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Cost Effectiveness of a Pharmacy-Based Coaching Programme to Improve Adherence to Antidepressants

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Abstract

Introduction: The efficacy of antidepressants in the treatment of depression has been convincingly demonstrated in randomised trials. However, non-adherence to antidepressant treatment is common.

Objective: To evaluate, from a societal perspective, the cost effectiveness of a pharmacy-based intervention to improve adherence to antidepressant therapy in adult patients receiving treatment in primary care.

Methods: An economic evaluation was performed alongside a 6-month randomised controlled trial in The Netherlands.

Patients who came to 19 pharmacies with a new prescription for a non-tricyclic antidepressant, i.e. those who had not received any prescription for an antidepressant in the past 6 months, were invited to participate. They were then randomly allocated to education and coaching by the pharmacist or to usual care. The coaching programme consisted of three contacts with the pharmacist, with a mean duration of between 13 and 20 minutes, and a take-home video reviewing important facts on depression and antidepressant treatment.

The clinical outcome measures were adherence to antidepressant treatment measured using an electronic pill container (eDEM) and improvement in depressive symptoms measured using the Hopkins Symptom Checklist (SCL). Resource

use was measured by means of questionnaires. The uncertainty around differences in costs and cost effectiveness between the treatment groups was evaluated using bootstrapping.

Results: Seventy patients were randomised to the intervention group and 81 to the usual care group; of these, 40 in the intervention group and 48 in the control group completed all of the follow-up questionnaires.

There were no significant differences in adherence, improvements in the SCL depression mean item score and costs over 6 months between the two treatment groups. Mean total costs (2002 values) were €3275 in the intervention group and €2961 in the control group (mean difference €315; 95% CI −1922, 2416). The incremental cost-effectiveness ratio associated with the pharmacist intervention was €149 per 1% improvement in adherence and €2550 per point improvement in the SCL depression mean item score. Cost-effectiveness planes and acceptability curves indicated that the pharmacist intervention was not likely to be cost effective compared with usual care.

Conclusion: In patients starting treatment with antidepressants, there were no significant differences in adherence, severity of depression, costs and cost effectiveness between patients receiving coaching by a pharmacist and patients receiving usual care after 6 months. Considering the resources needed to implement an intervention like this in clinical practice, based on these results, the continuation of usual care is recommended.

Depression is highly prevalent in the general population. In a pan-European survey of depression in the community, the 6-month prevalence of major depression was 6.9%.[1] It is expected that depression will be the second leading cause of disability (in terms of disability-adjusted life-years [DALYs]) worldwide in 2020 (11.6% of DALYs worldwide).[2] Depression is associated with increased healthcare costs, impaired functioning and well-being, and lost work productivity.[3] Thus, depression is associated with substantial social and economic burdens.

The efficacy of antidepressants in the treatment of depression has been convincingly demonstrated in randomised controlled trials.[4,5] However, dropout rates for antidepressant treatment are 21–33% in the first 4–24 weeks of antidepressant treatment.[6] The dropout rate is influenced by many factors, including the pharmacological properties of the antidepressant and patients' and providers' characteristics.[6] Multifaceted primary care interventions have been shown to improve adherence to antidepressants.[7-9] A similar effect has also been found for counselling about drug treatment.[10] In other chronic diseases, pharmacist interventions have been shown to improve patient care and outcomes.[11-14] There is mixed evidence on the effectiveness of pharmacist interventions in the management of depression.[15-17]

Economic data were collected as part of a study to evaluate the costs and effectiveness of a pharmacist intervention that aimed to improve adherence to antidepressants and to reduce depressive symptoms. This article presents the results of the economic evaluation.

