Improving long-term outcome of major depression in primary care

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Chapter 6

Cost-effectiveness of a recurrence prevention programme for depression in primary care

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Abstract

Background

Major depression often runs a chronic-recurrent course with multiple episodes during the life course, and is associated with a considerable economic burden for society. The present study examined the cost-effectiveness of a Psycho-Educational Prevention programme (PEP) aimed at improving the long-term outcome of depression in primary care.

Methods

Patients with depression were randomly assigned to four intervention arms; PEP only, PEP with psychiatric consultation (PEP+PC), PEP with cognitive behavioural therapy (PEP+CBT), and care as usual (CAU). The economic evaluation was performed from a societal perspective, costs and health outcomes were registered during a period of 36 months. Proportion of depression-free time was used as the primary outcome measure in the cost-effectiveness analysis.

Results

Mean costs were €8200 in the CAU group, €9816 in the PEP group, €9844 in the PEP+PC group, and €9254 in the PEP+CBT group. Health outcomes in the PEP+PC and PEP+CBT groups were slightly better than in the CAU group. PEP+CBT had the most positive outcomes of the three PEP interventions, as indicated by cost-effectiveness acceptability curves.

Conclusions

The basic PEP intervention was not cost-effective in comparison with CAU. For the other variants of PEP, costs were higher but health outcomes were slightly better. If decision-makers are willing to pay up to €1500 for an additional proportion of depression-free time, the probability that PEP+CBT will be cost-effective increases to 70%. Findings of this study seem to provide little support for the implementation of PEP in current healthcare systems.

Introduction

Major depression is a prevalent mental disorder that often runs an intermittent lifelong course, with multiple relapses and recurrences, and frequently incomplete remission between episodes. It is considered to be among the most disabling illnesses (Üstün *et al.* 2004), and both treated and untreated depression negatively affects many aspects of life (Wells *et al.* 1989; Ormel *et al.* 1994, 2004). From an economic perspective, the consequences of depression are substantial as well. It has been estimated that 1-2 % of national healthcare expenses in Western countries is spent on the treatment of depressive disorders (Polder *et al.* 2002; Greenberg *et al.* 2003). Important factors contributing to the considerable costs associated with depression are the high prevalence, early age of onset, and large risk of relapse and recurrence. Moreover, for many patients depression becomes a chronic condition, leading to an extensive use of healthcare resources in subsequent years. When including costs outside the healthcare sector, like costs of productivity losses, the financial consequences of depression are even considerably larger (Berto *et al.* 2000).

Since depression has such a large impact on national healthcare budgets, information on the cost-effectiveness of alternative interventions in depression, aiming to improve the relation between costs and health outcomes, is highly relevant for decision-makers. Various economic evaluations focusing on both psychopharmacological therapies and psychologically oriented interventions for depression have been conducted, but no strong (economic) preference for a single approach can currently be identified (Barrett *et al.* 2005; Bosmans, 2006).

Only a few economic studies specifically focused on the prevention of relapse and recurrence, despite the high risk of recurrences in patients with depression and the associated negative long term consequences in terms of both health outcomes and costs (Mc Intyre & O'Donovan 2004). In order to improve long term outcomes of patients with depression, an intervention was developed to prevent recurrences. This Psycho-Educational Prevention programme (PEP: Katon *et al.* 1996; Tiemens *et al.* 1998) was designed to be carried out within primary care settings, since most patients with depression are treated in

primary care. PEP consists of contacts between patients and prevention workers, educational meetings on depression management, and telephone monitoring (Tiemens *et al.* 1998; Ludman *et al.* 2000; Smit *et al.* 2005). An economic evaluation focusing on the cost-effectiveness of PEP in primary care was recently performed, situated within the US healthcare system. In contrast to expectations, the study found only modest differences in favour of PEP (Simon *et al.* 2002).

The current study was conducted to provide information on the (cost-) effectiveness of PEP in a European healthcare system. The design of the present study differs in several respects from the US study. The PEP programme was slightly adjusted (Tiemens *et al.* 1998; Smit *et al.* 2005) to the situation in The Netherlands. Additional treatment conditions were included in the design, consisting of two enhancements of PEP; the addition of psychiatric consultation (PEP+PC) and cognitive behavioural therapy (PEP+CBT). Furthermore, patients were followed during 36 months instead of 12 months.

This paper will present the results of the economic evaluation assessing the cost-effectiveness of three variants of PEP (added to care as usual) in comparison with care as usual for primary care patients with depression.

Material and Methods

The economic evaluation was part of a 36-month clinical study on the effectiveness of the PEP programme in primary care patients. Details on the design and results of the clinical study are provided elsewhere (Smit *et al.* 2005, 2006; Conradi *et al.* submitted).

