**Cost-effectiveness of antidepressants versus active monitoring for mild-to-moderate major depressive disorder: a multisite non-randomized controlled trial in primary care (INFAP study)**

**Maria Rubio-Valeraa,b,c,\*, María Teresa Peñarrubia-Maríad, Maria Iglesias-Gonzáleze, Martin Knappb,f, Paul McCroneg, Marta Roiga,c, Ramón Sabes-Figuerab,h, Juan V. Lucianoa,i,j, Juan M. Mendivei,k, Ana Gabriela Murrugara-Centurióna,i, Jordi Alonsob,l,m, Antoni Serrano-Blancob,e**

a Research Unit, Institut de Recerca Sant Joan de Déu, C/ Pablo Picasso 12, 08830, Sant Boi de Llobregat, Spain.

b Centre for Biomedical Research in Epidemiology and Public Health, CIBERESP, Madrid, Spain.

c Dept. Pharmacology, Toxicology and Therapeutic Chemistry, School of Pharmacy, Universitat de Barcelona, Barcelona, Spain.

d Primary Care Health Centre Bartomeu Fabrés Anglada, Servei d’Atenció Primària Delta Llobregat, Àmbit Costa de Ponent, Institut Català de la Salut, Gavà, Spain.

e Research Unit, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain.

f Personal Social Services Research Unit, London School of Economics and Political Science, Houghton Street, London, UK.

g Institute of Psychiatry, King’s College London, De Crespigny Park, London, UK

h Faculty of Economic and Business Sciences, Universitat Pompeu Fabra, Barcelona, Spain

i Primary Care Prevention and Health Promotion Research Network (RedIAPP), Barcelona, Spain.

j Open University of Catalonia (UOC), Barcelona, Spain.

k La Mina Primary Care Centre, Institut Català de la Salut. Sant Adrià de Besós (Barcelona), Spain.

l Health Services Research Unit, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain.

m Dept. Experimental and Health Sciences, Pompeu Fabra University (UPF), Barcelona, Spain.

**Corresponding author**

Dr. M Rubio-Valera

Research & Development Unit,

Parc Sanitari Sant Joan de Déu

C/ Dr. Antoni Pujadas 42, 08830

Sant Boi de Llobregat, Barcelona, Spain

Tel: +34 936406350 (Ext. 1-2540)

Email address: mrubio@pssjd.org

**Abstract**

**Background**

The purpose of this study was to evaluate the cost-effectiveness of antidepressants vs active monitoring (AM) for patients with mild-moderate major depressive disorder.

**Methods**

A 12-month observational prospective controlled trial. Adult patients with a new episode of major depression were invited to participate and assigned to AM or antidepressants according to General Practitioners’ (GP) clinical judgment and experience. Patients were evaluated at baseline, 6 and 12-month follow-up. Quality adjusted life years (QALYs) gained were estimated and used to calculate incremental cost-utility ratios (ICUR) from the healthcare and government perspective. To minimize the bias resulting from non-randomization, a propensity score-based method was used.

**Results**

At 6 and 12-month follow-up, ICUR was 2,549 €/QALY and 6,142 €/QALY, respectively, in favor of antidepressants. At 6 months, for a willingness to pay (WTP) of 25,000 €/QALY, antidepressants had a probability of 0.89 (healthcare perspective) and 0.81 (government perspective) of being more cost-effective than AM. At 12 months, this probability was 0.86 (healthcare perspective) and 0.73 (government perspective).

**Conclusions**

Incremental cost-utility ratios favor pharmacological treatment as a first-line approach for patients with mild-moderate major depressive disorder. While our results should be interpreted with caution and further real world research is needed, clinical practice guidelines (CPG) should consider antidepressant therapy for mild-moderate major depressive patients as an alternative to active monitoring in PC.

**Keywords**

Depression/Mood Disorder; Antidepressant Medication; Primary Care; Health economics.

# Background

Active monitoring (AM) has been proposed as an adequate approach for the management of mild-to-moderate major depression [1, 2], which is usually treated in primary care (PC) [3, 4]. Mild-to-moderate forms of major depression fulfil all DSM-IV criteria for major depression, including the presence of five out of the nine of possible symptoms for at least 2 weeks, but present with mild-moderate functional impairment. In AM, the patient and general practitioners (GP) agree to observe the development of symptoms before starting treatment with antidepressants [5]. Although variations exist across regions, AM implies close monitoring of the course of the illness by the GP, who may accompany monitoring with low-intensity psychosocial interventions such as brief cognitive behavioral therapy (CBT), counseling or problem-solving therapy (PST) [1, 2]. The GP can also recommend self-help programs or moderate-intensity exercise programs. If symptoms worsen, the GP could suggest initiating treatment with antidepressants or refer the patient to specialized care as part of the AM intervention.

