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Do depressed patients comply with treatments prescribed? A cross-sectional study of adherence to the antidepressant treatment

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Introduction. Compliance with antidepressant treatment is a very relevant factor in the outcome of depressive disorders. Poor compliance has been associated with worse outcome, increased rate of relapses and greater cost. This study has aimed to describe adherence to antidepressant treatment in a sample of primary care patients with a diagnosis of depression in 2007.

Methods. Randomized sampling was made of patients with depression and antidepressant treatment attended in two primary care teams. Their medical records were reviewed to obtain the total number of prescriptions given to patients and the total number of prescriptions dispensed in the pharmacies. The difference between prescriptions written and collected was calculated. A difference of ± 2 was considered as good compliance. Results are shown as percentages. Comparisons were made with the chi-square, Student's T and ANOVA tests, where appropriate.

Results. The sample was made up of 212 patients. Mean age was 63.2 years (SD 15.27). In the sample, 66.5% were treated with only one antidepressant and 24.1% with two. The percentage of non-compliance was 33.96% (95% CI: 25.35–40.57). Treatment-adherent patients have a lower percentage of long-term treatment with other drugs. The percentage of treatment-adherent women was higher than non-adherent ($p=0.015$). No differences were found in compliance among patients treated in the mental health center.

Conclusions. One third of patients on antidepressant drug treatment were non-compliers because the drugs were not picked up properly from the pharmacies. We need to develop strategies to improve the therapeutic adherence of patients.

Key Words:
 Depressive disorder, Antidepressant treatment, Compliance, Descriptive study

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¿Toman los pacientes deprimidos el tratamiento prescrito? Estudio descriptivo sobre el cumplimiento del tratamiento antidepresivo

Introducción. El cumplimiento del tratamiento antidepresivo es un aspecto importante en la evolución de los trastornos depresivos. El mal cumplimiento se ha asociado a una peor evolución, a un mayor número de recaídas y mayor coste económico. El objetivo de este estudio es describir el cumplimiento del tratamiento antidepresivo en una muestra de pacientes de atención primaria (AP) con diagnóstico de depresión durante el año 2007.

Método. Se realizó un muestreo aleatorio de pacientes con diagnóstico de depresión y tratamiento con antidepresivos atendidos en dos equipos de (AP) y se revisaron las historias clínicas. En ellas consta el número de recetas prescritas y el número de recetas recogidas en la farmacia. Se calculó la diferencia entre recetas prescritas y recogidas. Una diferencia de ± 2 se consideró un buen cumplimiento. Se mostraron los resultados en porcentajes y se realizaron comparaciones Ji cuadrado, t-student y ANOVA cuando procedía.

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Resultados. La muestra estaba compuesta de 212 pacientes. La edad media era de 63,2 años (DE =15,27). El 66,5% estaba en tratamiento con un antidepresivo y el 24,1% con dos. El porcentaje de pacientes no cumplidores era del 33,96% [IC 95% (27,35-40,57)]. Los pacientes cumplidores presentaban un menor porcentaje de tratamiento con otros fármacos crónicos. En los cumplidores el porcentaje de mujeres era superior que en el de no cumplidores ($p = 0,015$). No había diferencias en el cumplimiento en los pacientes atendidos en el centro de salud mental.

Conclusiones. Un tercio de los pacientes en tratamiento farmacológico antidepresivo no eran cumplidores puesto que no lo retiraban de forma adecuada de las farmacias. Es necesario desarrollar estrategias de mejora de la adherencia terapéutica de los pacientes.

Palabras clave:

Trastorno depresivo, Tratamiento antidepresivo, Cumplimiento, Estudio descriptivo

INTRODUCTION

Major depression is a frequent disease having a very significant psychosocial impact. In the ESEMeD epidemiological study carried out in Spain,¹ a life-long prevalence of depression was calculated to be 10.6%, and at one year 4%. It affects almost twice the number of women as men, with 14.4% prevalence in women and 4.3% in men.² In the primary care clinics of Catalonia, 20% of the patients seen had a major depressive disorder or dysthymic disorder.³ The World Health Organization (WHO) calculated the impact of depression in 2008, determining that it was the first cause of loss of years of health due to disease in the world.⁴ Patients with depression tend to take less care of their health⁵ and comply three times less with the medical recommendations in comparison to non-depressed patients.⁶

