Journal of Affective Disorders 159 (2014) 85–93

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Cost-effectiveness analysis of a collaborative care programme for depression in primary care

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ARTICLE INFO

Article history:
Received 26 July 2013
Received in revised form
30 January 2014
Accepted 31 January 2014
Available online 13 February 2014

Keywords:
Depression
Primary health care
Disease management
Controlled clinical trial
Cost-effectiveness

ABSTRACT

Background: Collaborative care programmes lead to better outcomes in the management of depression. A programme of this nature has demonstrated its effectiveness in primary care in Spain. Our objective was to evaluate the cost-effectiveness of this programme compared to usual care.
Methods: A bottom-up cost-effectiveness analysis was conducted within a randomized controlled trial (2007–2010). The intervention consisted of a collaborative care programme with clinical, educational and organizational procedures. Outcomes were monitored over a 12 months period. Primary outcomes were incremental cost-effectiveness ratios (ICER): mean differences in costs divided by quality-adjusted life years (QALY) and mean differences in costs divided by depression-free days (DFD). Analyses were performed from a healthcare system perspective (considering healthcare costs) and from a society perspective (including healthcare costs plus loss of productivity costs).
Results: Three hundred and thirty-eight adult patients with major depression were assessed at baseline. Only patients with complete data were included in the primary analysis (166 in the intervention group and 126 in the control group). From a healthcare perspective, the average incremental cost of the programme compared to usual care was €182.53 ($p < 0.001$). Incremental effectiveness was 0.045 QALY ($p = 0.017$) and 40.09 DFD ($p = 0.011$). ICERs were €4,056/QALY and €4.55/DFD. These estimates and their uncertainty are graphically represented in the cost-effectiveness plane.
Limitations: The amount of 13.6% of patients with incomplete data may have introduced a bias. Available data about non-healthcare costs were limited, although they may represent most of the total cost of depression.
Conclusions: The intervention yields better outcomes than usual care with a modest increase in costs, resulting in favourable ICERs. This supports the recommendation for its implementation.

1. Introduction

Over the course of a year, 4–7% of the European adult population suffers from major depression (Wittchen et al., 2011; Gabilondo et al., 2010). For society and for the healthcare system, the costs associated with depression are very high due to its prevalence as well as to other factors, such as increased use of healthcare resources, and most importantly, lost productivity, which can represent more than three-quarters of the total cost (Gustavsson et al., 2011; Salvador-Carulla et al., 2011).

The WHO's strategy for mental health considers primary care to be the most appropriate and efficient level of healthcare for the management of the most common mental health problems found in the general population —including depression— even in economically developed countries, and has proposed expanding and improving capacities to address this issue (WHO, 2001, 2008). In fact, most individuals with depression are handled either solely in primary care or in primary care combined with other services (Aragonès et al., 2004). However, difficulties have been described in the management of depression in primary care, particularly with regard to ensuring that treatments are adhered to, proper patient follow-up and the continuity of care (Fernández et al., 2010; Pinto-Meza et al., 2008).

There is evidence that collaborative care programmes designed to improve the management of depression based on the chronic

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http://dx.doi.org/10.1016/j.jad.2014.01.021
0165-0327

care model are effective in improving clinical care and in obtaining better outcomes (Thota et al., 2012). The core elements of these interventions consist of the systematic use of evidence-based treatments, promoting adherence to treatment plans, proactive monitoring of patients to closely track progression, and adjusting treatment in accordance with the clinical status of the patient at all times. These programmes usually have case managers, a role often filled by primary care nurses, and establish mechanisms for cooperation and coordination between primary care and psychiatry (Katon and Seeling, 2008). We recently published data on the clinical efficacy of a programme of this nature designed to improve the management of depression in primary care in Spain. The programme resulted in improved evolution of depressive symptoms (effect size: 0.35 at 6 months and 0.23 at 12 months), better response rates to treatment, and higher remission rates (66.9% vs. 51.5%, and 48.8% vs. 35.4% at 12 months) (Aragonès et al., 2012).

Implementing a care model for the management of depression depends not only on its clinical efficacy, but also on the additional costs associated with its execution. A recent systematic review concluded that, in general, these models of collaborative care for managing depressive disorders provide a good return on investment (Jacob et al., 2012). However, most of the studies analysed were from the United States and the results obtained cannot easily be extrapolated to other health systems (i.e., to European health systems) (Jacob et al., 2012; Gilbody et al., 2006).

Our objective is to evaluate the cost-effectiveness and the cost-utility ratios of a collaborative care programme for the management of depression in primary care compared to the usual care in the Spanish healthcare system.

2. Methods

2.1. Design

This is a bottom-up cost-effectiveness analysis of a collaborative care programme for depression in primary care following a randomized controlled trial with primary care centres participating in two alternative arms: (a) the intervention arm (a new programme for depression) and (b) the control arm (usual care).

The Research Ethics Committee of the Jordi Gol Primary Care Research Institute (IDIAP) approved the study protocol in Barcelona, on 29 March 2006 (ref: P06/16). All participants provided written informed consent. This study is registered as International Standard Randomized Controlled Trial number ISRCTN16384353. A more detailed description of the study's design and procedures has already been published (Aragonès et al., 2012, 2007).