Antidepressants are the first-line treatment options for high-risk patients with mild-to-moderate major depression [1, 2] but have been shown to have limited benefits in patients with mild-to-moderate depressive symptoms [6]. Most clinical practice guidelines (CPG) for the treatment of major depression in PC recommend AM as the first-line treatment. Diagnostic concordance between GP and structured validated interviews is low [7, 8] and a high proportion of patients without mood disorders are treated with antidepressants and other psychotropic drugs [9]. Routine use of AM could limit the exposure of patients with minor depression or psychological distress to antidepressants. Other advantages of AM include avoiding the side-effects of drugs and their interactions as well as limiting the burden of the stigma associated with the treatment.

However, in real-life routine practice conditions, the heavy burden on physicians, their lack of training in psychotherapy and their attitudes towards mental health could limit adherence to clinical-guideline recommendations on AM interventions [10, 11], leading to patients receiving no treatment at all [5]. Lack of treatment could result in worsening symptoms and increasing costs associated with health service use and productivity losses.

Available evidence on the efficiency of AM in comparison with antidepressants is limited and contradictory. An economic evaluation comparing treatment with and without antidepressants in patients with minor or mild-major depressive disorder observed no differences in cost-effectiveness between the two treatment strategies [12]. Conversely, the THREAD study [13] showed that the use of antidepressants plus supportive care could be more efficient than supportive care alone, although the probability of the intervention with antidepressants being more cost-effective was only 75% for a value of £30,000 per QALY and the probability of the intervention being more cost-effective diminished from 12 to 26 weeks.

In this study, we evaluated the cost-effectiveness of AM in comparison with antidepressants for the treatment of mild-to-moderate major depression in PC. The study aimed to evaluate AM in an observational controlled trial.

# Methods

This was a 12-month observational controlled trial conducted in 12 PC practices in Barcelona (Spain) [14]. The participating GPs (n=53) received two 1.5-hour training sessions on the diagnosis of major depression and non-pharmacological treatment (AM, sleep hygiene, counseling, frequency of follow-up visits, health education and low-intensity psychological therapies) and pharmacological treatment for major depression. Monthly newsletters were sent to the GPs to remind them about the content of the training sessions.

## Participants

Adult patients with a new episode of major depression were invited to participate (June 2013-July 2014). We excluded patients who had taken an antidepressant medication in the previous 60 days; those presenting psychotic or bipolar disorders or those who had taken antipsychotics, lithium or antiepileptics in the previous six months; those with history of drug abuse or dependency; and those with cognitive impairment that prevented an assessment interview.

## Interventions

Participants were assigned to AM or antidepressants according to GPs’ clinical judgment and experience. AM was delivered as in real-life routine practice. The Catalan CPG recommends monitoring the patient within 15 days following diagnosis when conducting AM [2]. Over the following 10-12 weeks, the guidelines recommend six to eight follow-up visits. The GPs could consider low-intensity psychosocial therapies and structured moderate-intensity exercise programs. If the patient’s condition does not improve, GPs can initiate antidepressants. Adherence to AM was controlled through patient interviews.

The patients in the medication group received the antidepressants typically prescribed in Spanish PC at doses usually recommended according to their symptoms and characteristics. The national guidelines recommend initiating treatment with SSRIs [2]. Adherence to antidepressants was assessed though medical record information (prescription filled).

## Data Collection and Measures

Prior to the study, GPs completed a questionnaire on sociodemographic characteristics, job characteristics, training, attitude towards depression, interest in mental health and participation in communication groups [15]. Patients were evaluated at baseline, 6 and 12-month follow-up.

Service utilization and cost measures

Healthcare sector and government perspectives were used for the analysis. Using the Client Service Receipt Inventory [16], we collected information on medical tests, emergency visits, hospital stays and visits to psychologists, psychiatrists, other specialists, GP, nurse and social worker. Information on the use of psychotropic medicines and productivity losses were collected from medical records to improve accuracy.