Study population and randomisation procedure

Recruitment took place in the Northern part of the Netherlands, patients were referred by 49 general practitioners (GPs) working in the catchment area. Inclusion criteria required that patients were aged between 18 and 70, had no life threatening medical condition, and were diagnosed with a current, or only very recently in partial remission, DSM-IV major depression. Patients were excluded when suffering from psychotic disorder, bipolar disorder

or dementia, in case of alcohol or drug dependency, when pregnant, or when they were already receiving treatment for depression. Of the 397 patients initially referred by GPs, 267 met study criteria and were subsequently randomised. The applied randomisation procedure (Smit *et al.* 2006) was designed to assign most patients to the basic PEP condition and CAU, and less to PEP+PC and PEP+CBT. A sampling ratio of 2:3:1:1 was applied for CAU, PEP, PEP+PC, and PEP+CBT, respectively.

Interventions

Psycho-Educational Prevention program (PEP) 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 psycho-educational techniques. Patients attended three individual face-to-face contacts with trained prevention workers (one psychiatric nurse and two psychologists), followed by telephone monitoring contacts at three month intervals during the 36 months of the study. The PEP intervention, including the accompanying book and video, was developed by Katon and co-workers (1996) and translated and adapted to Dutch culture and healthcare system (Tiemens *et al.* 1998; Smit *et al.* 2005).

PEP with psychiatric consultation (PEP+PC) Before the start of the basic PEP program, patients had an appointment of one hour with a psychiatrist. The psychiatrist subsequently advised the GP in particular on psychopharmacological treatment of the patient.

PEP with cognitive behavioural therapy (PEP+CBT) Before entering the basic PEP program, patients attended 10 to 12 individual 45 minute sessions of cognitive behavioural therapy (Boelens, 1997), provided by one of three clinical psychologists. At the conclusion of the CBT program, the therapist informed the prevention worker about the results of CBT.

Care as Usual (CAU) CAU was provided by the GP. In the Netherlands, treatment of depression by GPs consists of brief supportive counselling and antidepressant prescription, when needed referral to specialty psychiatric treatment. The variants of PEP provided in this study all included treatment by the GP to assess the additional benefit of PEP.

Outcome measures

Primary outcome measure of the study was the proportion of depression-free time (i.e. free of the diagnosis depressive disorder). This outcome was defined in accordance with the consensus-paper of Frank (Frank *et al.* 1991) combined with DSM-IV criteria. A depressive episode is defined as 2 consecutive weeks of depression, remission as 2 to 7 consecutive weeks without depression, relapse as 2 consecutive weeks of depression started *within* remission, recovery as 8 consecutive weeks without depression, and finally recurrence as 2 consecutive weeks of depression started *within* recovery. Power analyses were based on expected cumulated relapse/recurrence percentages of 50% in CAU, 30% in basic PEP, 25% in PEP+PC, and 20% in PEP+CBT.

Outcome measures were mainly collected by means of three-monthly interviews during the 36 months of the study. Additional outcomes included mean severity of depression during follow-up, proportion of symptom-free time (i.e. free of any DSM-IV depressive symptom), and percentage of patients who relapsed or met criteria for recurrent depression. Furthermore, the use of antidepressants was assessed.

The economic evaluation will mainly focus on the proportion of depression-free time. The results of additional outcome measures and clinical aspects of the study are presented elsewhere (Smit *et al.* 2005, 2006; Conradi *et al.* submitted).

Costs and unit prices

The economic evaluation was conducted from a societal perspective, costs were assessed both within and outside the healthcare sector. Medical costs that were registered included various types of costs related to inpatient and community care, general healthcare, and medication use. Costs that were relevant for all three variants of PEP included costs related to support provided by prevention workers trained in PEP, costs of regular telephone contacts with patients, and travel cost of the prevention workers. In the PEP+PC condition, additional costs were related to psychiatric consults. In the PEP+CBT condition, cognitive behavioural therapy (10 to 12 sessions by trained therapists) led to additional costs. Costs of

travelling and invested time by patients related to the PEP contacts were registered during the study. Costs of invested time were valued in monetary terms based on the net income of a patient during that time. Costs of informal care were based on the monetary valuation of the time invested by relatives or acquaintances in helping or assisting the patient. Additional costs related to the illness, like costs of non-prescribed medication, are referred to as out-of-pocket costs. The friction cost method (Koopmanschap *et al.* 1995; Jakob-Tacken *et al.* 2005) was applied for estimating costs associated with productivity losses.

Quantities of used resources were registered at three-month intervals for all the patients available at the various times of measurement. The information on costs was primarily collected by means of a questionnaire developed for the current study. This questionnaire assessed, among others, number of admissions to psychiatric hospitals, contacts with psychiatrists and psychologists, sick leave days of patients, and medication use. In order to facilitate comparisons with other economic evaluations, unit prices, i.e. the price of one unit of each included cost type (available on request), were mainly based on Dutch standard prices (Oostenbrink *et al.* 2000). True costs of used resources were estimated when standard prices were not available. All unit prices were based on the price level of the Euro in the year 2003. Reference prices established for previous years were adjusted to prices of 2003 by applying the consumer price index.