2.2. Randomization

The centres agreed to participate before the random allocation. The participating centres were matched according to their characteristics: number of doctors, urban/rural location and the availability of a psychiatrist in the centre (some centres have mental health specialists available part time). Then, the centres in each pair were allocated to the intervention or control arm by a blinded person not involved in the study by means of a random sequence of numbers.

2.3. Settings and patients

The study was conducted in 20 public primary care centres in the province of Tarragona, Catalonia, Spain. In Spain primary care centres provide universal care to nearly 100% of the population in their catchment area and are coordinated with specialised mental health care and with hospital care. All approached centres agreed to participate in the study. The family physicians selected patients to take part in the study from among those who attended their surgery and were clinically diagnosed as depressed. They had to verify that the depressive episode complied with the diagnostic criteria (DSM-IV) for major depression using the Patient Health Questionnaire (PHQ-9) checklist. The inclusion criteria for patients were as follows: age of at least 18; the diagnosis of a major depressive episode (DSM-IV) with a score of >14 on the PHQ-9 (moderate to severe depression), or a score of 10–14 (mild depression) which had persisted for more than a month; and abstention from antidepressant medication for at least 3 months. Patients with physical, mental or language limitations, a concurrent illness that would impede understanding of or participation in study assessments, psychotic or bipolar disorder, alcohol or drug dependence, or who were pregnant or breastfeeding were excluded from the study.

2.4. Intervention

INDI (Interventions for Depression Improvement) is a multicomponent programme based on the chronic care model (Bodenheimer et al., 2002) adapted to primary care settings within the Spanish public health system. It is of a training-based, organizational, clinical, and psycho-educational nature and aims to look at how the management of depression is organized within the primary care team and how the skills of health professionals can be improved in this area. One of its noteworthy features in terms of costs is that the intervention model is based on the optimization of available resources rather than the acquisition of additional resources. Moreover, the intervention model did not require more professionals than were already available at the primary care centres. The programme has been described in detail elsewhere (Aragonès et al., 2007, 2008) and an overview of the programme can be found in the online Appendix A1.

2.5. Usual care

In the control arm centres, patients with depression were attended using standard criteria and all available resources considered appropriate, including drug treatments, referrals to psychiatry, and recommendations for the use of private medical services.

2.6. Measurements and masking

The results were monitored using standardized telephone interviews conducted by a qualified independent survey taker (a psychologist). The interviewer did not know which study group the patients interviewed belonged to (blind). Follow-up interviews were conducted at 0 (base), 3, 6 and 12 months. Medication consumption data and information about work leave due to depression were obtained directly from patients' electronic medical records and pharmacy electronic billing databases.

2.7. Measurement of costs

Costs were estimated from the health system perspective, including direct intervention costs and healthcare costs related to depression care, and from the societal perspective counting direct costs plus costs for loss of productivity.

2.7.1. Direct costs

We have followed a conservative approach from a health provider and planner perspective. In order to do so, we took into account the previous analysis of the cost of depression in Catalonia

(Salvador-Carulla et al., 2011) and to have a bottom estimate for health planning and priority setting. Therefore direct costs not related to depression care and direct non-health costs were not taken into account. The costs of intervention include professional training costs (annual training workshops, periodic training sessions) and expenses related to the creation of materials (clinical manual, check-up forms, questionnaires, health education booklets, etc.). The total cost for the implementation of the INDI programme and the distribution of costs can be seen in the online Appendix A2.

The healthcare costs include costs for healthcare visits due to depression or related problems. Data on the number of primary care visits (physician, nurse and emergency services); visits with mental health specialists (psychiatrists and psychologists) at the primary care centre, a mental health centre and at private centres; hospital emergency room visits; and hospitalizations due to depression were obtained by means of patient interviews (at 3, 6 and 12 months). The costs applied for each visit were taken from official published rates and are reported in the online Appendix A2.

The costs of antidepressant, anxiolytic/hypnotic and other psychotropic medications were obtained from pharmacy billing information available on pharmacy databases. Prices were calculated using 2011 prices in Spain for each brand and pharmaceutical form used.

2.7.2. Indirect costs

These include costs incurred for temporary disability leave from work due to depression or related problems. We have incorporated the use of the conservative approach to our bottom-up estimates and minimum salary was used for calculating indirect costs related to productivity loss. These costs were calculated by multiplying the days of leave by the daily minimum wage in Spain in 2011 (España, 2010). Mortality costs were excluded as no suicide cases were identified.

2.8. Measurement of effectiveness and utility

2.8.1. Clinical effectiveness

The evolution of the severity of depressive symptoms was monitored using the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). We calculated the number of depression-free days (DFD) using the results of the PHQ-9. DFD is an outcome indicator that provides valuable insight into the experience of patients with depression (Vannoy et al., 2010; Lave et al., 1998).

A PHQ-9 score of <5 points indicates that the patient is totally free from depression. A PHQ-9 score of >14 (moderate to severe depression) indicates that the patient is fully depressed. Days with intermediate scores were assigned a value between "free of depression" (1) and "fully depressed" (0) by linear interpolation (e.g. a day with a score of 10 would correspond to 0.45 DFD). The sum of the estimations for each follow-up interval (0–3 months, 3–6 months and 6–12 months) yielded the total DFD number (Vannoy et al., 2010).

