks of 21 with a ratio of 2:3:1:1 for UC, PEP, psychiatrist-enhanced PEP and CBT-enhanced PEP resp. The decision to allocate smaller numbers to the psychiatrist-enhanced PEP and CBT-enhanced PEP groups was based on limited resources, the anticipated greater effect sizes for both interventions as compared to PEP and UC, and the priority given to the main comparison of PEP versus usual care. The sampling ratio of three patients to PEP and two to the UC condition was applied in order to optimize analyses within patients receiving PEP.

Setting, patients and inclusion criteria

We asked 80 GPs in the northern part of the Netherlands to participate in the trial and to refer patients aged 18-70 years, who were currently in treatment for a major depressive episode by their GP, who had a history of one or more major or minor depressive episodes (were at risk for an unfavorable course), and were not suffering from a life threatening medical condition. 49 GPs agreed and referred 397 patients in 41 months. After a short telephone screening, eligible patients were provided with detailed verbal and written information on the study, in order to obtain their consent. Subsequently, all eligible patients were interviewed, at the patient's home or in the GP's practice, by an experienced research assistant using the computerized lifetime version of the CIDI (WHO, 1997; Ter Smitten *et al.* 1998), in order to check: (1) whether the patient met the diagnostic criteria for major depression at the time of the interview (baseline), or had met these criteria in the past three

months (recent major depressive episode); and (2) the presence of additional exclusion criteria: psychotic disorder, bipolar disorder, dementia, primary alcohol or drug dependency or abuse, pregnancy, and receiving treatment for depression in a specialty mental health setting.

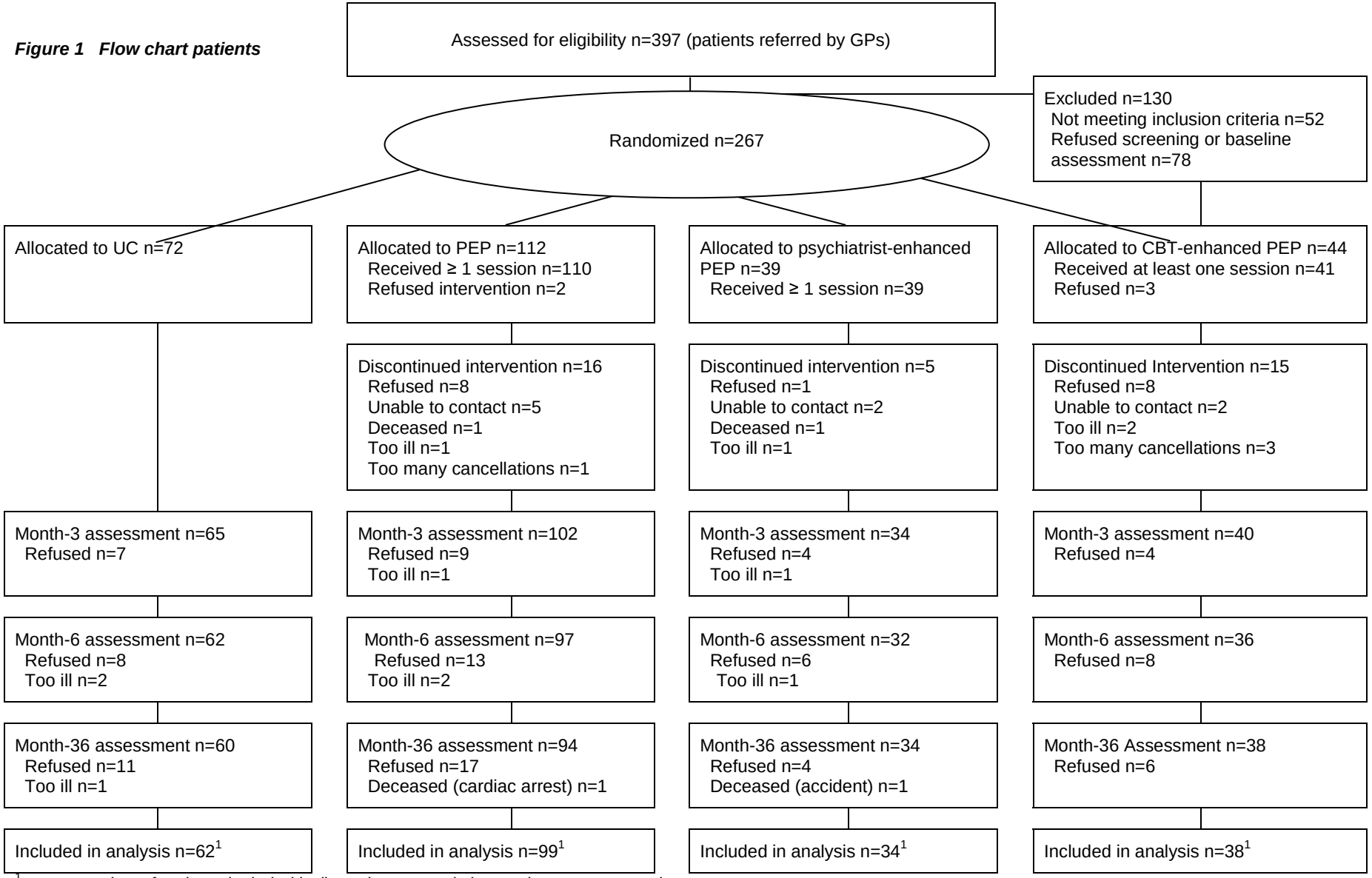
Of the 397 GP-referred patients, 267 met study criteria and were randomized (see Flowchart in Figure 1). Once the diagnosis of (a recent) major depression was confirmed by the CIDI, the interviewer contacted a research assistant by telephone, who opened the first sealed opaque envelope from the set representing the actual AD-stratum and informed the interviewer on treatment allocation. Although not encouraged, (self-) referral to mental health professionals was possible.