Methods

Setting and Participants

Forty-six pharmacists were approached to participate in the study. Of these, 26 agreed to participate in the study. Seven pharmacists stopped shortly after the start of the study (sick leave, n = 2; time shortage, n = 2; demotivated, n = 2; refusal by GP to let patients participate in the study, n = 1), leaving 19 pharmacists. These pharmacists were located in both urban and rural areas in different parts of The Netherlands and, thus, were representative of The Netherlands. From April 2000 to April 2001, these 19 community pharmacists recruited patients. In The Netherlands it is very uncommon for patients to visit more than one pharmacy. Inclusion criteria for patients were (i) visiting the pharmacy with a 'new episode' prescription (i.e. they had not used an antidepressant in the 6-month period before inclusion) for a non-tricyclic antidepressant from their GP for depressive complaints; (ii) age 18 years or older; and (iii) able to write Dutch. The protocol was approved by the medical ethical committee of the University Medical Centre of Utrecht.

Design and Randomisation

A randomised controlled trial was performed. After giving written informed consent, patients were randomly allocated to the group receiving education and coaching by pharmacists or to the group receiving usual care. Dutch guidelines for the treatment of depression recommend continuing antidepressant treatment for at least 6 months.[18] Therefore, a follow-up period of 6 months was used in this study. The methodological details of the trial are reported in more detail elsewhere.[19,20]

Intervention

All pharmacists were instructed during a plenary meeting on how to approach eligible patients and how to use the different study protocols for the control and intervention recipients. Patients in the control group received the standard oral and written information that is routinely issued in The Netherlands when they picked up their prescriptions at the pharmacy.

Patients assigned to the intervention group had three coaching contacts during the study. The first contact took place at baseline and had a mean duration of 20 minutes. During this contact, pharmacists gave the patients information about the use of antidepressants using the following list of educational messages: (i) take the antidepressant daily; (ii) antidepressants must be taken for 2–4 weeks for a noticeable effect; (iii) continue to take the antidepressant even when feeling better; (iv) do not stop taking the antidepressant without checking with a physician; and (v) do not hesitate to ask the pharmacist or GP if you have any questions regarding the antidepressants. Lin et al.[21] showed that patients who received these educational messages were more likely to comply during the first month of antidepressant therapy.[21]

The patients also received a take-home video and the usual written material on antidepressants. The videotape was made by the study team and reviewed the multifactorial origin of depression, the relationship of depression to stress, physical and emotional symptoms of depression, the treatment of depression, and the importance of adherence to medication even if depressive symptoms improved. The study team consisted, among others, of a psychiatrist and a pharmacist. The content of the videotape was based on expert material on depression.

The second contact took place when the index prescription of antidepressants ended, and had a mean duration of 14 minutes. The number of days supply for the index prescription was 14, so the second contact took place before or at 2 weeks after inclusion. The third contact took place at 3 months from baseline and had a mean duration of 13 min-

utes. During these visits, patients were asked about adverse and/or positive effects of the antidepressants. Stimulation and motivation to continue to take their antidepressants was also provided.

Outcome Assessments

The primary outcome was adherence to the prescribed antidepressant therapy. Adherence was measured by electronic pill containers (eDEMs); these record the precise time of opening of the container. When data from the eDEM were not available (for instance, due to technical failure), data from the computerised pharmacy records were used to estimate adherence. At baseline and at 3 and 6 months of follow-up, depressive symptoms were measured using the depression 13-item subscale of the Hopkins Symptom Checklist (SCL).[22] Each SCL item is scored on a 5-point scale, ranging from 1 'not at all' to 5 'extremely'. A mean item score was calculated for the depression subscale.

Cost Measurement and Valuation

The economic evaluation was conducted from a societal perspective. Direct healthcare costs, direct non-healthcare costs and indirect costs were estimated over 6 months. Information on resource use and absenteeism from paid work was obtained through questionnaires administered to patients at 3 and 6 months of follow-up (copies of the questionnaire used are available from the author upon request). Information on medication use (including the antidepressants) during the full 6 months of the trial was obtained through the pharmacies' computerised medication records.

Dutch guideline prices were used to value resource use.[23,24] If these were not available, tariffs were used. Table I lists the cost categories and prices used in the economic evaluation. The costs of medication were estimated on the basis of the prices established by the Royal Dutch Society for Pharmacy.[25] All costs were adjusted to 2002 values using consumer price index figures.[26] Discounting was unnecessary, because neither costs nor benefits were recorded beyond 12 months.