2.8.2. Utility

Utility was measured using quality-adjusted life years (QALY). QALY measure health in terms of years of life in good health. It is a measurement of subjective health that, in every period, assigns a value ranging from "perfect health" (1) to "as bad as being dead" (0) based on the subject's quality of life for that period. This parameter was obtained by applying the conversion algorithms proposed by Brazier and Roberts (2004), which are based on the relative desirability (utility) for individuals of the different outcomes on the SF-6D scale, derived from response data from the SF-12 health-related quality of life questionnaire. QALY calculations for the 12-month follow-up period used measurements at 0, 3, 6 and 12 months, with linear interpolation between these evaluation points, followed by calculation of the area under the curve (Matthews et al., 1990).

2.9. Statistical methods

The unit of analysis was the patient. The analysis was performed allowing for the mean cost per patient and mean effect per patient in each group on the basis of the initial study group assignment, regardless of the centre, the health professionals and the patient adherence to the programme. Costs and health effects were not discounted because the period of study was limited to 12 months.

Primarily, we used the data from patients with complete information during the monitoring period, and additionally we performed a sensitivity analysis where missing values were imputed using multiple imputation techniques by lineal regression models, concatenating them with the variables that have complete values (Sterne et al., 2009). Ten different imputation datasets were created using the MI programme of the STATA-11.1 package.

We determined the incremental cost-effectiveness ratio (ICER), which was calculated as the ratio between the difference in mean costs (incremental cost, ΔC) and the difference in mean health effects (incremental effect, ΔE) (ICER$=\Delta C/\Delta E$). The ICERs represent the additional cost per additional DFD and the additional cost per additional QALY obtained with the INDI programme compared to usual care.

The estimated model contemplates the differences between the intervention group and the control group and is represented by means of the following functional form:

$$\text{Cost}_i = \alpha_0 + \mathbf{Assessment}_i\alpha_1 + \mathbf{INDI}_i{*}\mathbf{Assessment}_i\alpha_2 + u_{1i}$$

$$\text{Effect}_i = \beta_0 + \mathbf{INDI}_i\beta_1 + \mathbf{Assessment}_i\beta_2 + \mathbf{INDI}_i{*}\mathbf{Assessment}_i\beta_3 + u_{2i}$$

where Assessment$=0$ if the data of the individual is from the first interview (basal), Assessment$=1$ if the data of the individual is from the last interview (12 months), INDI$=0$ if the individual belongs to the control group (usual care), and INDI$=1$ if belonging to the intervention group (INDI programme). Depending on the type of analysis, cost-utility or cost-effectiveness, Effect_i represents QALY_i or DFD_i respectively for each individual.

The ICERs are plotted on a cost-effectiveness plane with the uncertainty of these estimates represented by confidence ellipses (van Hout et al., 1994; Briggs, Fenn, 1998) where the contour lines represent the cost and effectiveness combinations with a constant density function (Nixon et al., 2010). The slope of the ellipse varies according the correlation between incremental cost and effectiveness, and was obtained by the econometric method called SURE (Seemingly Unrelated Regression Estimator) (Zellner, 1962) because the general linear model does not provide a reliable measure of the relationship between cost and effectiveness.

The likelihood that a programme will be considered cost-effective in terms of decision making depends on the willingness to pay for a given health effect, which is represented by cost-effectiveness acceptability curves (CEAC) (van Hout et al., 1994; Fenwick et al., 2004). The CEAC shows the likelihood of the cost-effectiveness of the INDI programme as compared to usual care, in a range of different willingness-to-pay values per DFD or per additional QALY.

3. Results

3.1. Sample

The study involved 338 patients, 149 in the control group and 189 in the intervention group. The baseline evaluation indicated that patients in both study groups were comparable in terms of socio-demographic and clinical characteristics (Table 1). Eight out of ten were women and the mean age was around 47. Sixty per cent were actively employed. From a clinical perspective, the baseline severity of depression was in the moderate range, and half of the patients had a prior history of depression. The primary economic evaluation was based on the 292 (86.4%) patients for whom complete data of clinical outcomes and costs were available (166 patients in the intervention group and 126 in the control group) (Fig. 1). There was a higher proportion of men in the group of patients not included in the analysis than in the group that was included (37% vs. 18.2%; χ^2: 8.559; f.d.=1; p=0.003), the mean age was lower (42.4 ± 11.2 vs. 48.5 ± 15.0; t: −2.662; f.d.=336; p=0.009) and there were no differences in other baseline socio-demographic and clinical characteristics, or in the evolution of depressive symptoms or quality of life throughout the follow-up period.

3.2. Cost of services and total costs

Table 2 shows the direct and indirect costs related to depression that were considered in this analysis. In the intervention group, the highest direct costs correspond to the use of healthcare services, especially primary care, which all together (primary care physician, nurse and emergency services) accounted for 49% of direct healthcare costs. Medication (mostly antidepressants) accounted for 13% of healthcare costs. Absenteeism accounted for about half of total costs. The distribution of costs by classification in the two study groups was not very different. The most notable differences were in the cost of nursing visits – although this represented less than 10% of direct costs – and, of course, in costs directly related to the implementation of the programme, which were only assigned for patients in the intervention group.