Cost-effectiveness analysis

In cost-effectiveness analysis, costs and the primary health outcome associated with an intervention are used to calculate the incremental cost-effectiveness ratio relative to one or more alternatives (Drummond *et al.* 1997). The main focus of the current study was on the comparison of costs and health outcomes between patients who received basic PEP and CAU, additional analyses addressed the extended types of PEP (PEP+PC and PEP+CBT). Primary outcome measure used in the cost-effectiveness analysis was the proportion of depression-free time. In the additionally planned economic analysis, Quality-Adjusted Life Years (QALY: Schwappach, 2002) were included as primary outcome measure. QALYs

combine life years and quality of life into one single outcome measure, and are calculated by multiplying observed survival with utilities. Utilities can be considered as the societal preference for health states. In the present study, raw scores of the EQ-5D (EuroQol Group, 1990) assessed at 6-month intervals were transformed into utilities by applying the algorithm of Dolan (Dolan, 1997). An important advantage of QALYs is that outcomes can be compared across studies and illnesses, which is required for prioritising between various health programmes on a national level.

The method applied for calculating incremental cost-effectiveness ratios (ICER) is provided below (only displayed for basic PEP).

$$ICER = \frac{(C_{PEP} - C_{CAU})}{(PDT_{PEP} - PDT_{CAU})}$$

Where
C_{PEP} = mean costs per patient in the PEP group
C_{CAU} = mean costs per patient in the CAU group
PDT_{PEP} = mean proportion depression-free time in the PEP group
PDT_{CAU} = mean proportion depression-free time in the CAU group

In the standard analyses, costs and health outcomes were discounted by 0%. Alternative discount rates (3% and 5%) were addressed in sensitivity analyses. Uncertainty surrounding the calculated ICERs was examined by the bootstrap method (Efron & Tibshirani, 1993). Bootstrapping is an iterative method that consists of randomly selecting patient data (with replacement) from the observed population to create a simulated distribution of data. ICERs were calculated for each of the bootstrap iterations (2000 in the present study), simulated values of the mean estimates for the cost and outcome differences were added to the cost-effectiveness plane (Black, 1990). Finally, cost-effectiveness acceptability curves (CEACs: Van Hout *et al.* 1994; Fenwick *et al.* 2004) were calculated. CEACs inform decision-makers on the probability that an intervention will be cost-effective for increasing monetary values placed on an additional unit of health outcome.

Statistical analysis

Results of longitudinal studies can be biased by missing data due to patients who drop out or are lost to follow-up, especially if their missingness is not completely at random (Little & Rubin, 1987). Recently, the potential impact of missing data has also been acknowledged in the area of economic evaluation (Briggs *et al.* 2003). In the current study, the expectation maximisation (EM) algorithm with a bootstrap approach (Oostenbrink & Al, 2005) was applied to deal with patients for whom not all the data were available at the various measurements. In the current study, the bootstrap method was used to create 2000 simulated patient populations, including patients with missing data. Subsequently, the EM-algorithm was applied for each of these 2000 data sets. The EM algorithm consists of an iterative process, estimating values for missing data based on the observed data. Finally, outcomes of these 2000 derived data sets were combined to estimate overall parameters, like overall means and confidence intervals.

Between-group baseline characteristics were analysed with Student's T-tests for continuous variables and Pearson chi-square tests for categorical variables. P-values less than 0.05 were considered statistically significant. All the analyses were carried out with SPSS 12.0.2 for Windows (SPSS, Inc, Illinois, USA).

Results

Patient characteristics at baseline

Mean overall age of the included patients was 42.8 years (SD=11.3), 65% was female, mean age at first onset of depression was 31.3 years (SD=13.2), 67% suffered from DSM-IV recurrent depressive disorder, and 36% had experienced more than three previous episodes of depression (for details see Smit *et al.* 2006). There were no statistically significant differences in clinical characteristics between groups at baseline, except for severity of depression (x^2=7.762, p=.02); patients in the CAU group were suffering from more severe depression than patients in the PEP group. Due to drop-out of patients during the study, results of the conducted longitudinal analyses presented in this paper are based on the data

of 226 patients (85% of the initially included patients): 69 in CAU, 107 in PEP, 33 in PEP+PC, and 36 in PEP+CBT. For these patients, relevant cost data could be collected and sufficient information was available to assess the proportion of depression-free time.

Service use and costs

Table 1 shows information on medical and non-medical cost. Means of each cost type are based on available patients per measurement in each group. If a patient did not make use of a specific cost type, costs of €0 were applied when calculating group means. In addition, the percentage of patients who actually used the health services concerned are presented as well.