Indirect costs caused by lost productivity were estimated using the friction cost approach.[27] The friction period was estimated to be 5 months for 2002 in The Netherlands. Calculations were based on the mean income of the Dutch population according to age and gender.[23] Although depression often causes patients to work less productively while still being present at work (presenteeism), we did not include this aspect in the cost-effectiveness analysis.

Data Analysis

It was calculated that 150 patients were needed (2-sided $\alpha = 0.05$, $\beta = 0.20$) to detect a difference in adherence of 13% assuming a standard deviation (SD) of 40%. All analyses were limited to patients completing all follow-up assessments (complete case analysis) regardless of whether they received the assigned treatment. To maximise the contrast between the two treatment groups, per protocol analyses were also performed. Patients were included in the per protocol analysis if the prescription for antidepressant medication was written out by the patient's GP and they completed all of the follow-up assessments. Patients in the intervention group were excluded from the per protocol analysis if they indicated that they had not watched the intervention videotape or did not receive the three coaching contacts.

To compare costs between groups, confidence intervals for cost differences were computed by bias-corrected and accelerated (BCa) bootstrapping with 2000 replications.[28] A cost-effectiveness analysis was performed in which the primary clinical outcome of the trial was expressed as mean adherence within each group over 6 months of follow-up. The SCL depression score was expressed as the mean improvement within each group between baseline and 6 months of follow-up. Incremental

Table I. Costs used in the economic evaluation

Resource	€ (2002 values)[a]
Direct medical costs	
GP (per visit)[b]	18.42
Psychologist (visit of ≤1 hour)[c]	70.00
Social worker (visit of ≤1 hour)[c]	46.97
Psychiatrist (per visit)[b]	45.32
Outpatient appointment other specialist (visit of ≤10 minutes)[b]	45.32
Physiotherapist (visit of ≤30 minutes)[b]	20.14
Mensendieck physiotherapist (per visit)[b,d]	19.64
Regional Institute for Community Mental Healthcare (visit of ≤1 hour)[b]	113.80
Abdominal x-ray	95.00
Medication	Depending on type and dose
Homeopath (per visit)[c]	54.00
Haptonomist (visit of ≤1 hour)[c,e]	61.88
Magnetic therapist (per visit)[f]	22.75
Acupuncturist (visit of ≤30 minutes)[c]	40.00
Spiritualist (per visit)[f]	38.17
Foot reflex therapist (per visit)[f]	25.67
Company doctor (visit of ≤20 minutes)	20.80
Indirect costs	
Absenteeism from paid labour (per day)[g]	Depending on age and gender
Intervention costs	
25-Minute take-home video[h]	3.78
Drug coaching contacts at the pharmacy (per hour)	52.94

a €1 = $US1.27.

b Price according to recently published Dutch guidelines.[23]

c Price according to professional organisation (psychologist: National Society of Psychologists [Landelijke Vereniging van Eerstelijnspsychologen]; social worker: Dutch Society of Social Workers [Nederlandse Vereniging van Maatschappelijk Werkers]; homeopath: Dutch Society of Classic Homeopaths [Nederlandse Vereniging van Klassiek Homeopaten]; haptonomist: Society of Haptonomists [Vereniging Van Haptotherapeuten]; acupuncturist: Dutch Society for Acupuncture [Nederlandse Vereniging voor Acupunctuur]).

d Physiotherapy within the Mensendieck tradition may be described as active exercise treatment and functional training, in which the patient through action, experience and recognition gains insight into his/her own situation, potential and limitations. As well as instructing, the physiotherapist acts as a counsellor.

e Haptonomy is the science of affectivity and is based on relating through psychotactile contact.

f Mean of the price according to two or more therapists (magnetic therapist: four therapists; spiritualist: three therapists; reflexologist: two therapists).

g Indirect costs for paid labour were calculated according to the friction cost approach on the basis of the mean income of the Dutch population stratified for age and gender.[23]

h Cost of duplication only; the costs of production were not included in the base-case analysis.