3.3. Cost-utility and cost-effectiveness analysis

The health outcomes achieved with the INDI model were higher than those obtained through usual care, both in terms of incremental utility (0.045 additional QALYs) and incremental clinical effectiveness (40.09 DFD). Table 3 shows these results together with incremental costs (direct and total costs).

The incremental cost-utility ratio of the INDI model compared to usual care was €4056/QALY, taking into account the cost of the intervention as well as healthcare costs (healthcare system perspective), or €3499/QALY including costs for lost work productivity (societal perspective). The incremental cost-effectiveness ratio was €4.55/DFD from the point of view of healthcare, and €3.93/DFD from the societal perspective.

Fig. 2 graphically illustrates the position of these results in terms of cost-effectiveness: the centre of the ellipse represents point estimates of incremental costs and effects, and the ellipses represent the uncertainty of the estimates. In the cost-utility analysis from the point of view of the healthcare system, the estimates (practically the entire surface of the 95% confidence ellipse) are positioned in the quadrant indicating greater utility associated with increased cost (Fig. 2(a)). At the same time, from the societal point of view, the greater the majority of the surface area of the ellipse at 95% is located in the same quadrant although a part of it is located in the area where greater utility is associated with a lower cost (Fig. 2(b)).

In the cost-effectiveness analysis, healthcare cost estimates are also positioned in the quadrant where greater effectiveness is associated with increased cost. If the cost of absenteeism is included, part of the area of the ellipse is positioned in the quadrant where greater effectiveness is associated with cost savings (Fig. 2(c) (d)).

Whether these increases in utility and effectiveness and their associated increases in cost infer a recommendation to implement

Table 1
Baseline characteristics of the sample of patients.

	INDI programme group (n=189) n (%)[a]	**Usual care group** (n=149) n (%)[a]	p value[b]
Gender: *Female*	153 (81.0%)	115 (77.2%)	0.396
Age (mean and SD)	47.5 (14.5)	47.8 (14.9)	0.857
Marital status			
Single	16 (8.5%)	20 (13.4%)	0.403
Married/living with partner	129 (68.3%)	100 (67.1%)	
Divorced/separated	27 (14.3%)	20 (13.4%)	
Widowed	17(9.0%)	9 (6.0%)	
Level of education			
No studies	20 (10.6%)	19 (12.8%)	0.843
Primary	74 (39.2%)	59 (39.6%)	
Lower secondary	36 (19.0%)	22 (14.8%)	
Upper secondary	43 (22.8%)	37 (24.8%)	
University	16 (8.5%)	12 (8.1%)	
Currently working	114 (60.3%)	88 (59.1%)	0.823
Severity of depression (PHQ-9[c] score; mean and SD)	18.10 (5.20)	17.66 (4.80)	0.429
Recurrent depression	98 (51.8%)	69 (46.3%)	0.313
Length of the current depressive episode ≥ 6 months	62 (32.8%)	43 (28.9%)	0.606
Health-related quality of life (mean and SD)			
SF-12 MCS[d]	22.27 (9.05)	22.73 (10.44)	0.533
SF-12 PCS[e]	47.48 (10.98)	48.24 (11.24)	0.661

[a] Unless stated otherwise.
[b] T test for continuous variables and Chi square test for categorical variables.
[c] Patient Health Questionnaire (qualitative scoring: > 15 points: mild depression; 15–19: moderate depression; > 19 points: severe depression).
[d] Mental Health Summary.
[e] Physical Health Summary.

