Title:

Evaluation of a pharmacist intervention on patients initiating pharmacological treatment for depression: a randomized controlled superiority trial

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Abstract:

Major depression is associated with high burden, disability and costs. Non-adherence limits the effectiveness of antidepressants. Community pharmacists (CP) are in a privileged position to help patients cope with antidepressant treatment. The aim of the study was to evaluate the impact of a CP intervention on primary care patients who had initiated antidepressant treatment. Newly diagnosed primary care patients were randomised to usual care (UC) (92) or pharmacist intervention (87). Patients were followed up at 6 months and evaluated three times (Baseline, and at 3 and 6 months). Outcome measurements included clinical severity of depression (PHQ-9), health-related quality of life (HRQOL) (Euroqol-5D) and satisfaction with pharmacy care. Adherence was continuously registered from the computerised pharmacy records. Non-adherence was defined as refilling less than 80% of doses or having a medication-free gap of more than 1 month. Patients in the intervention group were more likely to remain adherent at 3 and 6 month follow-up but the difference was not statistically significant. Patients in the intervention group showed greater statistically significant improvement in HRQOL compared with UC patients both in the main analysis and PP analyses. No statistically significant differences were observed in clinical symptoms or satisfaction with the pharmacy service. The results of our study indicate that a brief intervention in community pharmacies does not improve depressed patients' adherence or clinical symptoms. This intervention helped patients to improve their HRQOL, which is an overall measure of patient status.

Key words:

Depressive Disorder; Medication Adherence; Antidepressive Agents; Pharmaceutical Services; Primary Health Care

1. Introduction

Almost 13% of Europeans will suffer major depression at some point in their life (Alonso et al. 2004). Depressive disorders are associated with considerable disability (Mathers and Loncar 2006) and with increased suicide rates (Angst et al. 1999). This results in a high burden for patients and society and is costly to the system, mainly due to patients' inability to work (Salvador-Carulla et al. 2011;Wade and Haring 2010).

The detection, prevention and treatment of depression should improve to minimize relapse. Antidepressants decrease risk of relapse, especially in adherent patients (Geddes et al. 2003). Low adherence to antidepressants has been systematically reported (Lingam and Scott 2002) and, in primary care, largely explains low concordance of real practice with clinical guidelines for depression (Pinto-Meza et al. 2008).

Community pharmacists (CPs) are easily accessible to ambulatory patients and can help improve adherence. A systematic review evaluating the effectiveness of pharmacist intervention in improving adherence to antidepressants identified six relevant studies (Rubio-Valera et al. 2011). Although most of the individual studies had shown non-statistically significant results, when pooled, a statistically significant effect was observed favouring pharmacist intervention. The review included interventions conducted by pharmacists in hospital services and CPs and sub-group analyses showed that, when pooled separately, CPs studies produced non-statistically significant results. This sub-group analysis included only 3 studies, implying that the power of the meta-analysis to detect differences may be limited.

Only one of the studies had been conducted in a European country (Brook et al. 2005). In the per protocol (PP) analysis, Brook found that patients who received a CPI with an informative videotape showed better antidepressant adherence. It is not possible to isolate the relative impact of each intervention component.

The aim of the present study was to evaluate the effectiveness of a community pharmacist intervention (CPI) compared with usual care (UC) in improvement of adherence to antidepressants and patient wellbeing in a population initiating pharmacological treatment following diagnosis of depression by their general practitioner (GP).

2. Experimental procedures

2.1 Study Design

This was a six-month follow-up naturalistic parallel-group controlled trial with random allocation of participants into UC and UC plus CPI. A detailed description of the study protocol has been provided elsewhere (Rubio-Valera et al. 2009).

2.2 Participant recruitment and randomisation

Participants were recruited at 4 Primary Care Health Centres (PCHC) (30 GPs) from two satellite towns in the Barcelona metropolitan area (Gavà and El Prat) (October 2008-May 2011). At first, only the PCHC from Gavà participated in the study but to accelerate patient inclusion, a population from El Prat was included in March 2010. Eligible participants were patients aged between 18 and 75 who had been prescribed an antidepressant by a GP due to a depressive disorder. Patients who had taken any antidepressants or consulted a mental health specialist in the previous 2 months; those with a history of psychotic, bipolar disorder or drug abuse; and those with cognitive impairment, were not included.

Spanish patients can choose any pharmacy countrywide to fill their prescription and can switch from one to another in successive visits. Patients were asked to refill their antidepressant prescriptions at the same pharmacy during the study. Those who agreed were included.

GPs invited eligible patients to participate and obtained signed informed consent. To ensure allocation concealment, every GP received a set of 10 sequentially numbered, opaque, sealed

envelopes generated by an external investigator (MRV) containing patient assignment. Randomisation was generated at the patient level by a computerised random-number generator following a permuted block design (1:1). As patients were enrolled, the GP sequentially stapled one of the envelopes to the prescription.

When the patient gave the prescription to their CP, the pharmacist opened the envelope and created a patient study chart distinguishing between UC and CPI groups. Interventions performed by the pharmacists, both in the UC and CPI groups, were recorded on the patient study chart. Blinding of participants and pharmacists was not possible but outcome assessors were blind to the allocation. Patients were asked to avoid discussing the study among them.