The Catalan Government Official Bulletin was reviewed to retrieve public health service tariffs for 2015. The reference price of the generic version of drugs was extracted from the Spanish Drugs Catalogue and used to calculate the mean price per milligram of the antidepressants prescribed. Productivity losses were calculated based on the human capital approach using information on the minimum and average daily wage in Spain [17]. Table 1 shows unit costs used in the study.

Clinical outcomes

Clinical outcomes were assessed at baseline, six and twelve months by an external researcher. The European Quality of Life instrument (EuroQol-5D-3L) was used to measure health-related quality of life [18, 19]. QALYs were calculated by multiplying the utility based on EQ5D by the amount of time a patient spent in this particular health state. Transitions between health states were linearly interpolated [20]. We used the Patient Health Questionnaire 9 (PHQ-9) to assess changes in depression severity [21–23].

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used to confirm clinical diagnosis [24]. GPs were blind to the DSM-IV diagnosis and patient inclusion was based on their criteria. Sociodemographic characteristics and chronic physical conditions were assessed using check-lists.

Further details on the battery of measures are provided elsewhere [14].

## Statistical Analysis

A detailed description of the statistical methods is provided in the Supplementary files. The base-case analysis was an intention-to-treat analysis. To deal with missing data, we used multiple imputations by chained equations. To minimize the bias resulting from non-randomization, a propensity score-based method –the inverse probability-weighted and regression-adjustment method (IPWRA)– was used [25].

Differences in costs and QALYs between groups were estimated using weighted regression models. A secondary analysis was performed in which effects were measured in terms of increased probability of remission of depressive symptoms. We ran these models in each of the imputed databases and combined resulting estimates in differences in costs and QALYs to calculate incremental cost-effectiveness ratios (ICER=mean difference in costs/mean difference in effects).

We used bootstrapping (5000 replications) to assess uncertainty and to construct cost-effectiveness planes and cost-effectiveness acceptability curves.

Five sensitivity analyses were performed: 1) an analysis not adjusted for the propensity score; 2) an analysis including only patients that fulfilled DSM-IV criteria for MDD; 3) an analysis using the mean average salary instead of the minimum average salary for productivity losses; 4) a per protocol (PP) analysis; 5) an analysis of completers.

For the PP analysis, adherence in the AM group was defined as receiving at least 3 follow-up visits and one of the recommended interventions. Adherence in the antidepressants group was defined as having a medication possession ratio≥0.8.

Based on previous experience in studies with similar populations and setting,[26–28] we aimed to include 150 patients per treatment arm [14].

# Results

Figure 1 presents the study flow chart. Overall, 263 patients with a new episode of mild-moderate major depressive disorder were included in the study and received AM (118) or antidepressants (145). Some 26% of the participants were lost to follow-up and there were no statistically significant differences between study arms in attrition rate. Forty (AM) and 88 (antidepressants) patients adhered to the intervention and were included in the PP analysis.

Table 2 presents the characteristics of the sample. Most participants were women, with a mean age of 49 years and either primary or primary/secondary level of education. Only 30% of participants were in paid employment and only 31% had major depressive disorder according to DSM-IV criteria. Most GPs were women (85%; n=45) with a mean age of 44.3 (SE=1.03) (range: 30-60).

At baseline, patients with a panic disorder with agoraphobia or dysthymia and those with more positive perceptions about medications or a higher disability had a higher probability of receiving antidepressants (p<0.05). After adjusting for the propensity score, no statistically significant differences existed between groups.

Table 2 shows the number and type of non-pharmacological interventions applied, as reported by patients. The AM arm received a greater number of interventions although a low number of interventions were applied. Considering specific interventions, the only differences between groups were observed in the proportion of patients receiving physical exercise recommendations and alternative therapies. There were no differences between arms in the mean number of follow-up visits.

## Cost-effectiveness of antidepressants vs AM

A comparison of components of costs is provided in Supplementary table 1. Both at 6 and 12 months, the antidepressants arm made higher costs on pharmacological treatment. No other statistically significant differences in costs were observed. Table 4 shows the results of the cost-effectiveness analysis after 6 and 12-month follow-up for the base-case and all the sensitivity analyses.

### Base-case Analysis

At 6 months, there was a small non-statistically significant difference in costs between groups from both the government and healthcare perspectives. Non-statistically significant gains in QALY were observed in favor of patients prescribed antidepressants. The incremental cost-utility ratio was 2,177€/QALY gained (government perspective) and 2,549€/QALY gained (healthcare perspective) in the antidepressants treatment arm.