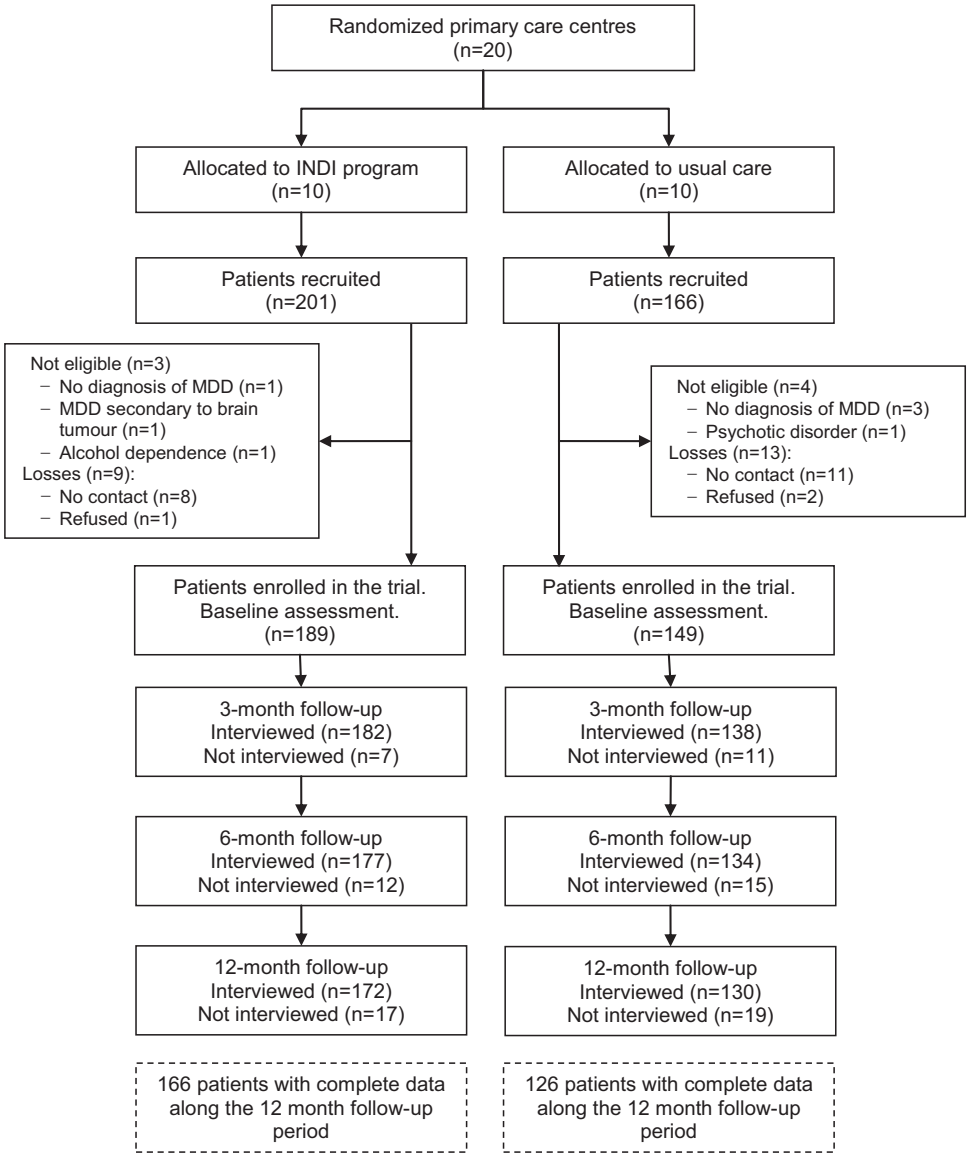

Fig. 1. Flowchart: randomization of centres and sampling and monitoring of patients.

Table 2
Direct and indirect costs related to depression in a 12-month period in patients treated in the INDI programme group and in the usual care group.

	INDI programme group ($n=166$) *mean* (*SD*)	**Usual care group** ($n=126$) *mean* (*SD*)	*p* value[a]
INDI programme	71.30	0	<0.001
Medication (total)	104.00 (143.5)	127.80 (218.30)	0.264
Antidepressants	87.2 (131.40)	91.50 (128.40)	0.781
Other psychotropic drugs	16.80 (37.80)	36.30 (129.50)	0.067
Use of health services (total)	601.00 (625.00)	466.00 (498.70)	0.047
Primary care (doctor)	296.90 (256.10)	296.90 (280.50)	0.999
Primary care (nurse)	70.20 (68.10)	27.00 (51.80)	<0.001
Primary care (emergencies)	12.00 (43.80)	11.10 (40.50)	0.859
Outpatient specialized care (psychiatrist)	56.80 (201.50)	30.90 (62.20)	0.165
Outpatient specialized care (psychologist)	108.00 (278.90)	76.30 (181.80)	0.269
Hospital (emergencies)	24.10 (96.40)	19.30 (113.20)	0.695
Hospital (inpatient)	33.10 (328.90)	4.50 (37.60)	0.333
Total direct costs[b]	776.30 (664.10)	593.80 (603.10)	0.016
Temporary disability leave from work (indirect cost)	718.30 (1587.70)	743.40 (1582.10)	0.894
Total costs (direct+indirect)	1494.60 (1911.10)	1337.20 (1806.20)	0.476

Costs are reported in euros (€).

[a] Student's T test.

[b] Direct costs include costs of the programme, psychotropic drugs and use of health services.

Table 3
Incremental costs, utility and effectiveness of the INDI program with regard to usual care.

	Cost/utility		**Cost/effectiveness**	
	(*N*=292; control=126, INDI=166)		(*N*=292, control=126, INDI=166)	
	mean (*SD*)	p value[d]	*mean* (*SD*)	p value[d]
Analysis of complete cases				
Incremental costs[a] (direct costs)	182.53 € (53.16)	0.000	182.53 (53.16)	0.000
Incremental costs[a] (including direct and indirect costs)	157.44 € (155.42)	0.311	157.44 € (155.42)	0.311
Incremental utility and effectiveness[b]	0.045 QALY (0.019)	0.017	40.09 DFD (15.79)	0.011
ICER[c] (direct costs)	4056.22 €/QALY		4.55 €/DFD	
ICER (including direct and indirect costs)	3498.67 €/QALY		3.93 €/DFD	
	(*N*=338; control=149, INDI=189)		(*N*=338; control=149, INDI=189)	
	mean (*SD*)	p value[d]	*mean* (*SD*)	p value[d]
Analysis with imputed missing values (sensitivity analysis)				
Incremental costs[a] (direct costs)	165.10 € (46.41)	0.000	165.10 € (46.41)	0.000
Incremental costs[a] (including direct and indirect costs)	186.57 € (137.79)	0.176	186.57 € (137.79)	0.176
Incremental utility and effectiveness[b]	0.043 QALY (0.017)	0.011	37.45 DFD (14.224)	0.009
ICER (direct costs)	3838.53 €/QALY		4.41 €/DFD	
ICER (including direct and indirect costs)	4338.84 €/QALY		4.98 €/DFD	