Table 1. Medical and non-medical costs (€) during 36 months

	CAU Mean costs (%[1])	PEP Mean costs (%[1])	PEP+PC Mean costs (%[1])	PEP+CBT Mean costs (%[1])
Interventions				
Variants of PEP	0 (-)	748 (100)	911 (100)	1440 (100)
In-patient and semi-inpatient care				
Psychiatric hospital admission	692 (14)	528 (14)	1675 (24)	455 (17)
Psychiatric daycare	27 (6)	57 (10)	113 (19)	53 (10)
General daycare	262 (57)	244 (60)	385 (78)	210 (50)
Outpatient and community care				
Psychiatrist	82 (7)	205 (7)	151 (8)	80 (5)
Psychologist	97 (25)	121 (20)	118 (22)	20 (5)
Social worker	38 (14)	60 (17)	22 (11)	15 (10)
RIAGG [2]	857 (16)	646 (15)	168 (11)	1097 (7)
CAD [3]	0 (-)	19 (4)	0 (-)	0 (-)
Other care for addictions	0 (-)	98 (2)	30 (3)	0 (-)
Other outpatient care	143 (28)	153 (41)	43 (24)	94 (29)
General healthcare				
General practitioner	287 (97)	317 (99)	323 (100)	187 (93)
Physiotherapist	180 (33)	191 (36)	214 (27)	56 (26)
Manual therapist	14 (7)	23 (5)	3 (3)	0 (-)
Chiropractor	0 (-)	11 (5)	0 (-)	0 (-)
Hapto therapist	216 (10)	72 (11)	22 (5)	0 (-)
Home care	20 (17)	19 (11)	35 (16)	6 (7)
Medication				
Prescribed medication	498 (86)	510 (88)	463 (86)	399 (81)
Various non-medical costs				
Travel costs	6 (91)	9 (100)	9 (100)	11 (100)
Time costs	0 (-)	88 (100)	96 (100)	189 (100)
Informal care	154 (58)	189 (57)	125 (68)	100 (43)
Out-of-pocket costs	271 (14)	194 (21)	75 (11)	286 (24)
Productivity losses paid work	3442 (59)	4441 (70)	3896 (68)	3936 (64)
Productivity losses unpaid work	850 (15)	928 (15)	893 (16)	269 (5)

[1] Percentage of patients using the cost type concerned.
[2] Regional institution for mental healthcare.
[3] Consultation Office for Alcohol and Drug addiction.

Mean total costs of providing the basic PEP intervention were estimated at €748 per patient. Mean costs of PEP+PC and PEP+CBT were €911 and €1440, respectively. Costs related to care provided by general practitioners are presented separately for each of the intervention groups. Costs that contributed to a large extent to the total amount of costs were costs related to productivity losses, psychiatric hospital admissions, contacts with regional institutions for mental healthcare (RIAGG), and medication use. An overview of mean total costs generated during the study is presented in Table 2.

Table 2. Mean total costs (€) during 36 months

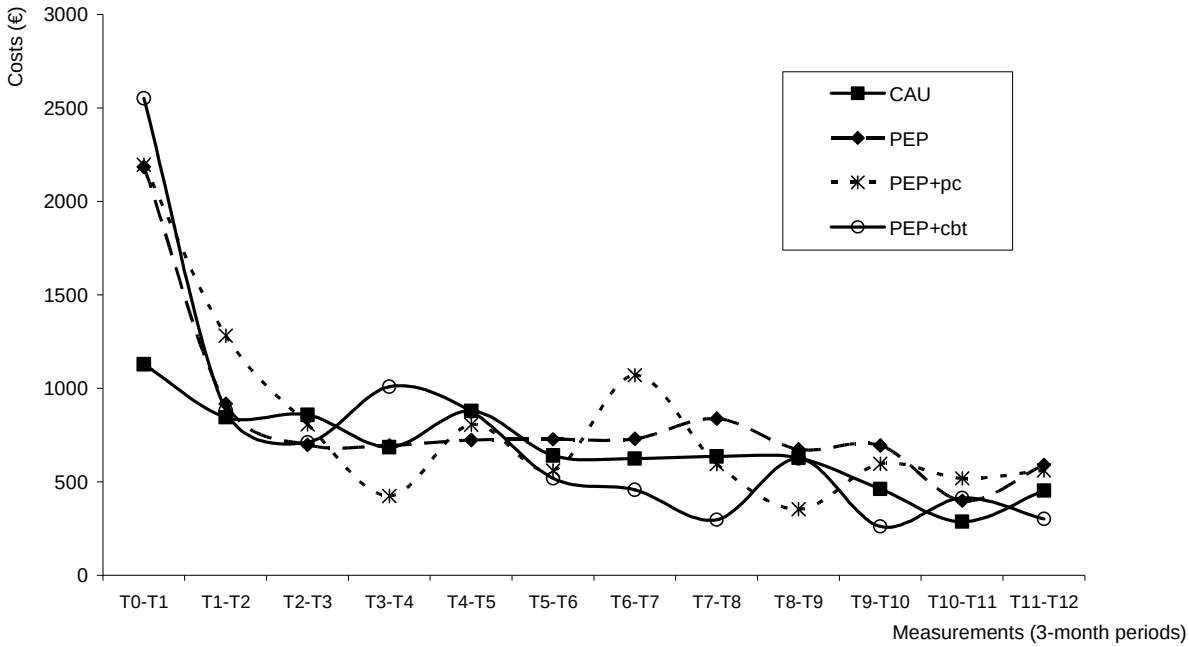
	CAU	PEP	PEP+PC	PEP+CBT
Mean total costs (95% CI) [1]	8200 (6123–10276)	9816 (8128-11504)	9844 (6484-13204)	9254 (5623-12885)

[1] Mean total costs based on the EM algorithm with bootstrap approach. The nonparametric 95% confidence interval is provided between brackets.