Interventions

Usual Care (UC). The control condition was UC by the GP. The clinical guidelines, issued by the Dutch College of General Practitioners (Marwijk *et al.* 1994), suggest brief supportive counseling, antidepressant prescription and eventually referring to psychological therapy or specialty psychiatric treatment. Dutch GPs are gatekeepers to specialist physical and mental health care services and regularly refer for additional psychotherapy. All conditions in the trial included usual care, because we wanted to test the excess benefit of the experimental interventions.

Psycho-Educational Prevention (PEP) program. The PEP program aims to improve the long-term outcome of depression through strengthening the patient's self-efficacy and proactive self-management skills, applying predominantly psychoeducational techniques. The intervention and the accompanying book and video the patient received, were developed by Katon and co-workers at the Center for Health Studies of the University of Washington in Seattle, United States (Katon *et al.* 1996; Ludman *et al.* 2000) and adapted for use in the Netherlands (Tiemens *et al.* 1998). Adherence to the PEP-protocol by the three PEP providers (an experienced psychiatric nurse and two psychologists) was monitored by the project psychiatrist (JJ).

Figure 1 Flow chart patients



[1] mean number of patients included in (intention-to-treat) depression outcome analyses

The PEP program started mostly within the first week after randomization. First, patients attended three individual face-to-face sessions (90 minutes each), which debouched into a patient tailored depression prevention plan. These plans contained the following parts: (1) regular self-registration of symptoms and warning signs to identify deterioration and recurrence in an very early stage; (2) personalized stress coping strategies; (3) (social) reactivation; (4) when appropriate a medication plan (how to cope with aversive effects of antidepressants?, and stimulation to contact the GP when necessary on medication issues); and (5) an emergency plan (what to do if depression returns?). A copy of the prevention plan was send to the GP, who remained responsible for the patient's care.

Second, a continuation phase of quarterly telephone-based contacts of approximately 20 minutes followed for a three-year period. Goals were monitoring of depressive symptoms on basis of the patient's self-registration, to discuss all symptoms, to adjust the prevention measures if needed, and to motivate patients to comply with their prevention plan (Smit *et al.* 2005). For that, PEP providers were trained in motivational interviewing (Miller & Rollnick, 1991).

Psychiatric Consultation plus PEP (psychiatrist-enhanced PEP). Patients in this condition first had an appointment of one hour with one of two study psychiatrists, who advised the patient's GP on treatment, particularly on type and dosage of antidepressant medication. Subsequently patients followed the PEP-program.

Brief Cognitive Behavioral Therapy (CBT-enhanced PEP) Before entering the PEP-program, patients attended ten to twelve individual 45 minutes sessions of cognitive behavioral therapy (Emanuels-Zuurveen & Emmelkamp, 1996; Boelens, 1997). The CBT was guided by a manual and provided by one of three clinical psychologists. They were supervised by a senior CB-therapist who monitored adherence to the treatment protocol during supervision. The protocol employed behavioral strategies based on Lewinsohn's operant model (Lewinsohn, 1975) and cognitive strategies based on Beck's cognitive model (Beck *et al.* 1979). The therapist motivated the patient for (social) reactivation by agreeing on a daily scheme of pleasurable activities. When patients lacked social skills, social skills

training became part of therapy. Restructuring of dysfunctional cognitions was not limited to specific situation contingent cognitions, but also included the patient's core assumptions. At the conclusion of the CBT, the therapist informed the provider of the PEP-program by letter on the main themes and results of the therapy and possible pitfalls of the patient.

Outcome measures

We collected outcome data by telephone every three months and mailed questionnaires every six months. At baseline and at the end of follow-up patients received a face-to-face interview.

Instruments The face-to-face interviews included the anxiety and phobic disorders, depression and dysthymia, and bipolar disorder sections of the *Composite International Diagnostic Interview* (CIDI), a structured psychiatric interview with good reliability and validity (Wittchen, 1994; Andrews & Peters, 1998). The three-monthly telephone interviews included an adapted CIDI depression section, with which we were able to measure the presence of each of nine DSM-IV criteria of depression per week in the bygone three months. In this way we could establish whether or not patients were meeting DSM-IV diagnostic criteria for a major depressive episode for each week during the entire follow-up period. The interviews also contained questions about medication use and health care utilization.

To determine severity of depression during follow-up we quarterly administered the *Beck Depression Inventory* (Beck *et al.* 1961). The BDI has 21 items, each consisting of four statements arranged in order of severity from absence of the symptom concerned, to very severe symptomatology. The Dutch BDI shows good reliability and validity (Luteijn & Bouman, 1988).