2.3 Intervention

All the pharmacies in the towns (39) were invited to participate but 6 declined; citing heavy workload (n=2) or lack of interest in the study (n=4). To homogenise the intervention, pharmacists received an 8-hour training session focused on implementation and information-collection guidelines. Only 24 of the participating pharmacies were finally approached by patients and took part in the study (58 CPs). Two pharmacies dropped out: one because the pharmacy closed and one because the CP responsible for the study left.

Patients received the CPI on visiting the pharmacy where they received their first prescription of the 6-month antidepressant course. The CPI consisted of an educational intervention centred on improving patients' knowledge of antidepressants and awareness of the importance of adherence. In patients with a sceptical attitude towards the medication, the intervention aimed to reduce stigma, reassure the patient about possible side-effects, and stress the importance of following GPs' advice.

As patients were beginning treatment with antidepressants, the first contact was considered crucial. During the first visit, the pharmacist provided the patient with information about the

medicine and briefly discussed various aspects of the illness to improve understanding of the treatment, eliminate erroneous preconceptions and reinforce the concept of illness to the patient. In subsequent visits, the pharmacist conducted a short review of some points covered in the first visit and checked patient progress (improvement, appearance of side-effects, or queries). First and subsequent contacts took a mean of 14.4 and 7.7 minutes, respectively.

Control patients received UC from their GP and CP. UC varied from one pharmacy to another but mainly consisted of dispensing the medication; answering patients' questions and giving some basic advice about how to take the medication. First and subsequent visits took a mean of 7.8 and 7.7 minutes, respectively.

2.4 Measurements

Three assessments (baseline, 3 and 6 months) were conducted by 8 trained psychologists. Adherence to antidepressants was assessed using the computerised pharmacy records that registered all the information about medication in the patient's clinical history at the time of purchase. Non-adherence was defined as refilling <80% of the prescribed doses; a definition that has a reasonable balance between sensitivity and specificity (Hansen et al. 2009) or having a treatment gap >1 month (Peterson et al. 2007).

Clinical severity of depression was measured with the Patient Health Questionnaire, 9-item depression module (PHQ-9) (Kroenke et al. 2001;Spitzer et al. 1999).

HRQOL was evaluated using the EuroQol-5D (EQ-5D) and Spanish tariffs or utility indexes were calculated (Badia et al. 1998, 1999;Dolan et al. 1995;The EuroQol Group 1990).

Satisfaction with the pharmacist service was measured with a patient-satisfaction questionnaire (Armando et al. 2008).

During recruitment, clinical diagnosis was made by the GP and, at the baseline assessment, was confirmed using the research version of the Structured Clinical Interview for DSM-IV Axis I

Disorders (SCID-I) (First et al. 1996, 1999). GPs were blind to the DSM-IV diagnosis and patient inclusion was performed according to their usual practice.

Chronic physical conditions were assessed using a "yes" or "no" check-list.

2.5 Sample size calculation and data analysis

Sample size calculation was based on the main study objective (i.e. improving adherence to antidepressants). The sample size was calculated for an expected difference between groups of at least 17 points in the percentage of medication intake, which is in agreement with the study by Brook et al. 2005. It was estimated that a sample of 162 patients would have a power of 80% at a significance level of 5% to detect these differences. There were no missing values for our main outcome.

Pre-treatment comparability between groups was assessed applying the χ^2-test or Fisher exact test for categorical data, the Student's t-test for continuous variables and the non-parametric equality-of-medians test for biased numerical data.

To evaluate intervention effectiveness, multilevel mixed-effects linear and logistic models were fitted that allowed the inclusion of all available data. A two-level longitudinal multilevel structure was used where observations were clustered within patients. The models predict treatment response using group as a fixed factor, time point (baseline, 3 and 6 months) as a within-participants repeated factor, and participants as a random factor. Models with variables not assessed at baseline (adherence and satisfaction) included only two time points.

For the main analyses, all participants were included as randomised regardless of whether they received the intervention or had incomplete follow-up data. To deal with the problem of missing observations in longitudinal studies, it has been suggested that applying multilevel analysis is a good option. Multilevel analysis is very flexible in handling missing data and it has been shown that it is better to apply multilevel analysis to an incomplete dataset than applying imputation methods (Twisk 2006). Consequently, missing data was not imputed.

A second analysis was conducted according to the PP principle. Participants in the intervention group were excluded if they had never received the pharmacist intervention (never bought medication or did so at a non-participating pharmacy). Participants in the control group that never bought medication (i.e. did not receive usual pharmaceutical care) were also excluded from the PP analyses.

The models were fitted using Restricted Maximum Likelihood. To account for correlation among several observations for each subject, an unstructured correlation matrix was used. In all models the gender and the interaction term 'time*group' were included in the model as covariates. When the interaction was significant in the model, the effect of the intervention was considered to vary during the course of the study (HRQOL models only). When this interaction term was not significant, the model without the interaction term was used.