cost-effectiveness ratios were calculated in which the difference in costs between intervention subjects and control subjects was divided by the difference in effects between both groups. The uncertainty associated with the incremental cost-effectiveness ratios was calculated by bootstrapping using the bias-corrected percentile method with 5000 replications.[29] The bootstrapped incremental cost/effect pairs were plotted on a cost-effectiveness plane[30] and were used to calculate a cost-effectiveness acceptability curve.[31]

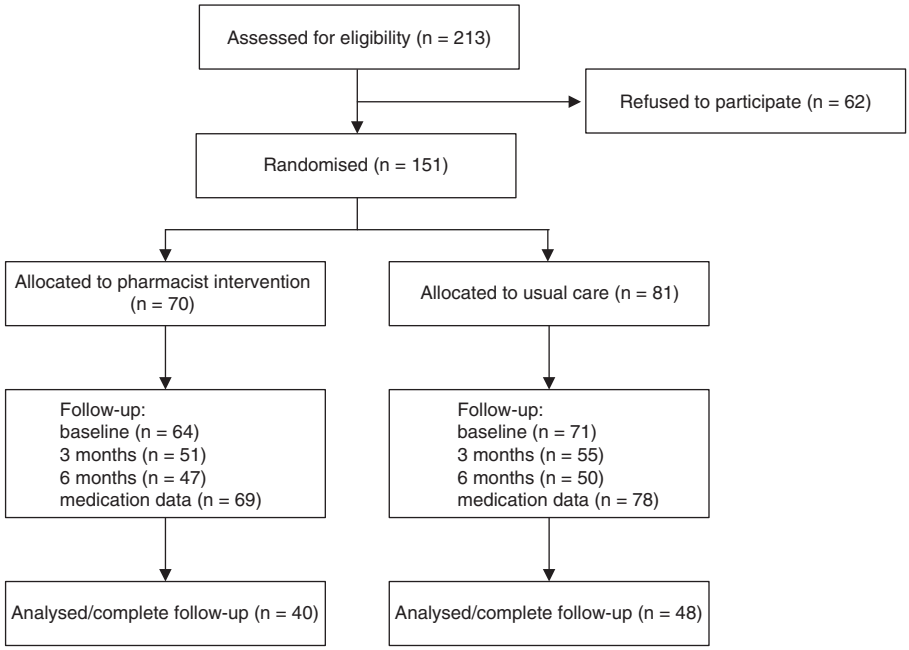

Fig. 1. Flow of patients throughout the study.

Sensitivity Analysis

In three sensitivity analyses, uncertainties in the variables and assumptions employed in the main analysis were varied in order to evaluate their influence on the estimated results.[32] In the first sensitivity analysis the costs of producing the videotape were included in the price of the videotape, while in the base-case analysis only the costs of duplicating the videotape were included. In the second sensitivity analysis, the indirect costs for lost productivity associated with paid labour were calculated according to the human capital approach to enable comparisons with other studies. Complete follow-up on SCL depression scores, healthcare utilisation and work days lost was available for only 89 patients (61%). Therefore, in the third sensitivity analysis the influence of imputing the mean value per treatment group for missing values in patients who did not complete all follow-up assessments was evaluated. Imputation was limited to patients who had completed the baseline assessment.

Results

A total of 151 patients were included in the trial; 70 patients were randomised to the intervention group and 81 to the usual care group. This difference in the number of patients per treatment group is caused by the fact that block randomisation was used to ensure equal numbers of intervention and control patients per pharmacy. The baseline questionnaire was returned by 135 patients (64 from the intervention group and 71 from the control group). At the 3- and 6-month follow-up visits, 106 and 98 patients, respectively, returned their follow-up questionnaires. Complete follow-up through questionnaires was available for 89 patients (41 from the intervention group and 48 from the control group). Of these, one patient from the intervention group was excluded because medication data were missing (see figure 1). Patients with higher levels of education were more likely to complete all of the follow-up assessments. Thirty-eight of the 70 patients (54%) included in the intervention group, and 34 of

the 40 (85%) in this group who completed all of the follow-up questionnaires, indicated that they had watched the educational video at least once. The intervention and control groups did not differ in the demographic and prognostic characteristics measured at baseline (table II). Although the difference in the percentage of married patients and the mean duration of depressive complaints was rather large between the intervention and control groups, this was not statistically significant.