Depression outcomes We defined the outcomes in accordance with the consensus-paper of Frank (Frank *et al.* 1991) combined with DSM-IV criteria. A depressive episode is defined as two consecutive weeks of depression, remission as two to seven consecutive weeks without depression, relapse as two consecutive weeks of depression started *within*

remission, recovery as eight consecutive weeks without depression, and recurrence as two consecutive weeks of depression started *within* recovery.

In order to cover multiple aspects of the long-term course of depression, we used five outcome measures: (1) time from remission of the index-episode to recurrence (derived from the CIDI); (2) severity of depression during follow-up (BDI); (3) proportion depressive disorder-free time, i.e. the time during follow-up that the patient did not meet DSM-IV criteria for major depression (CIDI); (4) proportion depressive symptom-free time, i.e. the time during follow-up that the patient did not meet any of the nine DSM-IV criteria for major depression (CIDI); and (5) percentage of patients with at least one relapse/recurrence during follow-up (CIDI).

Statistical power

Based on our previous studies in primary care (Ormel *et al*. 1990; Brilman *et al.* 1992; Tiemens *et al.* 1996), we postulated at the time of the grant application submission in 1998, a cumulative relapse/recurrence at the end of follow-up in the UC, PEP, psychiatrist-enhanced PEP and CBT-enhanced PEP groups of 50%, 30%, 25% and 20% resp. To attain a statistical power of 80% for the time-related endpoints for rejecting the null-hypothesis of no difference between usual care on the one hand and PEP, psychiatrist-enhanced PEP and CBT-enhanced PEP on the other, approximately 60 evaluable patients in the UC group would be needed, 90 in the PEP, and 30 in the psychiatrist-enhanced PEP and CBT-enhanced PEP groups. Significance level was set at 5%, one-sided, given the directional hypothesis of excess benefit for the experimental conditions. Allowing for a loss to follow-up of approximately 15% the initial numbers to be included were at minimum 70 for UC, 105 for PEP, and 35 for psychiatrist-enhanced PEP and CBT-enhanced PEP.

Statistical analyses

All analyses were based on intention-to-treat. We examined whether we were able to improve regular practice by comparing UC with: (1) PEP (2) psychiatrist-enhanced PEP; and

(3) CBT-enhanced PEP. Additionally we evaluated whether we could enhance PEP by comparing that program with: (4) psychiatrist-enhanced PEP; and (5) CBT-enhanced PEP. Cox survival analysis was applied to compare groups on time from remission of the index-episode to recurrence; hazard ratios are given. Mixed model analysis (Bryk & Raudenbush, 1987), with the baseline BDI score as covariate, was used to evaluate differential change over time between groups on the twelve repeated measurements with the BDI during follow-up. For comparison of groups on proportions of depression-free and symptom-free time, antidepressant and health care utilization, we calculated median differences, because these variables were not normally distributed. Chi-square tests were applied to examine differences between groups on relapse/recurrence rates; odds ratios are provided. Although the a priori statistical power calculation was based on one-sided testing, the current convention prescribes two-sided testing. Therefore we provide 95% confidence intervals for the calculated mean and median differences, and the hazard and odds ratios to examine the statistical significance of group differences.

Results

Patient characteristics and non-response

The study sample was socio-demographically and clinically diverse (Table 1). Of all patients mean age was 42.8 years (11.3) and 65% was female. Mean BDI at baseline was 20.1 (9.4) and patients scored on average 6.0 (2.1) of the maximum of nine DSM-IV criteria for depression on the CIDI. Almost 80% of all patients met diagnostic criteria for major depression at baseline, while the other 20% met these criteria in the three months before baseline. From DSM-IV recurrent major depressive disorder suffered 67%, and 37% had experienced even more than three previous episodes of major depression.

Non-response for the twelve three-monthly telephone interviews ranged from 8.9% to 25.0%. In the course of the first five interviews non-response increased slightly but stabilized at an average of 20% thereafter. More than 85% of all randomized patients participated in the final follow-up assessment, usually 36 months after randomization. Two patients