Other sociodemographic and clinical characteristics that could plausibly affect the outcome were tested using a likelihood ratio test (LR-test). We compared the models with and without these variables and included them if the LR-test was positive ($p \leq 0.10$). Number needed to treat (NNT) was calculated for the main outcome (adherence) by computing the inverse of the differences between groups in the probability of being adherent. For the continuous outcome variables showing statistically significant differences between groups, effect size (Cohen's d) was calculated by means of standardised mean difference between the two populations using the pooled standard deviation of the two groups at baseline. The effect size was categorised as small (0.2), medium (0.5) and large (0.8) (Cohen 1988).

All analyses were conducted with STATA 11.0.

3. Results

3.1 Participants and drop-outs

Figure 1 shows the study flow chart. A total of 234 patients were referred by the GPs. Finally, 179 patients were randomised to UC (92) and CPI (87), were evaluated at baseline and included in the main analysis. Only 87 (95%) and 64 (74%) in the control and intervention

group, respectively, received the intervention as allocated and were included in the PP analysis.

All assessment visits were completed by 120 (67%) patients. Nineteen (11%) participants were only evaluated at baseline. Forty (23%) patients missed 1 follow-up assessment (7 at 3-months and 33 at 6-months) because they could not be contacted or refused to attend.

-Figure 1-

3.2 Baseline data

Table 1 shows the participants' baseline characteristics. Most participants were women (75.4%), with mean age of 46.6 years. Fifty-one percent of the participants met DSM-IV criteria for major depression. The mean baseline severity of depression (PHQ-9) was 15.9 (moderately severe symptoms). Differences existed in the proportion of women between groups; all analyses were adjusted for gender.

-Table 1-

3.3 Adherence to antidepressants

Table 2 shows the patients' probability of remaining adherent, models-based mean satisfaction, severity of depression and HRQOL. Table 3 shows the regression models for adherence and satisfaction.

Eleven (6%) patients never bought medication (non-initiators) and a high proportion of patients discontinued at 3 (48.0%) and 6-month follow-up (57.0%).

In the main analyses, CPI group patients seemed more likely to remain adherent both at 3 (67.7% vs 83.3%) and 6-month (46.3% vs 67.3%) follow-up (Table 2) but the trend did not reach statistical significance (OR=2.24; p=0.209) (Table 3).

In the per PP analysis, the same trend was observed (Table 2) and differences between groups were close to statistical significance but did not reach it (OR=3.44; p=0.055) (Table 3). NNT was 5, indicating that to prevent non-adherence in one patient, we needed to implement the intervention in 5 (Table 2).

-Table 2-

-Table 3-

3.4 Satisfaction with pharmacy service

Overall, patient satisfaction with the pharmacy service was high in both groups. No differences were observed between groups at 3 or 6 months (Tables 2 and 3).

3.5 Clinical severity of depression

Both groups showed an improvement in symptoms at 3 and 6 months (Table 2). Table 4 shows the depression severity regression models (PHQ-9) and HRQOL. No differences in symptom severity were observed between groups (Table 4).

3.6 HRQOL

Figure 2 shows the multilevel-based mean utilities (EQ-5D tariffs) and the improvement in HRQOL in the control and intervention groups.

In both analyses, a significant time*group interaction was found in EQ-5D tariffs in favour of the intervention group (Table 4). Overall improvement was higher in the intervention group in both the main (0.25 vs 0.14) and PP (0.27 vs 0.16) analyses. The effect size was small to medium in both analyses (0.31 and 0.33 respectively).

-Figure 2-

4. Discussion

CPI group patients tend to have a higher probability of remaining adherent at 3 and 6 months than those receiving UC. In the PP analysis, this result did not quite reach statistical significance (p=0.055). However, the difference was clinically relevant since the NNT was relatively small for a fairly quick, easy-to-implement intervention (intervention implementation needed in 4 patients in order to help one extra patient to remain adherent at 3 and 6-month follow-up). One possible reason for not achieving statistical significance would be a lack of statistical power. The large amount of drop-outs and patients not following study protocol could have reduced the study power. Furthermore, we did not take into account the clustering

effect of the multilevel mixed-effects analyses when the sample size was calculated, which could have limited our capacity to detect differences between groups.

In general, our study results are consistent with those of Brook 2005 and Rickles 2006. In the intent-to-treat analysis, between-group differences were not found although these studies did observe statistically significant adherence differences between groups in the PP analysis. Both studies used a protocol that considered exclusively those patients that had received a minimum of 3 pharmacist contact sessions. Nevertheless, those patients who received one (or two) interventions before abandoning the medication may not have wanted to receive a second (or third) intervention session. Consequently, intervention group patients who abandoned the medication early may have been excluded from the PP analysis so increasing the difference between groups. As such, there may be some difficulty in generalizing from this result.

In our case, first patient contact was crucial and demanded a more flexible protocol stipulation.