Health resources use was considered for direct costs. Temporary unfitness for work was considered for indirect costs. Costs are reported in Euros (€), utility is reported in Quality Adjusted Life Years (QALY), and clinical effectiveness is reported in Depression Free Days (DFD).
NOTE: a complete version of these tables can be found at the online Appendix A2.

[a] Additional costs per patient of the intervention group with regard to usual care in 12 months.
[b] Additional utility (QALY) or effectiveness (DFD) per patient of intervention group with regard to usual care in 12 months.
[c] ICER: Incremental cost-effectiveness ratio.
[d] Seemingly unrelated regressions method.

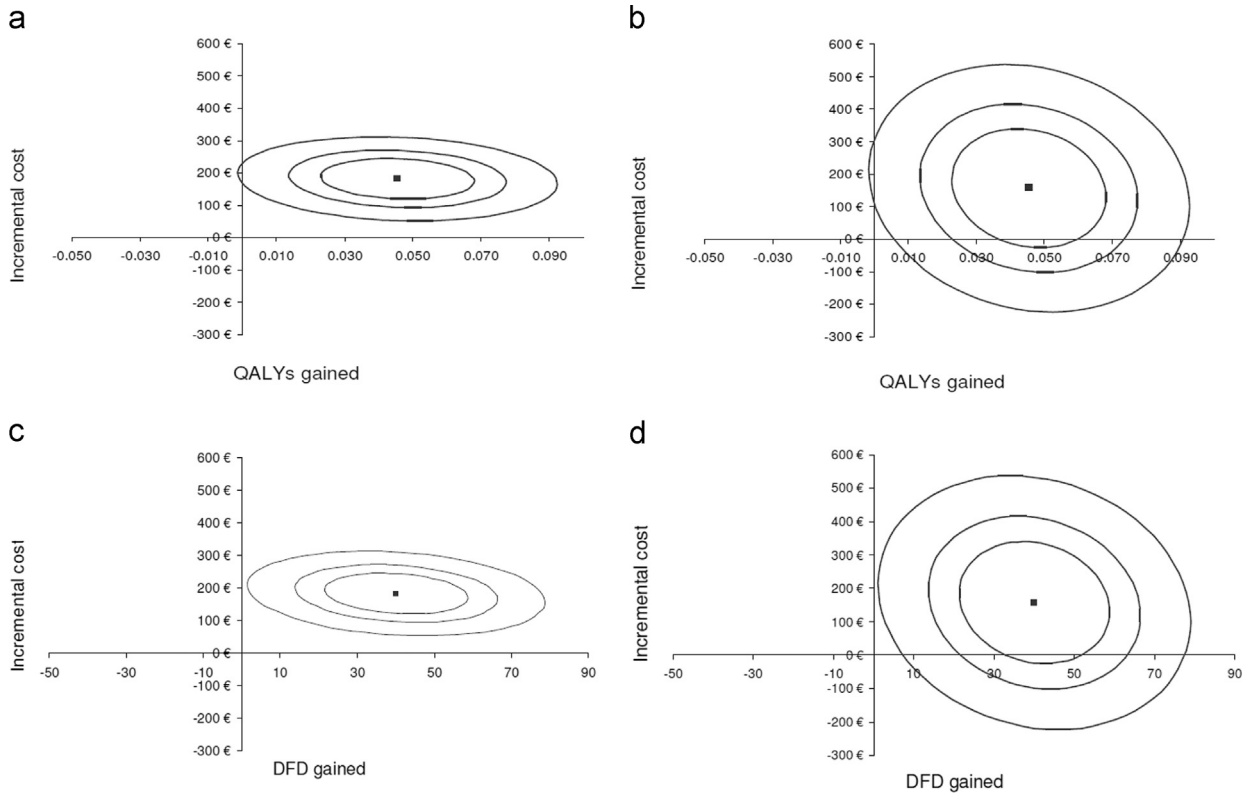

Fig. 2. Graphic representation on the cost-effectiveness plane of the incremental cost-utility ratio (cost per quality-adjusted life year; QALY) and incremental cost-effectiveness (cost per depression-free day; DFD), considering direct medical costs and total costs. a) cost-utility; diret costs, b) cost-utility; direct+ indirect costs, c) cost-effectiveness; direct costs d) cost-effectiveness; direct+ indirect costs

the INDI model depends on the degree of willingness to pay to achieve these healthcare effects. The cost-effectiveness acceptability curves (CEAC) (Fig. 3) have been plotted to facilitate well-informed decision-making. These indicate the likelihood that the cost-effectiveness (or cost-utility) ratio favours the INDI model over usual care in terms of the willingness to pay for an additional