Table 1 Socio-demographic and clinical characteristics at baseline

	UC n=72	PEP n=112	psychiatrist-enhanced PEP n=39	CBT-enhanced PEP n=44	ALL n=267
mean age (SD)	44.2 (11.3)	42.5 (10.6)	41.0 (13.0)	42.8 (11.6)	42.8 (11.3)
female	65.3%	65.2%	69.2%	54.5%	65.0%
social status					
married/cohabiting	68.1%	68.8%	66.7%	47.7%	64.8%
not married	12.5%	17.9%	17.9%	34.1%	19.1%
divorced	15.3%	9.8%	15.4%	13.6%	12.7%
widowed	4.2%	3.6%	-	4.5%	3.4%
educational attainment					
low	48.6%	42.0%	46.2%	38.6%	43.8%
medium	29.2%	41.1%	33.3%	38.6%	36.3%
high	22.2%	17.0%	20.5%	22.7%	19.9%
primary occupation					
employed	55.6%	65.2%	59.0%	56.8%	60.3%
homemaker	25.0%	17.0%	20.5%	13.6%	19.1%
other	19.4%	17.9%	20.5%	29.5%	20.6%
severity BDI	18.9 (9.5)	20.6 (9.3)	20.3 (9.8)	20.3 (9.3)	20.1 (9.4)
number of DSM-IV criteria for MDE	6.0 (2.3)	6.2 (2.0)	5.9 (2.3)	5.7 (2.1)	6.0 (2.1)
severity DSM-IV index-epsiode					
mild	28.2%	31.8%	35.9%	24.4%	30.3%
moderate	22.5%	38.2%	28.2%	34.1%	31.8%
severe	49.3%	30.0%	35.9%	41.5%	37.9%
recurrent DSM-IV depression	72.2%	63.4%	64.1%	71.4%	67.2%
> 3 DSM-IV depressive episodes	41.7%	32.1%	35.9%	41.9%	36.8%
mean age first onset (SD)	32.4 (14.3)	30.9 (11.8)	30.6 (15.4)	31.0 (12.9)	31.3 (13.2)
suicide attempt ever	12.5%	8.0%	10.3%	11.4%	10.1%
antidepressant medication	76.4%	74.1%	71.8%	72.7%	74.2%
last month comorbidity					
dysthymia	2.8%	11.6%	10.3%	6.8%	8.2%
panic disorder	12.5%	12..5%	15.4%	11.4%	12.7%
agoraphobia	8.3%	6.3%	12.8%	9.1%	8.2%
social phobia	13.9%	17.0%	15.4%	13.6%	15.4%

deceased during follow-up. A patient in the PEP condition died of cardiac arrest, the other in the psychiatrist-enhanced PEP group because of an accident. Socio- demographic and clinical characteristics at baseline were not associated with loss to follow-up.

Adherence to scheduled treatment contacts

Adherence in the psychiatrist-enhanced PEP group to the single psychiatric consult was 100%, and in the CBT-enhanced PEP group to the CBT sessions 75%. Adherence to the PEP face-to-face sessions, and thereafter to the follow-up contacts by telephone was 95.5% and 85.7% resp. in the PEP group, 97.4% and 87.2% in the psychiatrist-enhanced PEP condition, and 77.3% and 70.5% in the CBT-enhanced PEP group. Adherence to all scheduled sessions and telephone contacts was 84.8% in the PEP group, 87.2% in the psychiatrist-enhanced PEP group and significantly lower, 63.6%, in the CBT-enhanced PEP condition (x^2=10.417; df=2; p=.005).

Antidepressants and health care utilization

We compared groups on: (1) *proportion* of patients using antidepressants, or visiting their GP or psychotherapists outside the project during follow-up, and (2) *duration or frequency* of this utilization (Table 2). First, groups did not differ in proportions of patients using antidepressants or contacting their GP during follow-up, but a significant smaller proportion of CBT-enhanced PEP patients than UC and PEP patients contacted psychotherapists outside the project. Second, treatment groups did not differ in duration of antidepressants usage, but CBT-enhanced PEP patients less frequently visited their GP per year than usual care and PEP patients. Finally, within the *sub*group of patients who actually received additional psychotherapy, the number of sessions did not differ between treatment conditions.

Table 2 Antidepressants and health care utilization

	UC n=62/69[1]	PEP n=99/107[1]	psychiatrist-enhanced PEP n=33/37[1]	CBT-enhanced PEP n=37/42[1]		UC vs. PEP	UC vs. psychiatrist-enhanced PEP	UC vs. CBT-enhanced PEP	PEP vs. psychiatrist-enhanced PEP	PEP vs. CBT-enhanced PEP
AD										
% users during fu	79.0%	80.8%	84.8%	64.9%	odds ratio (95% CI)	1.12 (.51 – 2.46)	1.49 (.48 – 4.60)	.49 (.20 – 1.22)	1.33 (.45 – 3.90)	.44 (.19 – 1.02)
median prop. time usage during fu	.34 (0.08 – 0.81)	.39 (0.10 – 0.80)	.51 (0.17 – 0.89)	.26 (0.00 – 0.83)	median diff. (95% CI)	0.04 (-0.21 – 0.29)	0.17 (-0.20 – 0.53)	0.09 (-0.30 – 0.48)	0.12 (-0.22 – 0.47)	0.13 (-0.24 – 0.50)
GP										
% users during fu	97.1%	99.1%	100%	92.9%	odds ratio (95% CI)	3.16 (.28 – 35.58)	–[2]	.39 (.06 – 2.43)	–[2]	.12 (.12 – 1.21)
median no. visits per year (IQR)	3.85 (2.29 – 6.53)	4.33 (2.58 – 6.93)	3.62 (2.45 – 6.16)	2.29 (1.31 – 4.75)	median diff. (95% CI)	0.48 (-0.75 – 1.71)	0.23 (-1.20 – 1.66)	1.56 **(0.01 – 3.11)**	0.71 (-0.70 – 2.12)	2.04 **(0.51 – 3.57)**
psychotherapy[3]										
% users during fu	40.6%	40.2%	45.9%	21.4%	odds ratio (95% CI)	0.98 (.53 – 1.82)	1.25 (.56 – 2.79)	0.40 **(.17 – .96)**	1.27 (.60 – 2.69)	0.41 **(.18 – .93)**
median no. visits per year **of users only** (IQR)	4.61 (2.62 – 11.1)	6.03 (2.62 – 11.77)	3.90 (1.84 – 6.17)	5.61 (2.12 – 9.94)	median diff. (95% CI)	1.43 (-1.47 – 4.32)	0.71 (-1.83 – 3.24)	1.01 (-4.73 – 6.83)	2.13 (-0.38 – 4.64)	0.42 (-4.95 – 5.79)