Despite having detected statistically significant differences in the degree of adherence to antidepressants, none of the previous studies found differences in clinical improvement (Adler et al. 2004;Brook et al. 2005;Capoccia et al. 2004;Finley et al. 2003;Rickles et al. 2006). However, a powerful meta-regression based on collaborative care in depression showed a positive association between improved adherence and improvement in depressive symptomatology (Bower et al. 2006). The lack of difference in clinical improvement could imply that its relationship with adherence is not as direct as it may appear and is affected by diverse factors such as pharmacological efficacy or other environmental or social elements. Another factor could be diagnostic accuracy, as only half the patients met major depression SCID criteria and antidepressants have only shown an effect on moderate to severe major depression. This could explain the lack of correlation between adherence and clinical outcomes. The analysis performed on the major-depression patient subsample (SCID) showed

no statistically significant differences between groups (data available on request), although this study was not designed to observe differences in this population and the power of the study was insufficient to draw conclusions on subsample behaviour.

In contrast to Capoccia 2004, statistically significant HRQOL differences between groups were observed, indicating that patients who received extra pharmacy care perceived improved HRQOL. Effect size was small to moderate, which led us to question the clinical relevance of this difference. It could be due to placebo effect or desirability bias. Nevertheless, both groups showed very high levels of pharmacy-service satisfaction with no statistically significant differences between groups. As part of the intervention, the pharmacist discussed the nature of the treatment and illness with the patient. This may have helped the patient to cope with the new diagnosis, reducing stigmatization and even, in some cases, modifying inappropriate health beliefs. This could manifest itself as an improvement in self-perception with respect to HRQOL (the constructs of quality of mental life).

Although not directly related to intervention, we observed a high proportion of non-initiators (around 6%). These patients had agreed to participate in a study to improve the use of antidepressants and, as such, we concluded that the proportion of non-initiators would be much higher in normal practice. In previous studies, non-initiation rates reached 15% (Bull et al. 2002). We consider that non-initiators motives require detailed study.

This study had a number of limitations. Firstly, enrollment may have been biased against patients unwilling to take antidepressants. However, the figures regarding treatment discontinuation correspond to those found previously in Catalonia (Serna et al. 2010) and we conclude that our sample can be extrapolated to the primary care population.

Secondly, inclusion criteria were very broad which may have created great variability among subjects, although this did favour generalisation of the results and the study's external validity.

Third, the pharmacists attended both UC and CPI patients, which could have led to some contamination. This could have been prevented by performing a cluster randomisation at the

pharmacy level. The pharmacists were asked to exercise great care and to register the intervention carried out on control patients. Also, although they were asked not to share information with other participants, patients could have transmitted information among themselves.

Fourth, only 74% of intervention group patients received at least one pharmacy intervention and this may have limited its impact and affected the power to detect differences.

Fifth, patients could change pharmacy in successive visits. Consequently, even those patients who received the intervention attended very few sessions. However, this leads us to believe that even with a single, relatively simple, although slightly more intense, intervention applied at the point of initiating the medication, we can obtain significant improvements in adherence and patients' HRQOL; although this would require further exploration.

Sixth, as a result of the financial crisis, shortly after study commencement, a series of economic adjustments were made which affected the viability of pharmacies in Catalonia (Spanish Resolution 2008-2010). In addition, the low incidence of new cases meant that the inclusion period had to be extended. These two factors, taken together, may have demotivated and/or exhausted our pharmacists. This may be reflected in the results although the pharmacists recorded the interventions carried out and, as such, we believe that the impact was minimal.

Finally, the use of pharmacy registers as a measure of adherence involves a series of limitations. Patients may acquire the tablets but not take them and this measure does not provide us with information with respect to the time of taking the medication or reasons for non-adherence. However, it showed relatively good agreement with electronic pill container, especially in depressed patients (Hansen et al. 2009). Moreover, this measure allowed us to collect information without the patient being aware that he or she was being assessed even when the patients did not keep their evaluation appointments. Consequently, we had no missing data in our main study variable.

Despite all these limitations, this study is the first performed in Europe which focuses specifically on a community pharmaceutical intervention to improve adherence to antidepressants. In addition, it represents the largest study sample of patients undertaking a community pharmacy intervention. In spite of being low, adherence to the protocol is higher than that reported in previous studies (Brook et al. 2002). Finally, the naturalistic nature of the study design benefited the results external validity.

The study results indicate that a brief intervention in community pharmacy is not effective in improving patients' adherence to antidepressants or clinical symptomatology. Though not statistically significant, there was a clinically important improvement in the degree of adherence in the intervention group. Furthermore, this type of intervention does help patients with a new depressive episode to improve their HRQOL. As such, we believe that further studies are required to investigate the pharmaceutical intervention's active components with the aim of increasing the impact on improvements in quality of life. The greatest limitation on the CPI was the lack of continuity in the service. We would recommend designing a single but more intensive intervention to be applied at the beginning of the treatment, making a greater effort to attempt to modify patients' health concepts and beliefs about the treatment and the disease. Motivations for non-initiation of the treatment with antidepressants should be assessed in order to develop interventions that may be helpful in the recovery of these patients.