Figure 2 shows cost-utility planes from the government and healthcare perspectives at 6-month follow-up. In the analysis using the government perspective, 53.8% of the cost-utility pairs were in the north-east quadrant (more effective and more expensive) and 40.9% in the south-east quadrant (more effective and less expensive). Similar results were found from the healthcare perspective.

Figure 2 shows the cost-utility acceptability curves. For a willingness to pay (WTP) of 25,000€/QALY gained, the probability of antidepressants being more cost-effective than AM was 80.8% from the healthcare perspective and 89.1% from the government perspective.

At 12 months, no statistically significant differences in costs or effects were observed between groups. The mean difference in QALYs was 0.03 in favor of patients in the antidepressants arm. Patients receiving antidepressants generated a mean of 269€ (government perspective) and 156€ (healthcare perspective) extra costs, resulting in an ICUR of 10,593€/QALY and 6,142€/QALY from the government and healthcare perspectives, respectively.

Concerning cost-effectiveness planes, similar results were observed from both perspectives, with most of the cost-effectiveness pairs in the north-east quadrant (76.5% from the government perspective and 77% from the health-care perspective). Antidepressants had a 72.6% and 86.1% probability of being more cost-effective than AM if WTP was 25,000€ from the government and healthcare perspectives, respectively (Figure 3).

### Sensitivity Analyses

All five sensitivity analyses showed mostly consistent results with small differences in costs and effects between groups both at six and twelve-month follow-up. These results were in line with the findings of the main analyses. Statistically significant differences in QALYs were seen at 6 and/or 12 months in favor of antidepressants in the sensitivity analysis using generalized linear models without propensity score correction and when only those patients with major depression according to DSM-IV criteria were included.

At 6 months, differences in costs ranged from -548.3€ to 137.6€ while differences in QALY ranged between 0.01 and 0.03. In three scenarios (patients with a DSM-IV diagnosis of depression, PP analysis and completers’ analysis) antidepressants dominated AM. In the other analyses, the highest ICUR was 10,226€/QALY. Cost differences at 12 months varied from -162€ to 688€ while effect differences were 0.03 to 0.08. In the PP analysis, antidepressants dominated AM. In the remaining analyses, the ICUR ranged from 690 to 27,092€/QALY.

*Remission of Symptoms*

Supplementary table 2 show the results of the cost-effectiveness analysis in terms of remission of depressive symptoms after 6 and 12-month follow-up for the base-case and all the sensitivity analyses. No statistically significant differences between groups were observed in either difference of costs or remission of symptoms at any follow-up point or sensitivity analysis. At 6-month follow-up, the antidepressants arm generated higher costs and effects in the main analysis and most sensitivity analyses. Antidepressants dominated AM in the PP and completers’ analyses. At 12 months, antidepressants generated higher costs and had a lower probability of leading to a remission of symptoms in most of the analyses.

# Discussion

Although many CPG recommend AM for the treatment of mild-to-moderate major depression in primary care [1, 2], evidence regarding its effectiveness and efficiency is scarce and contradictory [29, 30]. Results from our non-randomized study show that incremental cost-utility ratios favor antidepressants as a first-line approach for patients with mild-moderate major depressive disorder over the active monitoring (AM) approach, in particular during the first 6-month follow-up, although neither differences in costs or benefits were statistically significant.

Differences in costs and QALY may not reach statistical significance in the main analyses nor in most of the sensitivity analyses but cost-utility acceptability curves show that antidepressants have a higher probability of being more cost-effective than AM, especially from a healthcare perspective and after 6 months of treatment. Nevertheless, this difference is not sustained over time, as results at twelve months show a decline in relation to ICUR values that could be due to many factors including the natural remission of the disease [31]. As a consequence, conclusions might be difficult to draw after one year.

Incremental cost-utility ratios for the main analyses and the sensitivity analyses at both follow-up points are below the recently published limits for Spain (20,000€-25,000€/QALY) [32] and well below values in other European countries [33]. Although the aim of this study was to shed light on whether AM in mild-moderate MDD could be a feasible and cost-effective alternative to pharmacological interventions in current PC practice, the results are inconclusive and difficult to interpret. Literature from other European countries also underlines difficulties in supporting a full AM approach for the treatment of mild- to-moderate MDD. The THREAD study [13] claimed that adding an antidepressant seemed to be more efficient although they only followed patients up for 6 months and the probability of the intervention being cost-effective dropped from 3 to 6 months, when it was only 75% for a WTP of £30,000 per QALY. Bosmans et al. 2008 followed up 89 patients for 12 months and found no differences between patients in the antidepressants group and the non-pharmacological group. However, they pointed out that the limited sample size and drop-outs could have limited their capacity to detect differences [12].