These costs were assessed by means of the EM algorithm in combination with the bootstrap method. Mean total costs per patient were €8200 in the CAU group, €9816 in the PEP group, €9844 in the PEP+PC group, and €9254 in the PEP+CBT group. In order to examine the statistical significance of cost differences between groups, nonparametric confidence intervals surrounding the difference scores between CAU and each of the PEP conditions were constructed. Lower and upper boundaries of the confidence intervals indicated that there were no statistically significant differences in total costs between groups (-969 to +4143 for PEP compared to CAU; -2078 to +5810 for PEP+PC compared to CAU; -2416 to +4803 for PEP+CBT compared to CAU).

The course of the mean total costs per group during the 36 months of the study is presented in Figure 1.

Figure 1. Course of mean total costs during the 36 months of the study



In the various PEP conditions, mean costs generated during the first months of the study were much higher than during later assessments, which is most obvious for the PEP+CBT condition. These higher initial costs are directly related to the PEP interventions that were mainly provided during the first months of the study. In the CAU condition, initial mean costs were only somewhat higher than at later assessments. After the first measurements, costs slowly decreased over time for all the groups.

Health outcomes

Results of the health outcomes relevant for the economic analyses are presented in Table 3. In contrast to expectations, there were no significant differences between groups in proportion of depression-free time.

This proportion varied from .71 to .78, indicating that patients did not meet DSM-IV criteria of depressive disorder for approximately three quarters of the study duration.

Table 3. Proportion of depression-free time and QALY results

Outcome measure	CAU	PEP	PEP+PC	PEP+CBT	Significance of differences[1]
Mean proportion of depression-free time	.74	.71	.78	.78	n.s.
QALYs [2]	2.31	2.10	2.15	2.27	n.s.

[1] Kruskal-Wallis test due to the skewed distribution.
[2] Derived QALYs are based on the data of 165 patients. CAU: 42, PEP: 70, PEP+PC: 27, PEP+CBT: 26.

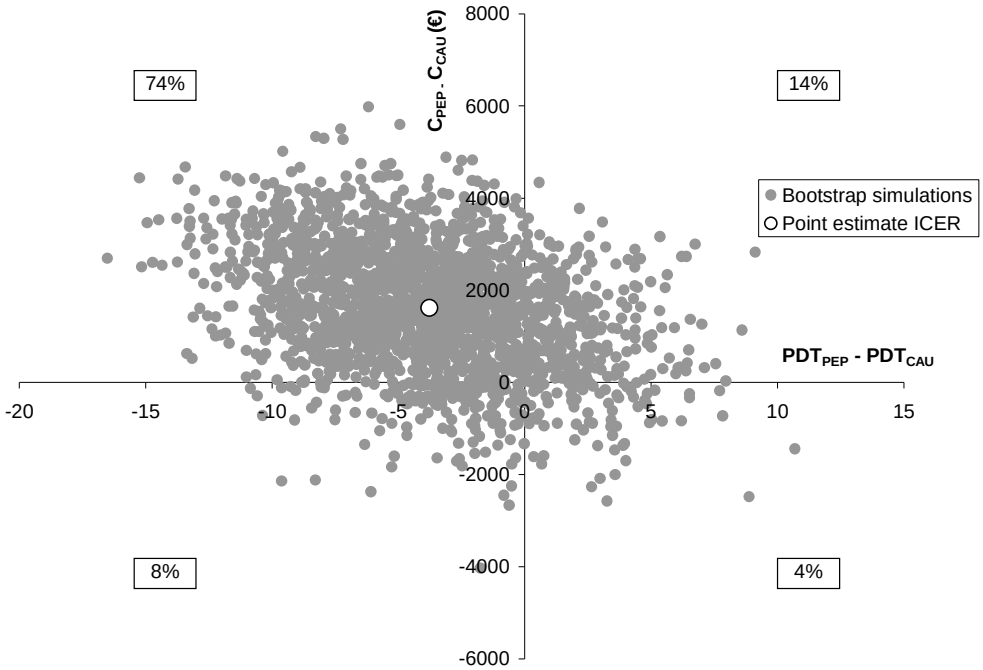
QALYs were derived from information collected for only some of the included patients (42 in CAU, 70 in PEP, 27 in PEP+PC, 26 in PEP+CBT). It was assumed that, after imputation with the EM algorithm, data of the available patients correctly represented data of patients for whom information could not be collected. Due to the applied approach, QALY results should be interpreted with some caution. If patients had experienced (nearly) optimal health during the 36 months of the study, QALY values would have been close to three. QALYs varied from 2.10 to 2.31 between groups, with the best outcomes for patients in the CAU condition and the worst outcomes for the basic PEP group. Differences between groups in QALYs assessed during the three years of the study were not statistically significant (Kruskall-Wallis test, x^2=4.73, p=.19). Economic analyses focusing on QALY results will not be presented in the current paper. Outcomes of these analyses were in accordance with results of the primary outcome measure favouring CAU, and therefore do not provide any relevant additional information for decision-makers.