Clinical Effects

A full evaluation of the effects of coaching and education by pharmacists on adherence and depressive symptoms has been reported elsewhere.[19,20] In summary, mean adherence did not differ significantly between the intervention group (88%) and the control group (86%) at 6 months (mean difference 2.1%; 95% CI −5.6, 9.8). At 6 months there were also no statistically significant differences between the two groups with regards to the improvements on the SCL depression scale, with a slight benefit being shown with the pharmacist intervention (mean difference −0.15; 95% CI −0.54, 0.23).

Utilisation of Healthcare Resources

Table III presents the resource use and work absenteeism that was reported during the 6 months of follow-up. As can be seen, there were no significant differences in resource use between the intervention and control group. Visits to healthcare providers were mainly restricted to GPs and psychologists. Twelve (30%) patients in the intervention group and ten (21%) patients in the control group each received >15 prescriptions of medication over 6 months (including prescriptions for antidepressants).

At baseline, 26 patients (65%) in the intervention group had a paid job compared with 34 patients (71%) in the control group. During the trial, 10 (25%) patients in the intervention group and 18 (38%) in the control group had been absent from paid labour, of which 5 (13%) and 8 (17%) patients, respectively, were absent for 1–5 months, and 2 (5%) and 2 (4%) patients were absent for the full 6 months, respectively.

Costs

Table IV lists the mean costs per treatment group and the differences in mean costs between the groups over 6 months. In both groups, the main contributor to total costs was indirect costs. There were no statistically significant differences in direct, indirect or total costs. Direct non-healthcare costs were higher in the control group because of more visits to alternative therapists.

Table II. Baseline characteristics of intervention and control patients completing all questionnaires and having medication data available

Characteristic	Intervention (n = 40)	Control (n = 48)
Age (y) [mean (SD)]	43 (13)	43 (12)
Female (%)	68	69
Married (%)	75	63
Duration of depressive complaints (months) [mean (SD)]	20 (34)	46 (83)
SCL depression item score [mean (SD)]	3.1 (0.84)	2.9 (0.77)
Severity of depression[a] (%)		
mild	15	23
moderate	43	44
severe	15	17
unknown	28	17

a As estimated by the GP.

SCL = Hopkins Symptom Checklist (range 1–5).

Table III. Utilisation of healthcare resources and work absenteeism in intervention and control patients completing all questionnaires and having medication data available during the 6-month follow-up period [mean (SD)]

Resource	Intervention (n = 40)	Control (n = 48)	p-Value
GP (visits)	3.6 (3.0)	3.0 (2.3)	0.273
Psychologist (treatment sessions)	3.1 (5.9)	3.4 (5.2)	0.834
Social worker (visits)	0.5 (2.4)	0.2 (0.9)	0.511
Psychiatrist (treatment sessions)	0.1 (0.5)	0.3 (1.4)	0.464
Medical specialist (outpatient visits)	0.1 (0.4)	0.0 (0.1)	0.283
Physical therapist (treatment sessions)[a]	0.4 (1.7)	0.8 (2.4)	0.411
Regional Institute for Community Mental Healthcare (treatment sessions)	0 (0)	0.0 (0.1)	0.364
Abdominal x-ray (x-rays)	0 (0)	0.0 (0.1)	0.364
Company doctor (visits)	0.1 (0.5)	0.1 (0.6)	0.942
Alternative therapist (visits)	0.2 (0.9)	1.0 (2.6)	0.064
Medication (prescriptions)	12.6 (7.5)	13.5 (11.1)	0.648
Absenteeism from paid labour (days)	28.7 (56.8)	22.9 (45.5)	0.597

a Physiotherapist and Mensendieck therapist.