[1] first and second numbers are numbers of: patients included in analyses on AD usage, and patients included in analyses on GP and psychotherapy visits resp.
[2] not possible to calculate due to 100% users in the psychiatrist-enhanced PEP group
[3] psychotherapy = private practices ran by psychologists and/or psychiatrists and psychotherapy in secondary care and psychiatric policlinics

Depression outcomes: all patients

Median time from remission to recurrence was 96.00 weeks. Patients reported a mean of 9.62 on the BDI during follow-up, and median proportion of follow-up time free of depressive episodes was 83% while median proportion time of follow-up totally free of DSM-IV depressive symptoms was 17%. One third of the patients did not relapse or suffer from a recurrence during the follow-up.

Depression outcomes: PEP versus UC

Table 3 and Figure 2 present the long-term outcomes. The PEP and UC groups did not differ in time from remission of the index-episode to recurrence, although there was a non significant trend towards a more favorable outcome for UC. Median duration was 129.00 weeks for UC patients and 71.00 for PEP patients. Mixed model analysis of the twelve quarterly BDI-measurements during follow-up (Figure 2) revealed no difference between UC and PEP, nor did any of the other long-term outcome measures differ significantly.

Depression outcomes: psychiatrist- and CBT-enhanced PEP versus PEP and UC

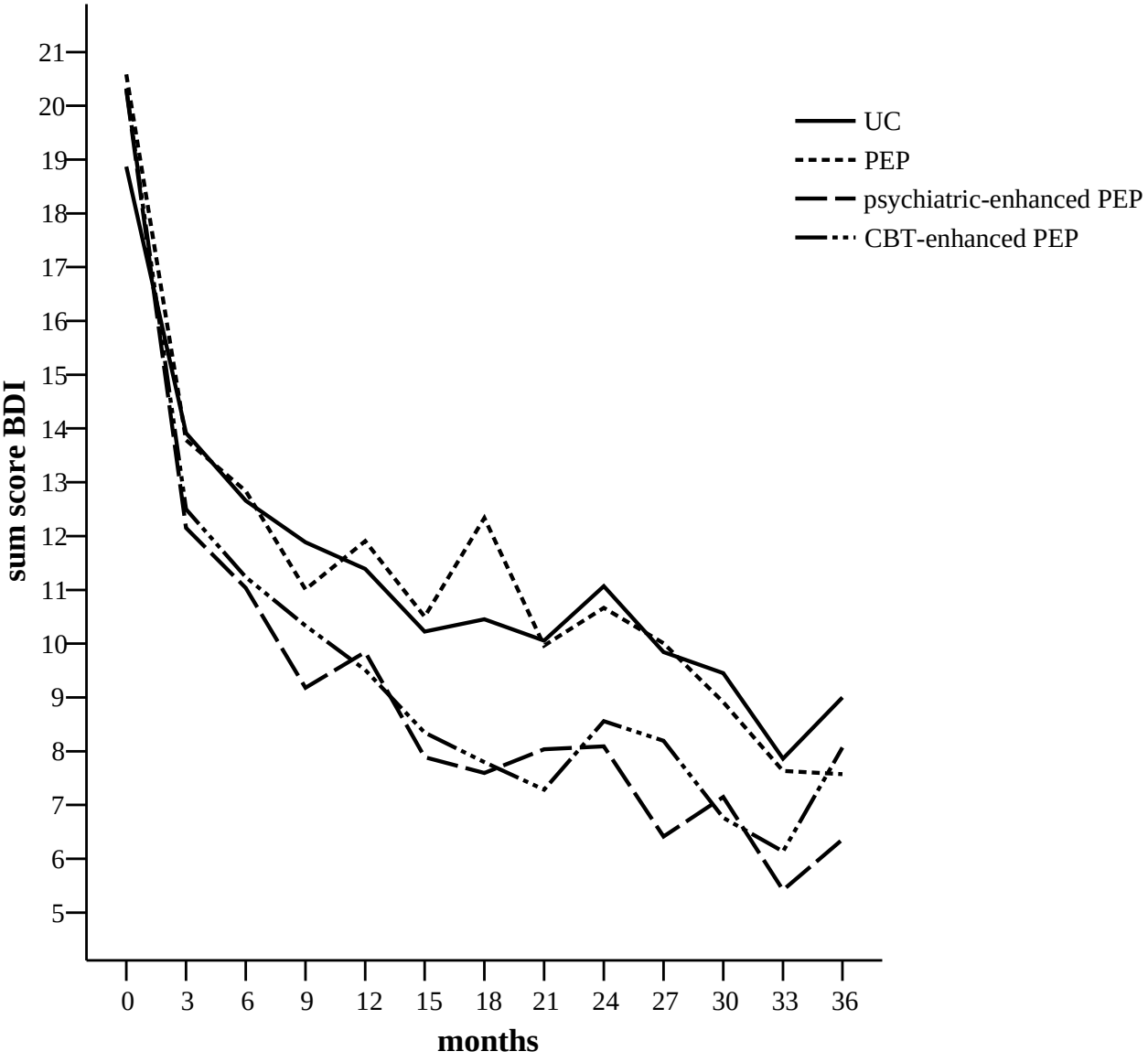
Because PEP did not improve outcomes relative to UC, we were not only interested in the comparisons of both enriched PEP interventions with UC, but with PEP-alone as well (are we able to improve PEP?). Analyses of time from remission of the index-episode to recurrence revealed no differences between groups; median duration in weeks was 149.00 for psychiatrist-enhanced PEP patients and 106.00 for CBT-enhanced PEP patients. Mixed model analyses of the twelve BDI assessments (Figure 2) showed that psychiatrist-enhanced PEP and CBT-enhanced PEP patients did better than UC and PEP patients. Although the differences were statistically significant only for the BDI, they were for some other outcomes rather substantial, such as the 9% and 6% differences of the two enhanced PEP conditions with PEP-alone in proportion of depression-free time which is equivalent to 12 and 8 weeks of major depression (Table 3).