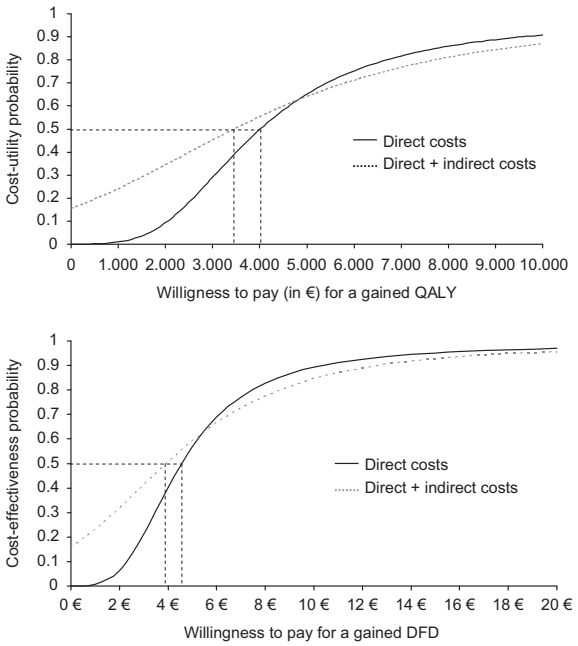

Fig. 3. Cost-effectiveness acceptability curves based on the willingness to pay for an additional quality-adjusted life year (QALY) or an additional depression-free day (DFD) achieved, considering the direct medical costs and total costs.

QALY or DFD. The estimate of €4056 per additional QALY is associated with a 50% likelihood of the INDI programme being cost-effective. If the willingness to pay is €10,000 per QALY, this likelihood increases to more than 90%.

The ICER used as a measurement of DFD effectiveness is €4.55 per additional DFD (50% likelihood), but with a willingness to pay of €13.00 per DFD, the likelihood of the intervention being cost-effective compared to usual care increases to 95%.

3.4. Sensitivity analysis

The results of the sensitivity analysis using the databases where the lost values were imputed gave rise to a slightly lower incremental cost when the direct healthcare costs are considered, whereas the total cost (including the cost due to loss of productivity) is somewhat higher. The values obtained from clinical utility and effectiveness are similar. The results of the sensitivity analysis agree with the results from the main analyses carried out with the complete cases, and reach the same conclusions (Table 3). Complete results of this sensitivity analysis are reported in the online Appendix A2 (Tables III and IV, Figures I and II)

4. Discussion

To the best of our knowledge, this is the first cost-effectiveness analysis of a collaborative care programme to improve the management of depression in primary care conducted in Spain, and one of the few studies of its kind carried out in a European healthcare system. The study shows that the INDI programme yields better health outcomes than usual care. These favourable effects were achieved with a modest increase in costs, resulting in cost-effectiveness ratios of €4,056/QALY and €4.55/DFD. When costs for lost productivity associated with depression (societal perspective) are included, the results are even more favourable for intervention (€3,499/QALY, and €3.93/DFD).

One of the notable features of the INDI programme is the low implementation cost. It uses available human and material resources more efficiently and does not require a large investment in additional resources. Furthermore, some of the costs included (e.g. costs for the actual implementation of the programme (training, materials)) have the benefit of economies of scale (i.e. the costs incurred for a few hundred patients in the clinical trial is similar to the cost of attending to a few thousand patients in a real healthcare setting). So, general implementation would result in lower per-patient costs and an even better cost-effectiveness ratio. Furthermore, the costs of the intervention itself would be progressively less significant in the long term.

It is difficult to make strict comparisons between cost-effectiveness studies conducted in different countries with different health systems because access to health resources, unit costs, the organization of healthcare levels and professional roles can vary greatly. Even if these discrepancies are taken into account, our results generally agree with those reported in the literature. In the review by Gilbody et al. (2006), most economic evaluations of programmes to improve the management of depression reported an improvement in clinical results and all of them reported increases in cost. However, our cost-effectiveness estimate of €4.55/DFD is considerably lower than the range reported ($13 to $24 per DFD). The estimates reported by Gilbody in terms of cost-utility in the range from $15,463 to $36,467 per QALY were also higher than our estimate (€4056/QALY). The results of the economic evaluation of a primary care case management programme in Germany have recently been published (Gensichen et al., 2013). In terms of direct costs, that study reported estimates of €16/DFD and €38,489 /QALY. Our more favourable results are due to lower direct costs as well as greater effectiveness. However, Gensichen shows that when lost workdays are included in the assessment, total cost is lower in the intervention group than the control group, and cost-effectiveness ratios are placed in a position of dominance (lower cost, greater effectiveness). In our study, we also saw better results when the costs of missed workdays were included, although the effect was not pronounced enough to translate into savings.

Our study has several features that should be taken into account when interpreting the results. First, we followed a conservative approach from a governmental perspective that does not include an assessment of direct non-health costs, or direct costs due to physical diseases. Following the governmental perspective, productivity losses were estimated according to the minimum wage salary and not average wages. Productivity losses only include the costs associated with workdays lost due to sick-leave attributed to depression. This conservative approach was agreed with the regional department of health in the previous study of the cost of depression in Catalonia (Salvador-Carulla et al., 2011). It is aimed at estimating 'floor' effects of the intervention and preventing overestimates due to a broad societal perspective. On the other hand, health costs due to physical conditions should not be included in the bottom-up cost-effectiveness analysis of low-resource mental health interventions on reduced samples, as a single unrelated event in one arm (e.g., a stroke, or a surgical intervention) may have a huge impact on the costs of the related group.