The sensitivity analyses showed small variations in the results. In all cases, the results favoured antidepressants, with ICUR below the willingness to pay threshold in Spain (25000 €/QALY) in all the sensitivity analysis with the exception of the one that used the average absenteeism salary for sick leave (ICUR = 27092 €/QALY). The antidepressants groups dominated the AM approach in the PP analysis and when patients with MDD according to DSM-IV criteria were examined. Although conclusions should be considered with caution, mainly due to limited sample size and follow-up duration, it seems that patients meeting diagnostic criteria for MDD and those who adhere to the interventions have a better response to the pharmacological treatment. It is increasingly recognized that the majority of patients who attend a PC practice present sub-threshold depressive symptoms, which do not meet the full diagnostic criteria for MDD but can be very disabling with respect to everyday life functionality [1]. As a consequence, and bearing in mind the naturalistic aim of the study, these results must be interpreted carefully when choosing the best treatment approach for depressed patients in a PC setting. Sensitivity analyses of this type were not conducted in previous studies and need to be explored in the future.

*Strengths and limitations*

This is the study with the largest sample size and longest follow-up period to compare the cost-effectiveness of antidepressants and AM [29, 30]. Furthermore, the naturalistic aim of the study and the participation of PCHCs from very different parts of the city and surroundings areas of Barcelona increase the external validity of the results. However, the study has a series of limitations that must be considered when interpreting its results. Although this was the study with the largest sample size evaluating this topic, it may have been underpowered to detect differences in cost-effectiveness. The naturalistic nature of the study implies the use of wide inclusion criteria, non-randomized group assignment and lack of blinding for physicians and participants and could have introduced bias. It seems likely that GPs will allocate patients presenting more severe symptoms to the antidepressants arm, giving it more opportunities for improvement. There were no statistically significant differences in the sociodemographic or clinical characteristics between the two treatment arms with the exception of the presence of panic disorder, which was more frequent in the AM group, which is likely a spurious result. Also, factors determining the use of pharmacological or non-pharmacological interventions are likely to be related to patient preferences, GPs’ habits and PC centre traditions (biomedical vs biopsychosocial models) and confidence in the use of antidepressants and/or brief psychological interventions. In order to reduce bias from the lack of randomization, propensity score techniques were used to balance groups. These techniques have previously been used in quasi-experimental studies and economic evaluations to limit the impact of non-randomization [34–37]. However, it is possible that observed differences are due to unmeasured confounders. This is a particular issue in this case since the differences in costs and effects are small so it would only take a small confounding effect to alter the results.

Participants reported that GPs applied very few interventions by in relation to the depressive episode. Around 50% of participants reported receiving active listening but among the interventions recommended by the CPG, the only differences between groups were for PST and only 15% of patients had received it in the AM group. Memory bias could partially explain these low rates of interventions reported. To guarantee naturalistic conditions in the present study, GPs received brief training on AM principles but no strict intervention protocol was used. Furthermore, non-adherence to antidepressants and AM could also reduce its effectiveness on the antidepressants group [38, 39]. A sensitivity analysis using a PP analytical strategy was performed to determine the impact of adherence to the protocol in both the AM and antidepressants groups.

Almost 26% of participants were lost to follow-up. To minimize this, we used multiple imputation techniques and also conducted a complete case analysis.

# The results of this study indicate that adherence to active monitoring is low. Future research should explore the barriers that primary care physicians encounter when trying to conduct active monitoring, taking into account also the patient perspective. The results of these studies would be useful to design strategies to enhance adherence to active monitoring recommendations, improving their effectiveness and their efficiency in the clinical practice. Furthermore, the cost-effectiveness of AM in comparison with antidepressants should be evaluated in patients with different psychiatric diagnosis. The problem of adequate diagnosis of depression in PC not only affects AM. Strategies to improve the adequacy of diagnosis and treatment of depression in PC should be developed and implemented and their impact on the efficiency of AM should be evaluated.