Cost-Effectiveness Analyses

The incremental cost-effectiveness ratio for coaching and education by pharmacists compared with usual care was €149 per 1% improvement in adherence and €2550 per point improvement in the SCL depression mean item score. The incremental cost-effectiveness plane for adherence shows that there is a great deal of uncertainty around the cost-effectiveness ratio for adherence (figure 2). Forty-two percent of the incremental cost/effect pairs were located in the northeast quadrant, 30% in the southeast quadrant, 11% in the southwest quadrant and 17% in the northwest quadrant, confirming the findings of no statistically significant differences in costs and effects. The incremental cost-effectiveness plane for improvement in the SCL depression score showed similar results (data not shown). Figure 3 presents the cost-effectiveness acceptability curve for adherence. This curve shows that decision mak-

Table IV. Costs and differences in costs (€, 2002 values[a]) in intervention and control patients completing all questionnaires and having medication data available during the follow-up period of 6 months

Costs	Intervention [mean (SD)] (n = 40)	Control [mean (SD)] (n = 48)	Difference [mean (95% CI[b])]
Direct medical costs	726 (482)	711 (443)	15 (−194, 197)
primary care costs[c]	314 (409)	319 (409)	−4 (−196, 157)
secondary care costs[d]	10 (30)	16 (62)	−6 (−25, 14)
medication costs	344 (269)	326 (252)	18 (−91, 128)
patient costs[e]	11 (49)	38 (96)	−27 (−51, 7)
company doctor	2 (10)	2 (12)	0 (−4, 4)
intervention/usual care costs[f]	45	10	
Indirect costs	2551 (4931)	2249 (4816)	300 (−1804, 2267)
Total costs	**3275 (5085)**	**2961 (5032)**	**315 (−1703, 2606)**

a €1 = $US1.27.

b 95% confidence interval obtained by bias-corrected and accelerated bootstrapping with 2000 replications.

c Primary care is defined as care that is directly accessible by patients.

d Secondary care is defined as care for which patients need a referral.

e Patient costs consist of costs of alternative therapists, which are generally paid by the patients themselves.

f Since there is no variation in intervention costs within the groups, SDs and 95% confidence intervals can not be calculated.

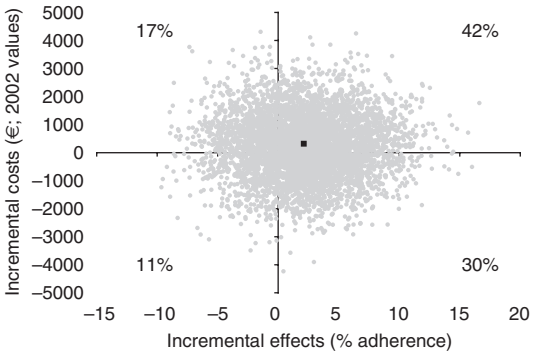

Fig. 2. Cost-effectiveness plane for adherence with antidepressant therapy (pharmacy-based coaching intervention vs control). The individual points on the plane represent the 5000 bootstrapped cost-effect pairs using the bias-corrected percentile method. The central black dot indicates the point estimate of the incremental cost-effectiveness ratio.

ers should have little belief that coaching and education by pharmacists is cost effective as a means of increasing adherence to antidepressants compared with usual care.

Per Protocol Analysis

The per protocol analysis was restricted to patients who had completed all follow-up assessments and fulfilled the criteria for per protocol analysis (26 intervention and 45 control group patients). In this analysis there were no significant differences in adherence (mean difference 4.2; 95% CI −4.7, 13.1) and improvements in the mean SCL depression item score (mean difference −0.27; 95% CI −0.69, 0.16) between the treatment groups. Total costs in both groups were higher than in the previous analysis. The difference in total costs between the two treatment groups was also somewhat larger, but was still not statistically significant (mean difference €507; 95% CI −1667, 3132). The incremental cost per 1% improvement in adherence was €120 and the incremental cost per point improvement in SCL depression mean item score was €2375. This analysis also did not show the intervention to be more cost-effective than usual care.

Sensitivity Analysis

In the first sensitivity analysis, the costs of producing the video were included in the intervention costs, resulting in a cost of €95.52 for the videotape. Direct healthcare costs in the intervention group increased to a mean of €818 (SD 482). This did not materially influence the results.