The study has some limitations to consider. The diagnosis of major depression in patients was made according to the clinical assessment of the participating doctors, and the PHQ-9 was used to ensure that the DSM-IV and severity criteria were complied with, but there was no independent diagnostic assessment with a standardized diagnostic interview. This may generate some uncertainty about the reliability of the diagnosis.

In our study, 13.6% of the patients in the initial sample lacked complete data on resource use or on their clinical evolution.

Although we used imputation techniques for the missing data and performed a sensitivity analysis leading to similar results to those obtained in the main analysis, we cannot rule out the possibility that the loss of this data may have introduced a bias into the results.

There is evidence that the non-healthcare costs of depression represent the largest share of the total costs of depression (Salvador-Carulla et al., 2011; Gustavsson et al., 2011), and in our study the data available related to the cost of depression in this respect was limited: we considered the costs associated with missed workdays, but not data on the financial impact of depression for unpaid work (e.g. housewives, students), on the family (e.g. the need for informal care), or the impact of presenteeism (reduced productivity without missed workdays).

Depression may be associated with increased costs due to a general increase in the use of healthcare services (not only services strictly related to the treatment of depression). The review by Jacob et al. (2012) reports that several studies have found that the improved evolution of depression (as a result of the effectiveness of collaborative care programmes) leads to a decrease in total healthcare costs due to a general decrease in the use of healthcare services (cost-offset). Katon et al. (2012) reports that a collaborative care programme aimed at optimizing the management of depression combined with interventions to improve diabetes and coronary heart disease achieved an increase in DFD in a range comparable to our study (47 DFD in the first year of follow-up). However, the cost calculations reflect greater savings for the intervention group resulting in an adjusted ICER of −$5.30/DFD. In our study we took the cost of using services directly related to depression into account; however, the design of the study does not shed light on the economic impact (potentially in the form of savings) of a decrease in overall healthcare use or the impact of improvement of depression in the evolution of other concomitant chronic diseases.

4.1. Implications

The primary purpose of this cost-effectiveness analysis is to guide the decision-making process with regard to the general application of the INDI programme for the management of depression. As such, considering and interpreting the results in terms of determining factors on a local level is equally or more important than comparisons with other studies. Willingness to pay is a critical factor in the decision to implement the programme. In Spain, allocating up to €30,000 to achieve an additional QALY has been considered a reasonable threshold (Sacristán et al., 2002). This is clearly higher than our cost-utility estimates (even taking into account their uncertainty). This may support the recommendation to implement the INDI model on a wide scale to improve the clinical results of depression in primary care in Spain. Naturally, this financial threshold is not an absolute condition, but must be evaluated and adjusted according to the availability of resources and the political and social priorities at any given time. Moreover, there are criteria other than financial efficiency that must also be taken into account, such as equity, sustainability and social responsibility. In this regard, we should note that the INDI programme is designed to be implemented in primary care, which is the level of care that provides greater accessibility and the level in which the most common mental healthcare problems in the population can be handled with the greatest equity and efficiency (WHO, 2001, 2008; Bower and Gilbody, 2005). It is important to note that Spain has a universal public health care system covering nearly the entire census population. The system is arranged into small health areas corresponding to a primary care centre. A number of primary care centres are related to a single community mental health centre and to a hospital for inpatient care. Primary care centres are the gatekeepers of the local health system. Therefore any intervention provided at a primary care centre will be available for the whole population of the related health area. The characteristics of the Spanish primary care system and the mental health system have been described elsewhere (Borkan et al., 2010; Salvador-Carulla et al., 2010). Furthermore, the programme is aligned – in its objectives and in its development – with the current priorities and strategies for addressing mental healthcare and chronicity established in Europe (Nolte and McKee, 2008; Busse et al., 2010) and with the Spanish healthcare system (Ministry of Health, Social Services and Equality, 2011; Orozco-Beltrán and Ollero Baturone, 2011).

Role of funding source

This study has been funded by grants from the Carlos III Health Institute of the Spanish Ministry for Health and Consumption (FIS Exp. PI060176), the IDIAP Jordi Gol (2007), and has received the 18th Ferran Salsas i Roig Award – Mental Health and Community (Rubí Town Council). Germán López-Cortacans is grateful to the IDIAP Jordi Gol for a predoctoral grant (2011). The funding sources had no role in the study design, data collection, analysis, interpretation, preparation or review of the manuscript, or the decision to submit the article.

Conflict of interest

Aragonès has received honoraria for educational activities from Esteve and Lilly, and as a research advisor and for meeting expenses from Lilly. All authors declare no other relationships, interests or activities that may appear to have influenced the submitted work.

Acknowledgements

This study has been possible thanks to the generous cooperation of the doctors and nurses involved at the participating primary care centres which make up the INDI research group, listed in the appendix A3 available online.

Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2014.01.021.

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