Table 3 Long-term depression outcomes during 3-year follow-up

	UC n=62[1]	PEP n=99[1]	psychiatrist-enhanced PEP n=34[1]	CBT-enhanced PEP n=38[1]		UC vs. PEP	UC vs. psychiatrist-enhanced PEP	UC vs. CBT-enhanced PEP	PEP vs. psychiatrist-enhanced PEP	PEP vs. CBT-enhanced PEP
median (95% CI) time from remission index-episode to recurrence	129.00 (75.41 – 182.59)	71.00 (30.15 – 111.85)	149.00[2]	106.00[2]	hazard ratio (95% CI)	1.45 (.93 – 2.24)	1.09 (.60 – 1.96)	1.13 (.64 – 2.01)	0.77 (.45 – 1.32)	0.79 (.47 – 1.33)
mean (SE) BDI from 3 to 36 months adjusted for baseline BDI	10.77 (.32)	10.47 (.24)	8.40 (.41)	8.85 (.40)	mean difference (95% CI)	.30 (-.49 – 1.09)	2.37 **(1.35 – 3.39)**	1.93 **(.92 – 2.94)**	2.07 **(1.13 – 3.00)**	1.62 **(.70 – 2.55)**
median (IQR) proportion depression-free time	.84 (.61 – .93)	.79 (.57 – .91)	.88 (.71 – .94)	.85 (.66 – .94)	median difference (95% CI)	.05 (-.03 – .13)	.04 (-.07 – .15)	.01 (-.07 – .09)	.09 (-.02 – .20)	.06 (-.02 – .14)
median (IQR) proportion symptom-free time	.21 (.00 – .53)	.12 (.00 – .55)	.17 (.04 – .45)	.23 (.00 – .54)	median difference (95% CI)	.09 (-.09 – 0.27)	.04 (-0.16 – 0.24)	.02 (-0.26 – 0.23)	.05 (-0.16 – 0.26)	.11 (-0.14 – 0.35)
% of patients with relapse or recurrence	63.93%	69.07%	57.58%	55.55%	odds ratio (95% CI)	1.26 (.64 – 2.48)	.77 (.32 – 1.82)	.71 (.30 – 1.63)	.61 (.27 – 1.37)	.56 (.26 – 1.23)

[1] numbers vary by outcome measure, given numbers are mean numbers over all outcome measures
[2] due to insufficient events the 95% CI of the median could not be computed

Figure 2 BDI curves during 3-year follow-up



Stratum specific analyses

Stratum specific analyses were restricted to patients in the stratum of antidepressant usage at baseline (+AD) because only 26% of patients were not using an antidepressant at that time. These analyses replicated the results in the whole sample regarding the twelve BDI measurements. We found no excess benefit for PEP compared to UC, but both enhanced PEP groups reported significantly better outcomes on the BDI during total follow-up relative to UC and PEP. Moreover, the CBT-enhanced PEP+AD group also reported a lower

relapse/recurrence percentage during total follow-up compared to PEP+AD patients, 50.0% vs. 74.6% (odds ratio=.34; 95% CI: .13 – .84).

Subgroup analyses

We conducted secondary analyses, limited to the twelve BDI measurement during follow-up with baseline BDI as covariate, in three subgroups: (1) severely depressed patients at baseline, because we wanted to examine whether light interventions can be useful or harmful for severe problems; (2) patients who attended sessions in the face-to-face phase of their treatment condition (completers); and (3) patients who were highly compliant with the PEP-component of their treatment (patients with a self-reported score above the median on compliance with their prevention activities early in the project), in order to examine the possibility that PEP did not outperform usual care because patients insufficiently complied with the measures in their prevention plans. In Table 4 mean differences and 95% CIs are displayed. Mean differences we found were in line with the trend in the whole sample on the BDI: psychiatrist-enhanced PEP and/or CBT-enhanced PEP patients did better than the PEP-alone and/or UC groups, with UC and PEP not differing from each other. Two deviations from this pattern were noticeable. In the 'highly PEP-compliant' group PEP patients did better than UC, while usual care patients with a severe index-episode did better than their PEP counterparts. In the groups with a mild or moderate index-episode (not displayed in Table 4), PEP patients did *not* outperform UC patients as well, while psychiatrist-enhanced and/or CBT-enhanced PEP patients did better than the UC and/or PEP groups.