Figure legends

Figure 1. Study flow chart

Figure 2. Multilevel based mean utility and overall improvement in the EQ-5D (95% CI) at 3 and 6 month follow-up for the main and PP analyses

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Table 1. Sample socio-demographic and clinical baseline characteristics

	Usual care (n=92)	Pharmacist's intervention (n=87)	P-value
Gender(% women (n))	83.7% (77)	66.7% (58)	0.008
Age (mean (95% CI))	46.3 (43.3, 49.2)	46.9 (44.0, 48.6)	0.742
Marital status (% (n))			0.881
Never married	14.1% (13)	18.4% (16)	
Married or living with someone	64.1% (59)	59.8% (52)	
Previously married	10.9% (10)	10.3% (9)	
Widow	10.9% (10)	11.5% (10)	
Education(% (n))			0.676
No studies	7.6% (7)	5.8% (5)	
Primary	22.8% (21)	23.0%(20)	
Graduated	23.9% (22)	19.5% (17)	
Secondary	26.1% (24)	31.0% (27)	
University	19.6% (18)	19.0% (34)	
Other	–	2.3% (2)	
Working status((% (n))			0.493
Househusband/housewife	13.0% (12)	17.2% (15)	
Paid employment	40.2% (37)	29.9% (26)	
Paid employment but on sick leave	21.7% (20)	24.1% (21)	
Unemployed	17.4% (16)	16.1% (14)	
Retired	7.6% (7)	9.2% (8)	
Other	–	2.3% (2)	
NS/NC (Missing)		1.2% (1)	
Clinical severity according to PHQ-9(mean (95% CI))	15.8 (14.6, 16.9)	16.1 (14.7, 17.4)	0.776
Number of co-morbidities(% of cases over the median (median=3) (n))	37.0% (34)	40.2% (35)	0.653

Table 2. Multilevel model-based probabilities of remaining adherent and multilevel model-based mean satisfaction and severity of depression at 3 and 6 month follow-up in the control and intervention groups for the main analysis and PP analyses

	Main analysis			PP		
	Baseline	3-months	6-months	Baseline	3-months	6-months
Probability of remaining adherent(95% CI) and number needed to treat (NNT)[¥]						
Usual Care	NA	61.9% (26.4, 88.1)	40.2% (12.9, 75.3)	NA	43.8%(15.7, 76.5)	25.7% (7.4, 59.8)
Intervention	NA	78.4% (48.0, 93.5)	60.1% (28.4, 85.11)	NA	72.9% (41.7, 91.0)	54.4% (24.6, 81.4)
NNT		6.1	5.0		3.4	3.5
Mean satisfaction (95% CI)[§]						
Usual Care	NA	38.3 (32.8, 43.8)	39.0 (33.4, 44.5)	NA	37.5 (31.4, 43.6)	37.9 (31.8, 44.0)
Intervention	NA	40.1 (35.1, 45.1)	40.8 (35.7, 45.8)	NA	39.2 (33.4, 44.9)	39.6 (33.8, 45.4)
Mean severity of depression (95% CI)[⊓]						
Usual Care	14.0 (12.3, 15.6)	6.8 (5.2, 8.5)	5.0 (3.2, 6.7)	14.0 (12.3, 15.8)	7.1 (5.2, 8.9)	5.1 (3.2, 7.0)
Intervention	14.5 (13.0, 15.9)	7.4 (5.8, 8.9)	5.5 (3.9, 7.1)	14.8 (13.1, 16.4)	7.8 (6.1, 9.5)	5.9 (4.1, 7.6)

NA=Not applicable

[¥]Values for male patients of age 45.5 with a baseline severity of depressive symptoms of 16 (moderately-severe symptoms).

[§]Values for male patients of age 45.5,never married and without comorbidities

[⊓] Values for male patients of age 45.5

Table 3. Multilevel model-based odds ratio (95% confidence interval) and p-values of the variables included in the models for adherence to antidepressants.

	Adherence to antidepressants (Odds Ratio (95% CI) and P-value)				Satisfaction with the pharmacy service (β coefficients (95% CI) and P-value)			
	Main analysis		PP analysis		Main analysis		PP analysis	
Constant[&]	1.63 (0.36, 7.37)	0.529	0.78 (0.19, 3.26)	0.734	38.3 (32.8, 43.8)	0.001	37.5 (31.4, 43.6)	0.001
Group								
Control	Reference		Reference		Reference		Reference	
Intervention	2.24 (0.64, 8.60)	0.209	3.44 (0.97, 12.22)	0.055	1.8 (-0.9, 4.5)	0.20	1.7 (-1.3, 4.7)	0.270
Gender								
Men	Reference		Reference		Reference		Reference	
Women	0.37 (0.08, 1.63)	0.188	1.21 (0.29, 4.97)	0.796	-1.2 (-4.6, 2.2)	0.48	-1.8 (-5.6, 1.9)	0.339
Age[Ç]	1.06 (1.01, 1.11)	0.013	1.04 (1.00, 1.09)	0.070	0.03 (-0.1, 0.2)	0.70	-0.02 (-0.2, 0.1)	0.849
Time								
3-months	Reference		Reference		Reference		Reference	
6-months	0.41 (0.21, 0.83)	0.012	0.44 (0.22, 0.90)	0.024	0.7 (-1.1,2.5)	0.45	0.4 (-1.6, 2.4)	0.673
Depression baseline severity(PHQ9)[Ç]	0.99 (0.89, 1.11)	0.911	0.98 (0.88, 1.09)	0.708	ni		ni	
Comorbidities	ni		ni		0.9 (0.3, 1.5)	0.01	0.8 (-5.6, 1.9)	0.339
Marital status								
Never married	ni		ni		Reference		Reference	
Married	ni		ni		2.7 (-1.7, 7.2)	0.23	4.8 (-0.3, 9.9)	0.065
Divorced	ni		ni		2.7 (-3.0, 8.5)	0.35	4.5 (-2.0, 11.0)	0.178
Widow	ni		ni		-5.1 (-11.9, 1.7)	0.14	-2.4 (-9.8, 5.0)	0.529

[&]Constant or reference value corresponds to male patients of age 45.5 in the control group at baseline and with a baseline severity of depressive symptoms of 16 (moderately-severe symptoms) in the model for adherence and to never-marriedmale patients of age 45.5 without comorbidities in the control group at baseline in the model for satisfaction.