# Conclusions

There is not enough information available to conclude that AM in mild-moderate MDD is a feasible and cost-effective alternative to pharmacological interventions in current PC practice. On the contrary, up to 12-months follow-up, it seems that incremental cost-utility ratios favor pharmacological treatment as a first-line approach to improve quality of life in these patients. Due to the high prevalence of the disease and the impairment generated by it, which is a great burden on the PC setting, efforts should be directed to train GP in effective and efficient interventions. In view of the results of this and previous studies, CPGs should review the recommendations for mild-moderate major depression so that they reflect available resources in PC while more research is carried out with larger sample sizes and longer follow-up periods and in different countries and contexts.

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**Legends**

Color should not be used for figures in print.

**Figure 1.** Flow of the participants in the study

**Figure 2.** Cost-utility planes and cost-utility acceptability curves of AM vs antidepressants

QALYs = Quality Adjusted Life Years.

Fig 2a: Cost-utility plane from the healthcare perspective at 6-month follow-up; Fig 2b: Cost-utility plane from the government perspective at 6-month follow-up; Fig 2c: Cost-utility acceptability curves from the healthcare and government perspective at 6-month follow-up; Fig 2d: Cost-utility acceptability curves from the healthcare and government perspective at 12-month follow-up.

Table 1. Unit costs for resources in Euros (€,year 2015)

|  |  |
| --- | --- |
| **Type of utilization** | **Unit costs (€)** |
| **Visit to family physician** | 40.0 |
| **Visit to nurse** | 28.0 |
| **Visit to psychologist** | 54.9 |
| **Visit to medical specialists (including psychiatrist)** | 54.9 |
| **Visit to dentist in the primary care practice** | 49.0 |
| **Hospital emergency visit** | 98.8 |
| **Hospital stay (per day)** | 536.0 |
| **Diagnostic test (range)** | 3.7-197 |
| **Pharmacological treatment** | Depending on type and dose\* |
| **Visit to social worker** | 40.0 |
| **Absenteeism from work (minimum daily wage)** | 21.6 |

\*The cost of prescribed medications was calculated by determining the price per milligram for each active principle

Table 2. Sociodemographic characteristics of the sample at baseline and interventions delivered, according to treatment arm

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Antidepressants (n=145)** | **Active monitoring (n=118)** | **p-value** | **p-value adjusted by PS** |
| **Gender, % women (n)** | 77.93 (113) | 84.75 (100) | 0.161 | 0.719 |
| **Age, mean (SD)** | 49.72 (14.91) | 47.96 (16.02) | 0.360 | 0.522 |
| **Civil status, % (n)** |  |  | 0.242 | 0.126 |
| Single | 11.72 (17) | 20.34 (24) |  |  |
| Married | 62.07 (90) | 59.32 (70) |  |  |
| Separated/divorced | 19.31 (28) | 14.41 (17) |  |  |
| Widow/widower | 6.90 (10) | 5.93 (7) |  |  |
| **Education, % (n)** |  |  | 0.806 | 0.638 |
| No formal education | 6.21 (9) | 8.47 (10) |  |  |
| Primary | 17.24 (25) | 16.95 (20) |  |  |
| Completed primary education | 25.52 (37) | 28.81 (34) |  |  |
| Secondary | 37.93 (55) | 31.36 (37) |  |  |
| University | 13.10 (19) | 14.41 (17) |  |  |
| **Work status, % (n)** |  |  | 0.579 | 0.826 |
| Paid employment | 26.90 (39) | 31.36 (37) |  |  |
| Unpaid work | 8.97 (13) | 16.10 (19) |  |  |
| On sick leave | 18.62 (27) | 15.25 (18) |  |  |
| Unemployed (with unemployment benefits) | 19.31 (28) | 15.25 (18) |  |  |
| Unemployed (without benefits) | 13.79 (20) | 11.86 (14) |  |  |
| Retired | 10.20 (12) | 10.17 (12) |  |  |
| **Place of birth, % (n)** |  |  | 0.912 | 0.589 |
| Catalonia | 50.34 (73) | 51.72 (60) |  |  |
| Other Spanish regions | 31.72 (46) | 29.31 (34) |  |  |
| Other countries | 17.93 (26) | 18.97 (22) |  |  |
| **Mental disorders according to DSM-IV criteria, % (n)** |  |  |  |  |
| Major depression | 33.79 (49) | 27.12 (32) | 0.244 | 0.188 |
| Past episode of major depression | 16.55 (24) | 14.41 (17) | 0.633 | 0.295 |
| Dysthymia | 8.28 (12) | 1.69 (2) | 0.018 | 0.708 |
| Panic disorder | 18.62 (27) | 12.71 (15) | 0.193 | 0.787 |
| Panic disorder with agoraphobia | 8.97 (13) | 2.54 (3) | 0.030 | 0.462 |
| Social phobia | 4.14 (6) | 3.39 (4) | 0.752 | 0.765 |
| Specific phobia | 0.69 (1) | 0 (0) | 0.366 | 0.298 |
| Generalized anxiety disorder | 4.83 (7) | 2.54 (3) | 0.335 | 0.176 |
| Adjustment disorder | 8.97 (13) | 13.56 (16) | 0.237 | 0.989 |
| **Health related quality of life, mean EQ-5D-3L score (SE)** | 0.571 (0.017) | 0.605 (0.017) | 0.167 | 0.634 |
| **Disability, mean WHODAS score (SE)** | 39.28 (1.81) | 32.93 (1.82) | 0.015 | 0.191 |
| **Beliefs about medication, mean BMQ (general medication) score (SE)** | 22.46 (0.44) | 24.31 (0.51) | 0.006 | 0.444 |
| **Comorbidities** |  |  |  |  |
| Cardiovascular diseases, % (n) | 37.24 (54) | 35.59 (42) | 0.782 | 0.623 |
| Respiratory diseases, % (n) | 7.59 (11) | 10.17 (12) | 0.461 | 0.474 |
| Pain, % (n) | 57.24 (83) | 63.56 (75) | 0.298 | 0.543 |
| Digestive diseases, % (n) | 80.28 (12) | 11.02 (13) | 0.451 | 0.513 |
| Sense organs diseases, % (n) | 51.03 (74) | 45.76 (54) | 0.395 | 0.674 |
| **GP characteristics** |  |  |  |  |
| Gender, % women (n) | 82.76 (120) | 84.75 (100) | 0.665 | 0.824 |
| Age, mean (SE) | 46.07 (0.55) | 45.61 (0.62) | 0.579 | 0.231 |
| **Mean number of non-pharmacological interventions received during follow-up (SE)$** | 1,05 (0.10) | 1,40 (0.09) | 0.009 | n.a. |
| **Mean number of follow-up visits in primary care (SE)**$ | 5.26 (0.52) | 4.90 (0.45) | 0.621 | n.a. |
| **Non-pharmacological interventions received, % (n)$** |  |  |  |  |