Table 4 Subgroup analyses on the twelve BDI measurements during 3-year follow-up

	mean BDI from 3 to 36 months adjusted for baseline BDI (SE); number of patients in analysis				mean difference (95% CI)				
	UC	PEP	psychiatrist-enhanced PEP	CBT-enhanced PEP	UC vs. PEP	UC vs. psychiatrist-enhanced PEP	UC vs. CBT-enhanced PEP	PEP vs. psychiatrist-enhanced PEP	PEP vs. CBT-enhanced PEP
severely depressed at baseline	12.42 (.51); 32	14.21 (.51); 31	10.25 (.80); 13	11.00 (.77); 17	1.79 **(.37 – 3.21)**	2.18 **(.31 – 4.04)**	1.42 (-.39 – 3.23)	3.97 **(2.10 – 5.83)**	3.21 **(1.39 – 5.03)**
completers	10.80 (.32); 63	10.46 (.25); 91	8.43 (.41); 34	8.73 (.42); 26	.34 (-.45 – 1.14)	2.37 **(1.35 – 3.39)**	2.07 **(1.03 – 3.11)**	2.03 **(1.09 – 2.97)**	1.73 **(.77 – 2.69)**
highly PEP-compliant	10.69 (.29); 63	7.62 (.32); 46	8.34 (.58); 14	6.96 (.57); 16	3.07 **(2.22 – 3.92)**	2.35 **(1.08 – 3.61)**	3.72 **(2.47 – 4.98)**	.72 (-.57 – 2.01)	.65 (-.63 – 1.93)

Finally, we examined whether providers of the experimental interventions with clear differences in educational background or clinical experience, i.e. the PEP-providers and CBT-therapists, achieved different results on the BDI during follow-up. Within the group of PEP-providers we found no difference between the nurse and the two psychologists, within the group of CB-therapists we found that the senior therapist achieved a significantly better result on the mean BDI during a two-year follow-up (7.86) relative to the other CBT-enhanced PEP, PEP and UC patients (10.40 to 11.70). Only with the psychiatrist-enhanced PEP group (9.66) the difference did not reach significance , probably due to the small number of patients.

Discussion

To our knowledge, this study is the first randomized controlled trial of enhanced treatment for depression in primary care that studied long-term outcome through regular assessments during a three-year follow-up. Contrary to expectations, we did not find evidence that the experimental psychoeducational prevention (PEP) program had excess benefit compared to the GP's usual care (UC). More in line with our expectations, was that the two additions to the PEP-program, psychiatric consultation and brief cognitive behavioral therapy, did improve the long-term outcome compared to usual care and PEP-alone. Both enhanced PEP groups, who by definition also received the ineffective PEP-program, reported a lower mean on the quarterly administered BDI during follow-up relative to UC and PEP-alone; a result repeated within the stratum of patients on antidepressants at baseline. In the same stratum, the CBT-enhanced PEP group suffered from a significant lower relapse/recurrence rate of 25% than PEP-alone patients as well.

Strengths and limitations

Strengths of this study are the very good (PEP and psychiatrist-enhanced PEP) to reasonable (CBT-enhanced PEP) treatment attendance, feasibility of the PEP-intervention in primary care (Smit *et al.* 2005), the long-term follow-up, the quarterly monitoring of

depression status and health care utilization during follow-up, and satisfying follow-up response rates. There are also limitations which should be taken into account when interpreting our findings. First, we did not succeed in blinding interviewers completely since patients every now and than spontaneously commented on their treatments. Second, within the constraints of the in- and exclusion criteria the GPs selected the patients themselves, which might limit the generalizability of the findings. Third, the study was designed as a randomized controlled effectiveness trial in primary care with usual care as the reference group. Although not encouraged, (self-) referral to mental health professionals did occur in all groups. Especially the rate of additional brief psychotherapy or counseling from a primary care psychologist during follow-up was substantial in all groups. This may have blunted contrast between groups if it has been differentially effective. However, correction for non-scheduled psychotherapy during follow-up is hard to interpret, as it may not have been independent of the course of the depression. A similar line of reasoning may account for usage of antidepressants during follow-up. Therefore, we did not correct for additional psycho- and pharmacotherapy during follow-up. As a consequence, the ecological and pragmatic validity of the study is high (what is the effect of the delivered treatments in daily practice?), at the expense of a less straightforward interpretation of the effectiveness of the interventions. Finally, the timing of the experimental interventions was pragmatic in that they started directly after randomization irrespective of whether the depression was in (partial) remission or not.

Why does the PEP-program not outperform usual care in the long run?

We consider several explanations: potential type II errors, limited treatment intensity and potential sensitizing effects, and the possibility of a ceiling effect.

Although underpowerment is a common criticism on negative trials, we do not think that more power would have resulted in statistically and clinically significant differences in favor of the PEP-program, because the absolute differences between UC and PEP were small and mostly in favor of UC, not PEP.