[Ç]Centered in the median. One-year or 1-point increase.

ni = variables not included in the model (negative LR-test).

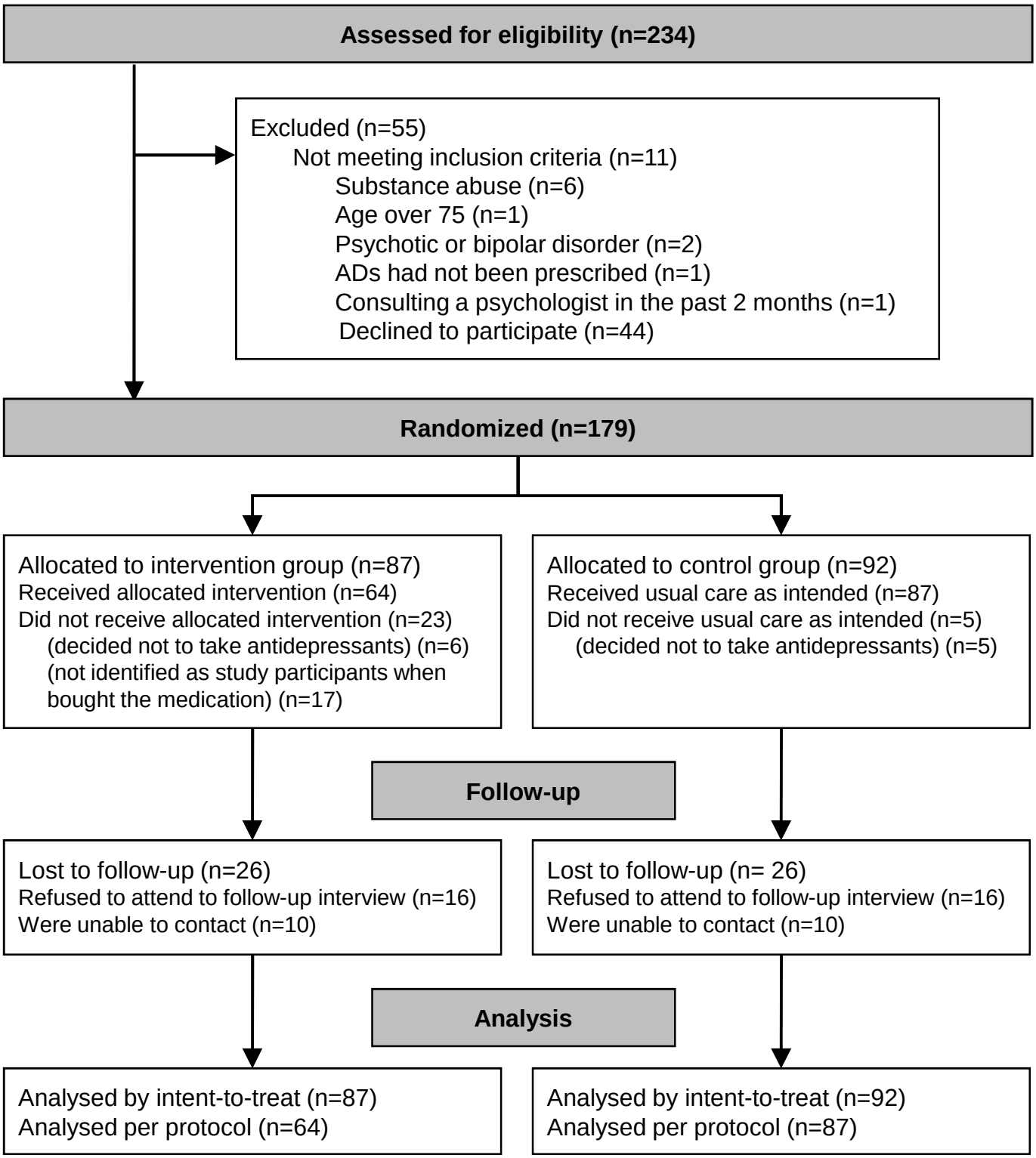
Table 4. Multilevel model based β-coefficients (95% confidence interval) and p-values of the variables included in the models for clinical severity of depression and health-related quality of life.