Table 3. Antidepressants incremental cost-utility ratios at 6 and 12-month follow-up for the main and sensitivity analyses\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Cost difference € (95% CI) | Difference in QALY (95% CI) | ICUR (€/QALY) | Cost difference €  (95% CI) | Difference in QALY (95% CI) | ICUR (€/QALY) |
|  | **6-month follow-up** |  |  | **12-month follow-up** |  |  |
| **Main analysis (ITT)** |  |  |  |  |  |  |
| Healthcare perspective | 27.6 (-102.0, 157.2) | 0.01 (-0.01, 0.03) | 2549 (-4616; 8413) | 156 (-149, 461) | 0.03 (-0.01, 0.06) | 6142 (-30117; 40286) |
| Government perspective | 23.6 (-289.4, 336.5) | 0.01 (-0.01, 0.03) | 2177 (-5394; 12088) | 269 (-260, 798) | 0.03 (-0.01, 0.06) | 10593 (-62446; 87687) |
| **Sensitivity analyses** |  |  |  |  |  |  |
| Analysis with generalized linear models (no correction for propensity score) | 137.6 (-246.4, 521.6) | **0.01 (0.002, 0.025)** | **10226 (4991; 20625)** | 294.9 (-298.6, 888.4) | 0.04 (-0.01, 0.09) | 10241 (-16288; 92294) |
| Patients with major depression according to DSM-IV criteria (n=82) | -59.1 (-593.1, 474.8) | **0.03 (0.01, 0.05)** | -2273 (-8163; 6310) | 53 (-782, 888) | **0.08 (0.02, 0.14)** | 690 (-21610; 52629) |
| Average absenteeism salary costs | 104.5 (-759.3, 968.2) | 0.01 (-0.01, 0.03) | 9659 (-4223; 37073) | 688 (-669, 2045) | 0.03 (-0.01, 0.06) | 27092 (-179307; 212583) |
| Per protocol analysis (n=128) | -548.3 (-1125.4, 28.8) | 0.02 (-0.01, 0.05) | **-23328 (-73422; -16738)** | -162 (-1003, 679) | 0.05 (-0.01, 0.11) | -3257 (-65604; 42122) |
| Completers’ analysis (6-month n=214; 12-month n=195) | -21.0 (-409.3, 367.4) | 0.01 (-0.01, 0.02) | -2017 (-89315; 174605) | 185 (-401.5, 771.1) | 0.03 (-0.01, 0.07) | 5940 (-52780; 135122) |

\* Active Monitoring is the reference group. Bold numbers indicate statistically significant differences between study arms. ITT: Intention to treat.