In the next sensitivity analysis, the indirect costs for paid labour were calculated using the human capital approach. This resulted in higher indirect and total costs in both groups. Mean indirect and total costs were €2733 (SD 5353) and €3458 (SD 5510), respectively, in the intervention group and €2402 (SD 5424) and €3112 (SD 5631), respectively, in the control group. These changes had little impact on the results.

Table V shows the direct, indirect and total costs after imputation of the mean value per treatment group in cases of missing values, resulting in somewhat lower direct, indirect and total costs in both groups. The difference in direct costs between the treatment groups increased, while the differences in indirect and total costs decreased slightly. The differences in direct, indirect and total costs between the two groups were not statistically significant. The differences in clinical outcomes and the cost-effec-

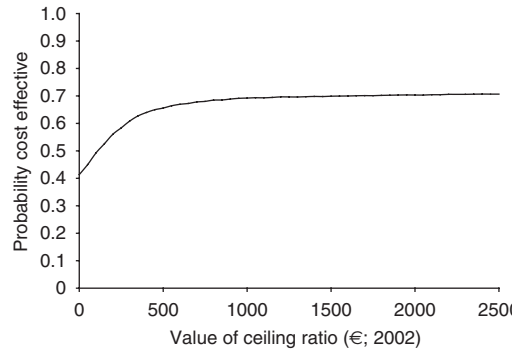

Fig. 3. Cost-effectiveness acceptability curve for adherence with antidepressant therapy (pharmacy-based coaching intervention vs control), as calculated by bootstrapping using the bias-corrected percentile method with 5000 replications.

Table V. Sensitivity analysis: mean 6-month costs (€, 2002[a]) in patients in the intervention and control groups who completed the baseline questionnaire after imputation of the mean per treatment group for missing data

Costs	Intervention [mean (SD)] (n = 64)	Control [mean (SD)] (n = 71)	Difference [mean (95% CI[b])]
Direct medical costs	707 (423)	669 (395)	37 (−106, 169)
Indirect costs	2477 (4048)	2206 (4011)	271 (−1055, 1619)
Total costs	3183 (4183)	2875 (4199)	308 (−1113, 1818)

a €1 = $US1.27.

b 95% confidence interval obtained by bias-corrected and accelerated bootstrapping with 2000 replications.

tiveness ratios did not change substantially between the sensitivity analysis and the base-case analysis.

Discussion

This study evaluated the cost effectiveness of a pharmacy-based intervention to improve adherence to antidepressants in primary care. After 6 months of follow-up there were no significant differences in adherence or in improvements in the mean SCL depression item score between the two treatment groups. Indirect costs were the main determinants of total costs: almost 80% of total costs in both groups consisted of indirect costs. Total costs were slightly higher, but not by a statistically significant amount, in the intervention group. The cost-effectiveness planes showed that there was substantial uncertainty around the cost-effectiveness ratios. The per protocol analysis also showed no significant differences in clinical outcomes or costs between the two groups after 6 months.

Several studies by Katon and colleagues[7-9,33,34] have shown that multifaceted primary care interventions, directed at both the patient and their physician, can lead to significant improvements in adherence to adequate dosages of antidepressant medication accompanied by moderate increases in costs. Peveler et al.[10] demonstrated that counselling by nurses had an effect on the duration of treatment, while information leaflets had no effect. In their study, there were no significant differences in the number of GP visits, hospital admissions, or work days lost, but the costs and cost effectiveness were not compared.

Of three studies evaluating the effectiveness of more intensive pharmacist interventions to improve adherence to antidepressants,[15-17] two found significant effects on adherence rates.[16,17] Thus, a possible explanation for the non-significant difference in adherence between the two treatment groups in our study is that the intervention tested was not intensive enough. We deliberately chose a minimal intervention that was easy to implement without disrupting the pharmacist's daily practice too much. Nevertheless, many patients did not complete all follow-up visits, or the visits were timed too late – as reflected in the small number of patients included in the per protocol analysis. The per protocol analysis that was not limited to patients completing all follow-up assessments and that was reported in the accompanying clinical paper,[20] showed that adherence was significantly higher in the intervention group than in the control group. Thus, better implementation of a minimal intervention like the one tested in this study may prove beneficial. However, we could not replicate these results because of missing cost data.