Cost-effectiveness analysis

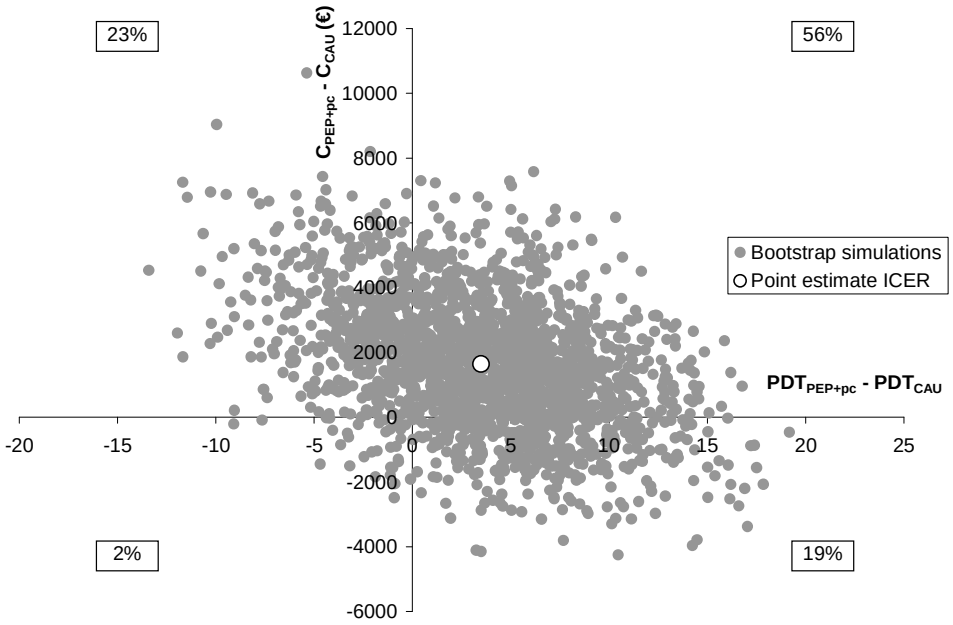
The point estimate of the ICER and the results of the bootstrap analyses are presented in the cost-effectiveness planes in Figure 2. For the comparison between basic PEP and CAU, the calculated value of the ICER was -€ 429 per proportion depression-free time (PDT). Here, the negative value indicates that PEP was associated with higher mean costs and worse health outcomes, i.e. was not cost-effective.