Supplementary Table 1. Unadjusted differences in costs between groups at 6 and 12 months follow-up and evolution of the severity of depression

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline** |  | **6 month** |  | **12 month** |  |
| **Type of utilization** | **Active monitoring (N=118)**  **Mean (SE)** | **Antidepressant (N=145)**  **Mean (SE)** | **Active monitoring (N=118)**  **Mean (SE)** | **Antidepressant (N=145)**  **Mean (SE)** | **Active monitoring (N=118)**  **Mean (SE)** | **Antidepressant (N=145)**  **Mean (SE)** |
| **Visit to family physician** | - | - | 136.8 (18.2) | 140.3 (13.9) | 95.2 (11.1) | 126.4 (13.7) |
| **Visit to nurse** | - | - | 5.1 (1.7) | 7.1 (1.8) | 5.9 (2.0) | 12.9 (2.9) |
| **Visit to psychologist** | - | - | 8.8 (4.3) | 21.0 (7.5) | 5.9 (3.9) | 15.7 (6.2) |
| **Visit to medical specialists (including psychiatrist)** | - | - | 52.7 (10.2) | 59.7 (8.7) | 66.1 (11.2) | 65.1 (9.8) |
| **Visit to dentist in the primary care practice** | - | - | 2.8 (1.8) | 2.3 (1.3) | 6.9 (4.6) | 5.8 (3.6) |
| **Hospital emergency visit** | - | - | 24.0 (4.1) | 28.5 (4.0) | 28.4 (4.6) | 36.5 (4.5) |
| **Hospital stay (per day)** | - | - | 83.6 (38.5) | 78.9 (35.2) | 140.4 (58.8) | 293.7 (134.4) |
| **Diagnostic test (range)** | - | - | 55.0 (10.6) | 64.1 (9.7) | 60.9 (10.2) | 99.9 (21.2) |
| **Pharmacological treatment** | - | - | **6.7 (1.0)** | **37.5 (4.3)** | **12.8 (2.2)** | **63.4 (8.0)** |
| **Visit to social worker** | - | - | - | - | 0.8 (0.6) | 0.7 (0.5) |
| **Absenteeism from work (minimum daily wage)** | - | - | 490.4 (103.6) | 526.0 (92.4) | 673.4 (133.6) | 831.0 (154.6) |
| **Severity of depression (PHQ-9)** | 15.5 (0.49) | 16.7 (0.44) | 9.34 (0.66) | 8.6 (0.59) | 8.7 (0.69) | 9.4 (0.66) |

Bold numbers indicate statistically significant differences between study arms.

Supplementary Table 2. Incremental cost-effectiveness ratios in terms of remission of symptoms at 6 and 12 months follow up for the main and sensitivity analysis\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Cost difference € | Difference in probability of remission (%) | ICER (€/extra remission per 100 cases) | Cost difference € | Extra remissions (per 100 cases) | ICER (€/extra remission per 100 cases) |
|  | **6 month follow-up** |  |  | **12 month follow-up** |  |  |
| **Main analysis** |  |  |  |  |  |  |
| Government perspective | 23.6 | 2.0 | 12 | 269 | -0.1 | -280 |
| Healthcare perspective | 27.6 | 2.0 | 14 | 156 | -0.1 | -162 |
| **Sensitivity analyses** |  |  |  |  |  |  |
| Analysis with generalized linear models (no correction for propensity score) | 137.6 | 7.1 | 19 | 294.9 | -6 | -51 |
| Patients with major depression according to DSM-IV criteria (n=82) | -59.1 | -4.4 | 13 | 53 | 9,6\*10-03 | 5554 |
| Average salary for absenteeism | 104.5 | 2.0 | 53 | 688 | -0.1 | -716 |
| Per protocol analysis (n=128) | -548.3 | 2.0 | -277 | -162 | -1.3 | 125 |
| Completers (6-month n=214; 12-month n=195) | -21.0 | 3.4 | -6 | 185 | -0. 03 | -5921 |

\* Active Monitoring is the reference group.