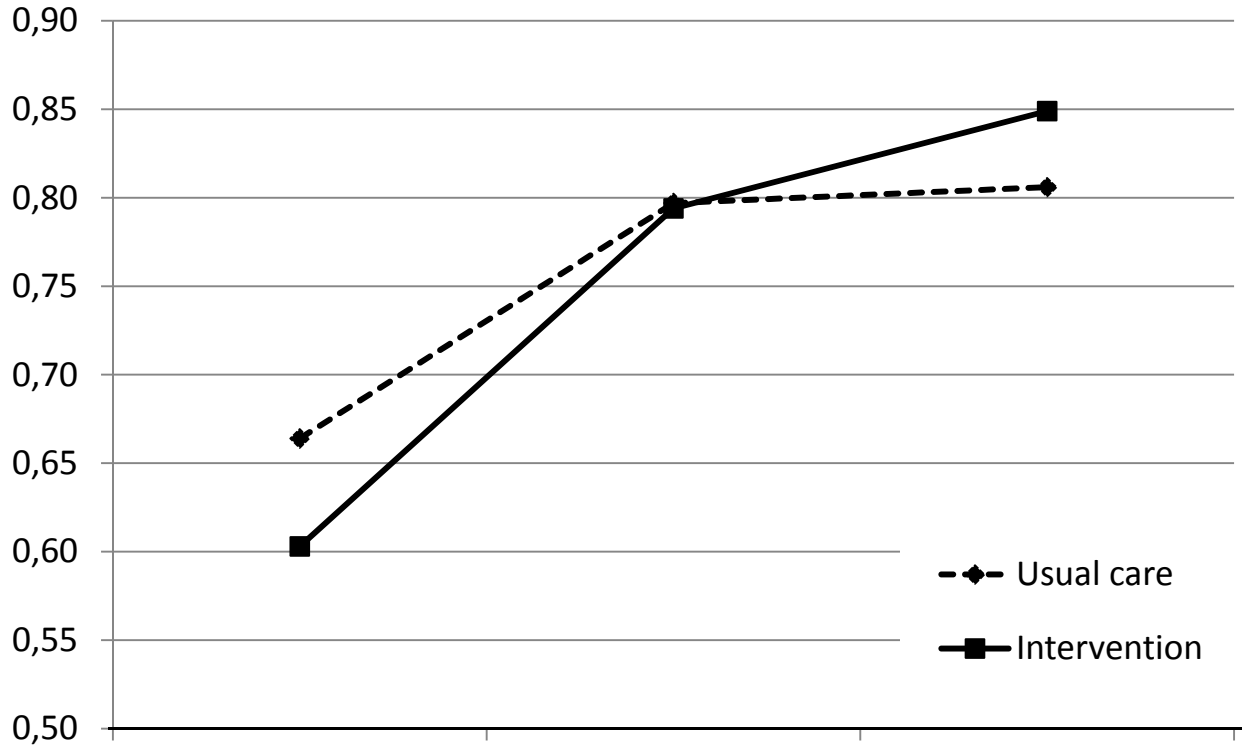
	Severity of depressive symptoms (PHQ-9)*				Health related quality of life (EuroQol-5D tariffs)*			
	Main analysis		PP analysis		Main analysis		PP analysis	
Constant[&]	13.95 (12.33, 15.58)	0.001	14.0 (12.27, 15.78)	0.001	0.67 (0.59, 0.74)	0.001	0.66 (0.58, 0.75)	0.001
Group								
Usual Care	Reference		Reference		Reference		Reference	
Intervention	0.51 (-0.77, 1.79)	0.432	0.77 (-0.67, 2.21)	0.297	-0.061 (-0.14, 0.01)	0.108	-0.09 (-0.17, -0.01)	0.038
Gender								
Male	Reference		Reference		Reference		Reference	
Female	2.37 (0.85, 3.89)	0.002	2.19 (0.49, 3.89)	0.011	-0.031 (-0.10, 0.04)	0.386	-0.031 (-0.11, 0.05)	0.438
Age[ç]	-0.04 (-0.09, 0.003)	0.067	-0.03 (-0.08, 0.02)	0.237	-0.003 (-0.01, -0.00)	0.008	-0.003 (-0.01, -0.00)	0.005
Time								
Baseline	Reference		Reference		Reference		Reference	
3-months	-7.12 (-8.21, -6.03)	0.001	-7.0 (-8.1, -5.8)	0.001	0.133 (0.07–0.20)	0.001	0.13 (0.07, 0.20)	0.001
6-months	-9.00 (-10.17, -7.80)	0.001	-8.9 (-10.2, -7.7)	0.001	0.142 (0.08–0.21)	0.001	0.16 (0.09, 0.23)	0.001
Depression baseline severity (PHQ-9)[ç]	ni		ni		-0.012 (-0.02–-0.01)	0.001	-0.01 (-0.02, -0.01)	0.001
TimexGroupinteraction								
Baseline					Reference		Reference	
Intervention group at 3-months	ni		ni		0.06 (-0.03, 0.15)	0.204	0.07 (-0.03, 0.17)	0.145
Intervention group at 6-months	ni		ni		0.10 (0.01, 0.20)	0.034	0.11 (0.004, 0.22)	0.042

[&]Constant or reference value corresponds to male patients of age 45.5 in the control group at baseline in the PHQ-9 model and to male patients of age 45.5 in the control group and with a baseline severity of depressive symptoms of 16 (moderately-severe symptoms) in the EuroQol-5D model.