Figure 2. Results of the cost-effectiveness analyses and bootstrap method

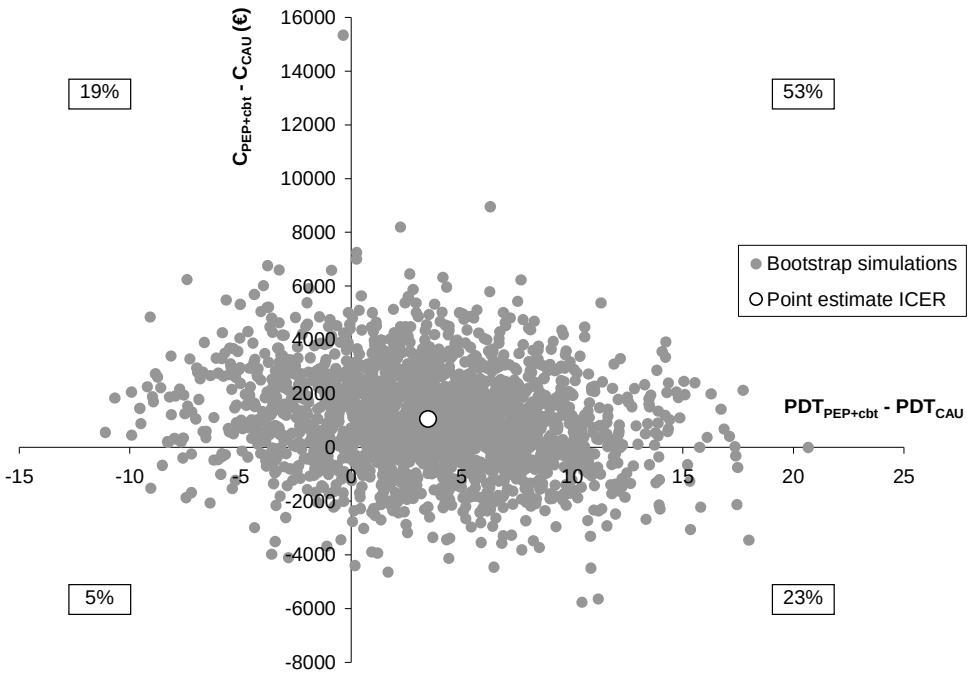
A. PEP compared to CAU



B. PEP+PC compared to CAU



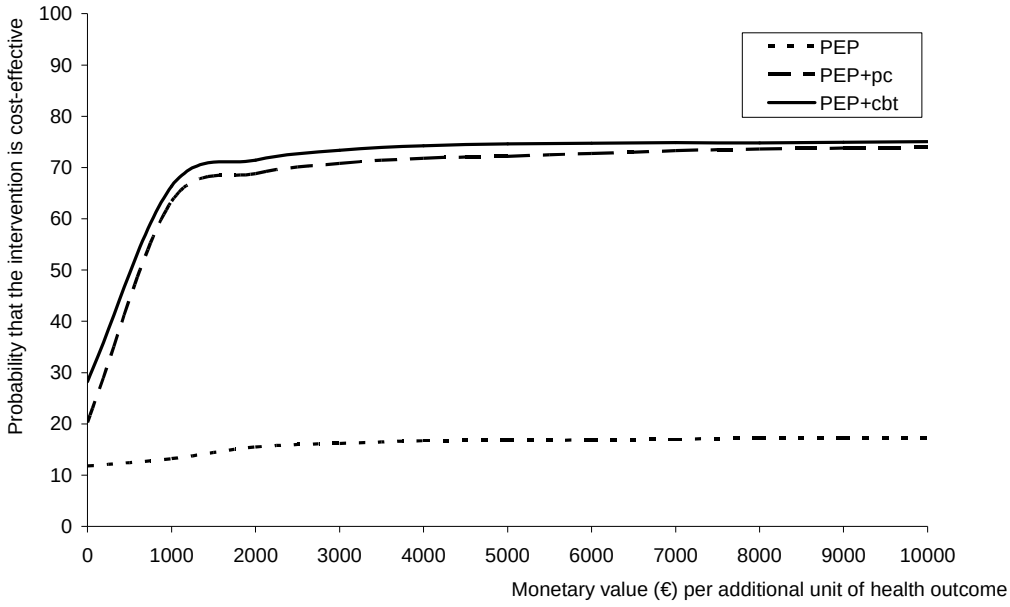
C. PEP+CBT compared to CAU



For each quadrant of the cost-effectiveness plane, information is provided on the percentage of bootstrap simulations located in that quadrant. For basic PEP, approximately 74% of the estimated mean cost and effect differences is located in the Northwest quadrant. In other words, CAU dominates basic PEP in 74% of the cases. For PEP+PC and PEP+CBT, the point estimate of the ICER is located in the Northeast quadrant, i.e. cost were higher but health outcomes were better. Interpretation of outcomes in the Northeast (and Southwest) quadrant depends on how much decision-makers are willing to pay for an additional unit of health outcome.

Figure 3 shows the calculated cost-effectiveness acceptability curves, presenting the probability that the various types of PEP will be cost-effective for increasing monetary values placed on an additional proportion of depression-free time.

Figure 3. Cost-effectiveness acceptability curves



Compared to basic PEP, results of PEP+PC and PEP+CBT seem (relatively) more positive. When decision-makers are willing to pay € 1000 to € 1500 per proportion depression-free time, the probability that PEP+PC or PEP+CBT will be cost-effective increases up to 70%.

Sensitivity analyses

In the first type of sensitivity analyses, discount rates were varied and consequences for differences in mean total costs between groups were studied. Costs were discounted at 3% and 5%, instead of 0% in the standard analyses, results are presented in Table 4.

The influence of discounting slightly differs between conditions, but is most pronounced for PEP+CBT. The difference between the mean total costs of PEP+CBT and mean total costs of CAU is approximately € 200 less when discounting with 5% instead of 0%. Furthermore, the consequences of excluding costs related to productivity losses from the analyses were examined. In the current study, interpretation of productivity costs was complicated by an initial difference between groups in the percentage of persons with paid work (49% of the persons in the CAU group had paid work, in contrast to 62% in the PEP group).

Table 4. Sensitivity analyses

Type of analysis	CAU Mean total costs	PEP Mean total costs	PEP+PC Mean total costs	PEP+CBT Mean total costs
Variation of discount rates				
3 %	7941	9647	9568	8750
5 %	7822	9505	9437	8652
Alternative analyses				
Exclusion productivity costs	3856	4509	5087	4569
Complete case approach [1]	7760	8658	9319	10225

[1] The complete case analysis of costs is based on the data of 105 patients (46% of patients included in the standard analyses). CAU: 26, PEP: 44, PEP+PC: 20, PEP+CBT: 15

Mean total costs were, unsurprisingly, much lower in all the groups when excluding productivity costs. Costs outcomes in this sensitivity analysis were in favour of the CAU group, which is comparable with previous results. Differences in mean total costs between the CAU condition and the other groups were smaller than in the standard analyses.

Additional sensitivity analyses focused on the cost data of 105 patients for whom all the measurements were available (46% of the patients included in the standard analyses). When comparing results of these complete case analyses with the standard analyses presented in this paper, the overall amount of assessed costs shows some changes. Mean costs of patients in the CAU condition were still considerably lower than in the other conditions. However, mean costs of the 15 patients who received PEP+CBT were now higher than costs of patients in the other PEP groups.

Discussion

This paper presented the results of an economic evaluation examining the cost-effectiveness of three variants of a depression recurrence prevention programme added to care as usual in primary care patients. In contrast to expectations, the basic PEP programme was not cost-

effective compared to CAU. Costs of patients who received PEP during the three years of the study were higher and the proportion of depression-free time was lower. Overall, current findings seem comparable to the results of an economic evaluation of PEP situated in the US healthcare system (Simon *et al.* 2002), although health outcomes were slightly more in favour of PEP in that study.