In general, the long-term outcomes of psychoeducationally oriented treatment programs for depression in primary care, predominantly published after the start of our project, have not yielded clear results (Mynors-Wallis *et al.* 1995; Mynors-Wallis *et al.* 2000; Rost *et al.* 2002). Our results are only marginally different from the meager one-year outcome observed by Katon et al. (2001) for the original PEP-program (on which ours was based). Although in that study antidepressant adherence improved and the average severity of depression slightly decreased, relapse/recurrence rates of patients in UC and in the PEP-program were similar. Katon and colleagues concluded their program had too little intensity to attain major improvements in depression outcomes. This seems a plausible explanation for the ineffectiveness of the PEP-program in our study as well. The chosen format of PEP, characterized by a low number of face-to-face contacts, minimal telephone contacts thereafter and deliberately not provided by therapists, was apparently too restricted to be effective in this group of vulnerable patients.

Moreover, low-intensity and long-lasting (psychoeducational) programs like PEP may have sensitizing effects on patients (Frasure-Smith *et al.* 1997). The systematic screening every three months of (residual) depressive symptoms may have increased the patient's awareness and sensitivity about their vulnerability for depression. Possibly this could not be counterattacked sufficiently by the PEP-program, because of the combination of its limited intensity and the fact that the providers were no trained psychotherapists, and not necessarily as a consequence of the psychoeducational elements of PEP itself. The finding that the subgroup of severely depressed UC patients at baseline, were significantly better off than the severely depressed PEP subgroup is interesting in this context. This does not mean that PEP-program was ineffective for all PEP patients compared to usual care. Subgroup analyses revealed that PEP patients who were highly compliant with the prevention measures of the PEP-program reported a better outcome on the BDI than UC patients. However, the latter comparison may be biased, as we could not differentiate between compliant and non compliant UC patients.

Finally, the ineffectiveness of PEP could be due to the possibility that the long-term treatment by the GP is highly effective and hard to outperform. However, this seems unlikely because 64% of the UC patients suffered a relapse or recurrence at least once and they were only 17% of the time free from any DSM-IV depressive symptom. These outcomes leave sufficient room for improvement, ruling out the possibility of a ceiling effect.

Psychiatric consultation and cognitive behavioral therapy

Interpretation of the results of the psychiatric and CBT enhancements is somewhat complicated by the fact that these interventions were combined with the ineffective PEP-program, that in patients suffering from severe depression even worsened long-term outcomes. Although both additions to PEP significantly outperformed usual care on BDI severity during follow-up, on other outcomes no differences were found. We discuss three possible explanations for this.

First, the possibly negative effect of the PEP-program in the psychiatrist-enhanced PEP and CBT-enhanced PEP groups might have downplayed the positive effects of psychiatric consultation and CBT. Possibly the difference between UC versus psychiatrist-enhanced PEP and CBT-enhanced PEP would become more salient if we were able to eliminate the assumed negative effect of PEP in both groups.

A second explanation for the lack of improvement relative to usual care on other outcomes than BDI severity, is limited treatment intensity of the CBT and psychiatric consultation components. The latter consisted of one single consultation with a psychiatrist that nonetheless resulted in 12 weeks longer duration of antidepressant usage compared to the PEP group. The consultation perhaps also improved type and dosage of the medication. However, to substantially ameliorate the long-term outcome, we think the vulnerable patient group in this study may need intensified psychiatric consultation, for example more regular contacts with a psychiatrist than the single consultation in psychiatrist-enhanced PEP.

Concerning CBT, successful studies mainly in outpatient settings with longer term follow-up, suggest that more intense acute treatment eventually followed by booster sessions, yield

better results than control treatments (Blackburn *et al*. 1986; Paykel *et al*. 1999/2005; Jarrett *et al*. 2001; Hensley *et al*. 2004). Interestingly, treatment intensities of CBT in these studies were all higher than CBT in the current study, ranging from 15 to 30 sessions (including booster sessions), while CBT in inconclusive or negative studies consisted of only 5 to 7 sessions (Scott *et al.* 1997; Ward *et al.* 2000). Mean number of sessions attended in the brief CBT of our study was 9.66 (4.1).

Third, especially in the case of *brief* CBT several studies (Scott *et al.* 1997; Paykel *et al.* 1999; DeRubeis *et al.* 2005) stress the importance of treatment experience. Subgroup analysis on the twelve BDI measurements revealed that patients treated by the most experienced CB-therapist reported relative to patients in the other groups a lower BDI-score. Taken together this suggests that prolonged CBT delivered by experienced CB-therapists may result in better outcomes. Combination with antidepressant therapy may yield even better results (Keller *et al.* 2000).

Conclusion

Enhancement of UC by the psychoeducational prevention (PEP) program did not result in better long-term patient outcomes; in some cases the PEP group did even worse. The long-term outcome of depression may be driven by autonomous processes fuelled by genetic and environmental vulnerabilities in part of the recurrent patient population (Post *et al.* 1999; Ormel *et al.* 2004a,b; Monroe & Harkness, 2005). Neurophysiologic abnormalities and deeply ingrained dysfunctional cognitive and behavioral patterns, may be difficult to treat or compensate and probably need more intensive treatment than usual care plus PEP in primary care. The modest improvement in long-term outcome that was found in the psychiatrist-enhanced PEP and CBT-enhanced PEP groups compared to usual care, suggests that: (1) more intense CBT followed by booster sessions over a protracted period of time delivered by experienced therapists, and/or (2) intensified psychiatric consultation to define optimal antidepressant maintenance therapy (e.g. Geddes *et al*. 2003), might be an

effective combination of acute, maintenance, and prophylactic treatment of recurrent major depression in primary care.