The present study has several strengths. First, adherence was measured by eDEMs, which record the precise times at which the container is opened. This method approaches a gold standard for measuring adherence.[35] Secondly, complete medication data were available for all patients except one who completed the baseline questionnaire. Thirdly, complete data on adherence were available either through the eDEM or, in the case of technical problems with the eDEM, through data on antidepressant refills. Finally, the new setting of this study

– the community pharmacy – should be mentioned. As GPs may not have time to provide drug coaching, community pharmacists could take over this task.[19]

There are also some limitations to our study. First, patients knew from the start that adherence was the primary outcome of the study and that it was measured by the eDEM. This may explain why adherence was higher than in other studies using electronic pill containers in which patients were not informed about the use of the device or the primary objective of the study.[36,37] It is also possible that the use of the eDEM in itself positively influenced adherence. In either case, mean adherence rates were rather high, leaving little room for further improvement.

Second, block randomisation was used in this study. It is possible that, despite instructions to pharmacists on how to use different protocols for the patients in the control and intervention groups,[20] there was contamination of usual care with elements of the intervention. This may also partly explain the remarkably high adherence rates in the control group. However, this seems unlikely, since patients in the intervention group were much more satisfied about their pharmacist's care than usual care patients.

Third, the withdrawal rate was quite high, and adherence was significantly higher in patients with complete follow-up. Therefore, in the sensitivity analysis the mean per treatment group was imputed for missing values in order to increase the statistical power of the study. In this analysis there were no significant differences in clinical outcomes, costs or cost effectiveness between both groups.

A fourth limitation is that costs of hospitalisations were not explicitly asked for. However, several other cost-effectiveness studies of interventions in depressed primary care patients demonstrated no significant differences in hospitalisation costs.[38,39] Hence, it is reasonable to assume that if hospitalisation costs had been included, this would not have influenced the results of this study.

Fifth, sample size calculations showed that 150 patients would be needed to show a relevant 13% difference in adherence. Although 151 patients were included, baseline data were available for only 135 patients and complete follow-up was available for only 88 patients. Therefore, the study was underpowered to detect significant differences in adherence. However, even when all patients for whom a baseline measurement was available were included in the study, the difference in adherence between the two treatment groups was small (3%) and non-significant (95% CI −7.3, 13.3).[20] We expect that this difference in adherence would not have been larger if more patients were included in the study, because withdrawal rates were equal in the two groups. As cost data are highly variable, studies comparing costs require greater sample sizes than studies comparing clinical effects. Thus, the study was also underpowered to detect significant differences in costs. However, it is considered unfeasible and unethical to continue a trial beyond the point at which the clinical efficacy of the intervention has been shown.[40] Therefore, most trials have sample sizes based on the expected clinical outcomes, which was also the case here.

Finally, in this study, the main analyses were limited to patients who completed all follow-up questionnaires and for whom complete medication data from the pharmacies' computerised medication records were available. In general, complete case analyses are considered inefficient. However, since cost data are in general heavily skewed, imputation may bias the results.[41] Nevertheless, we performed a sensitivity analysis in which we imputed the mean per treatment group for missing data. This may also lead to biased estimates, but the amount of bias seems to be acceptable when the dropout is completely at random.[42]

The study described in this article was a pragmatic study to resemble daily clinical practice as much as possible. This implies that only few inclusion and exclusion criteria were applied to the patients. Also, the treatment protocol was not very strict and the other care patients received for their depressive complaints was not restricted in any way. Moreover, our intervention was easy to implement by the pharmacists. Based on these arguments, we expect that the generalisability of our results is high.

Conclusion

In our study of patients starting treatment with antidepressants in a primary care setting in The Netherlands, there were no significant differences in adherence with treatment, severity of depression, costs and cost effectiveness after 6 months between patients who received coaching by a community pharmacist and patients who received usual care. Considering the resources needed to implement an intervention like this in clinical practice, based on these results, continuation of usual care is recommended.

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