Mean total costs generated by the various groups during the 36 months of the study ranged from € 8200 to € 9844. The total amount of costs was mainly influenced by costs related productivity losses, the PEP interventions, psychiatric hospital admissions, medication use, and visits to regional institutions for mental healthcare. Although indirect costs of depression are not always included in economic studies, the potential economic impact of productivity losses associated with depression has been widely acknowledged (Drummond et al. 1997; Greenberg *et al.* 2003). In the current study, approximately half of the total costs was related to productivity losses. One of the conducted sensitivity analyses focused on the exclusion of costs related to productivity losses, due to debates on this topic and initial differences between groups in the proportion of persons with paid work. Outcomes of this sensitivity analysis were in favour of CAU and supported the overall conclusions, but differences in mean total costs between PEP and CAU were smaller. When drawing a comparison between the (yearly) direct medical costs assessed in this study to previous studies, current findings generally seem comparable (Simon *et al.* 2002; Scott *et al.* 2003) or somewhat higher than previously published results (Lave *et al.* 1998). Unfortunately, the exact types of (medical) costs included in economic analyses are not always clearly indicated in published papers, which is one of the aspects complicating direct comparisons of medical costs between studies.

In contrast to earlier studies on the (cost-)effectiveness of PEP, the outcomes of two enhancements of the PEP programme were also examined, namely the addition of psychiatric consultation and cognitive behavioural therapy (CBT). Both alternatives to basic PEP led to better health outcomes than basic PEP, but effect differences with CAU were only

modest while costs were higher. Additional economic analyses indicated that outcomes were slightly more positive for PEP with CBT than for PEP with psychiatric consultation.

Previous studies have shown that CBT has a positive effect in various patient populations with moderate to severe depression (Hollon *et al.* 2005), and appears to be cost-effective as well (Revicki *et al.* 2005; Vos *et al.* 2005). A recently conducted study in primary care patients with depression and comorbid anxiety disorders showed that computer-delivered CBT was associated with lower costs and better health outcomes (McCrone *et al.* 2004). Based on the results of the current study, it seems unlikely that PEP could make a relevant contribution to improve the (cost-) effectiveness of CBT treatment for depression in primary care. Various possible reasons for the ineffectiveness of PEP have been discussed elsewhere (Smit *et al.* 2005, 2006; Conradi *et al.* submitted).

An important strength of the current study was the long follow-up period of 36 months, during which relevant consequences of the examined interventions could properly be studied. In the available literature, no studies could be identified that addressed the improvement of the long-term outcome of depression in primary care with comparable follow-up periods. Unfortunately, the combination of a long follow-up period and frequent measurements also led to methodological difficulties. Various patients dropped out of the study or became lost to follow-up, for others intermittent measurements were not always available. The negative consequences of missing data for longitudinal analyses have been widely acknowledged (Little & Rubin, 1987; Briggs *et al.* 2003), and various methodological approaches to account for missing data have been developed. In the current study, the expectation maximisation algorithm (EM) with a bootstrap approach was applied, which appears to be a valid method for handling missing data in economic evaluations (Oostenbrink & Al, 2005). In the current study, complete case analysis could only be conducted for less than half of the included patients. Results of the complete case analysis generally supported findings of the EM algorithm with bootstrap approach.

The use of QALYs, or comparable generic health outcomes, is strongly preferred from the perspective of a decision-maker. QALYs enable comparisons across studies and illnesses, and are required when constructing (national) league tables aiming to rank healthcare interventions in terms of cost-effectiveness (Mauskopf *et al.* 2003). In the current study, QALYs were assessed in addition to the primary outcome measure, the proportion of depression-free time, and were derived from information that could only be collected for some of the included patients. QALYs of patients in the CAU group were better than outcomes in the basic PEP group, which is in line with the results of the primary outcome measure. However, QALY outcomes indicated that patients in CAU were also functioning better than the patients who received PEP+PC and PEP+CBT. Some authors have expressed concerns about the use of (utility-based) QALY outcomes in patients with depression (Donald-Sherbourne *et al.* 2001), while others were more positive (Sapin *et al.* 2004). In general, it seems advisable to interpret QALYs assessed in patients with depressive disorders with some caution, and carefully consider results of additional outcome measures as well. In the context of the results of the current study, there seems to be no reason to expect that overall conclusions would have been different when QALYs had been collected for all the included patients.

In conclusion, results of the current study indicated that the basic PEP intervention was not cost-effective compared to CAU in primary care patients with depression. The economic analyses focusing on two enhancements of PEP showed slightly more positive results. Based on these findings, there seems to be little support for the implementation of PEP in current healthcare systems. Recently, various studies have demonstrated encouraging (economic) results with different formats of cognitive behavioural therapy in patient populations with depression. Future economic studies situated in different healthcare systems may focus on the long term (cost-)effectiveness of alternative formats of cognitive behavioural therapy in primary care patients with depression, in order to improve the well-being of patients, and reduce both direct treatment costs and productivity losses associated with this highly disabling disorder.