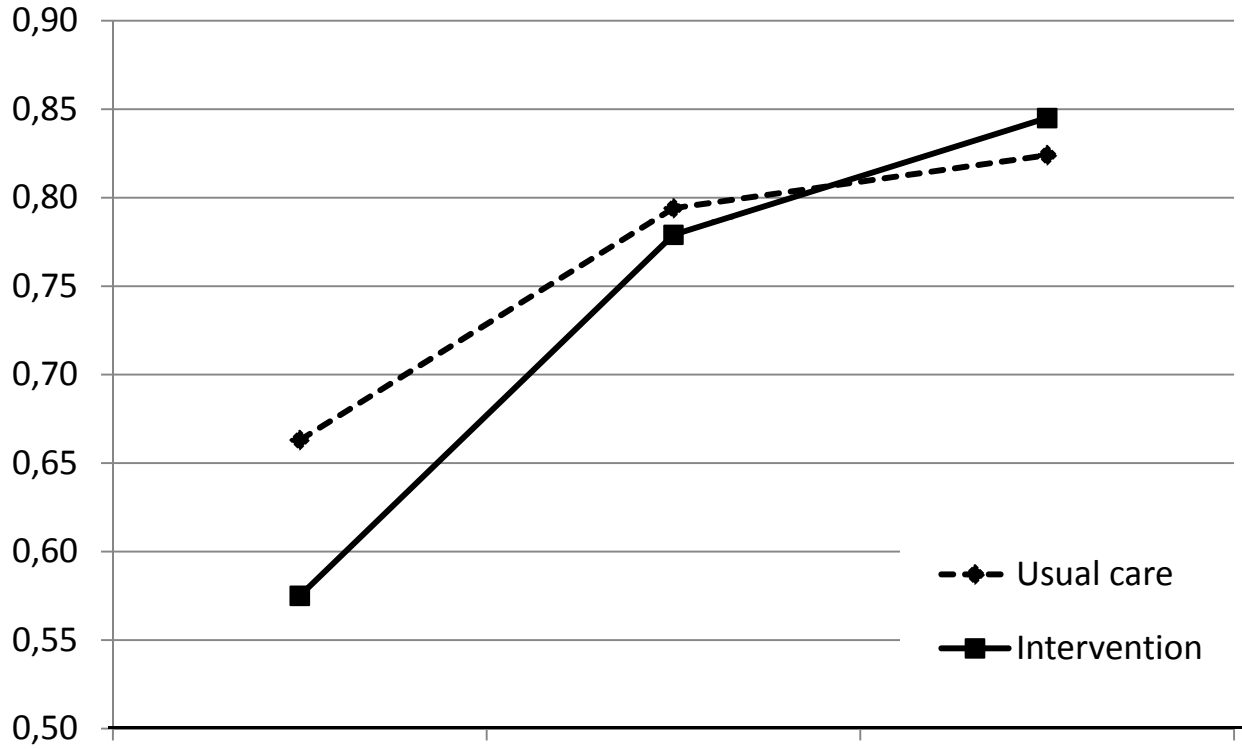
[ç]Centered in the median. One-year or 1-point increase.

ni = variables not included in the model


Assessed for eligibility (n=234)
Excluded (n=55)
Not meeting inclusion criteria (n=11)
Substance abuse (n=6)
Age over 75 (n=1)
Psychotic or bipolar disorder (n=2)
ADs had not been prescribed (n=1)
Consulting a psychologist in the past 2 months (n=1)
Declined to participate (n=44)
Randomized (n=179)
Allocated to intervention group (n=87)
Received allocated intervention (n=64)
Did not receive allocated intervention (n=23)
(decided not to take antidepressants) (n=6)
(not identified as study participants when bought the medication) (n=17)
Allocated to control group (n=92)
Received usual care as intended (n=87)
Did not receive usual care as intended (n=5)
(decided not to take antidepressants) (n=5)
Follow-up
Lost to follow-up (n=26)
Refused to attend to follow-up interview (n=16)
Were unable to contact (n=10)
Lost to follow-up (n= 26)
Refused to attend to follow-up interview (n=16)
Were unable to contact (n=10)
Analysis
Analysed by intent-to-treat (n=87)
Analysed per protocol (n=64)
Analysed by intent-to-treat (n=92)
Analysed per protocol (n=87)



Main analysis	Baseline	3-months	6-months	Overall improvement
Usual care	0.66 (0.59, 0.74)	0.80 (0.72, 0.88)	0.81 (0.72, 0.89)	0.14 (0.08, 0.21)
Intervention	0.60 (0.53, 0.67)	0.79 (0.72, 0.89)	0.85 (0.77, 0.93)	0.25 (0.18, 0.31)



PP analysis	Baseline	3-months	6-months	Overall improvement
Usual care	0.66 (0.58, 0.75)	0.79 (0.71, 0.88)	0.82 (0.74, 0.91)	0.16 (0.09, 0.23)
Intervention	0.58 (0.50, 0.65)	0.78 (0.70, 0.86)	0.85 (0.76, 0.93)	0.27 (0.19, 0.35)