Recurrence rates of depression have been calculated to be at least 50% after a first major depression episode and 80-90% if the patient has had two or more depressive episodes.^{7,8} Evidence in favor of maintenance treatment to prevent relapses has been increasing in recent years with the appearance of several meta-analysis confirming its efficacy,^{9,10} independently of the patient's age or severity of the depressive episode.^{11,12} These are the reasons why most of the treatment guidelines for major depressive disorder recommend carrying out treatment for six months after a major depressive episode and up to 2 years if the recurrence rate is elevated.^{13,14} Treatment noncompliance would represent an important obstacle to maintain remission of the symptoms. Lack of antidepressant treatment adherence has been associated to a decrease in efficacy and increase in the persistence of depressive symptoms^{15,16} as well as an increase in cost in the treatment and indirect costs.¹⁷

Lack of adherence may increase disease recurrence^{15,16,18} and is an obstacle to transfer the efficacy obtained in clinical trials to the common practice.^{19,20} The research performed in this area of interest has serious problems such as the definition itself of the term and the methods to measure it. Adherence would include two concepts: adherence to the dose and form of administration and persistence in the duration of the treatment prescribed.^{20,21} In regards to the procedure used to evaluate adherence, there are subjective and objective methods.²² The subjective methods are self-reports or interviews of the patients, the clinical opinion of the professional attending to them.^{20,21} The objective methods include, for example, counting the pills in the container, monitoring serum levels of the drug, electronic dispensation systems or databases of pharmacies.^{20,22}

The literature on antidepressant treatment adherence provides unequal results based on the instruments used to measure it in the population studied. Antidepressant treatment noncompliance varies from 10 to 60%^{23,24} and has not significantly changed with the introduction of new antidepressants. The most potent predictive factors are not related with clinical or sociodemographic variables but rather with the attitudes of the patient towards the disease and the treatment, as well as their system of beliefs on health.^{19,20,22} Socioeconomic status and gender seem to influence treatment adherence, this being greater in women and in persons with higher educational and economical level.^{24,25,26} In addition, it has been hypothesized that the prescription of multiple drugs may make treatment compliance more difficult.²⁷ A study in which therapeutic compliance was evaluated with a questionnaire seemed to indicate that it is worse in those patients who receive other treatment for organic diseases.²⁶

The objective of this study has been to estimate antidepressant treatment adherence indirectly, by counting of prescriptions withdrawn in the pharmacy, in patients with diagnoses of depression and attended by two primary care teams, and to analyze its relationship with the presence of other chronic conditions and other long-term treatments. The hypothesis of the study has been that worse treatment compliance would be found in those patients with more long-term drug treatments.

METHODOLOGY

A descriptive, cross-sectional study of retrospective data performed by two primary care teams (PCT) was conducted. The teams were Encants and Camp de l'Arpa, located in the city of Barcelona. The study subjects were the population assigned to the two PCTs (45,000 assigned patients) over 17 years of age who had the following diagnoses recorded in the computerized clinical record: diagnosis of depression (F32 -depressive episodes; F33 -recurrent depressive disorder;

F34.1 -dysthymia; F41.2 -mixed anxious depressive disorder; F43 -adaptive disorder - of the ICD10) and who were receiving active antidepressant treatment during 2007. Those patients who had been transferred from the site or died during this period or who had been prescribed treatment for less than 3 months during 2007 were excluded from the study. In all, 1734 patients were included in the sample.

Patients screening was performed by simple randomization from the list of those who complied with the selection criteria. The sample size was calculated to detect a prevalence of 63% (median of compliance according to different measurement methods of adherence²⁴), with an alpha error of 0.06 and 95% confidence level. The resulting sample was 212 patients.

The following variables were collected from the clinical record: gender, antidepressant drug (active ingredient, number of active ingredients, number of prescriptions prescribed during the year 2007, number of prescriptions dispensed in pharmacy during the year 2007), number of active long-term drugs prescribed (at least 3 months of prescription), prescription of anxiolytics in 2007 (yes /no), presence of chronic condition (arterial hypertension (AHT), ischemic heart disease, diabetes mellitus, chronic obstruction pulmonary disease (COPD), osteoporosis and dyslipidemia). The number of visits made to the PCT (family doctor and nurse) and to the reference mental health sites was also reviewed.

Drug compliance was determined through the information collected in the computerized clinical record (CCR) and prescription and dispensation. The CCR made it possible to access information on the dispensation of prescriptions in the pharmacy, monthly, and according to the drug specialty. The following formula was calculated: no. prescriptions prescribed - no. prescriptions dispensed in pharmacy, classifying them into complier when the patient had a difference of less than two prescriptions in absolute value and non-complier when the difference was greater. This difference was considered as valid when taking into account those prescriptions prescribed in the last two months of 2006 or dispensed in the first two months of 2008. Considering that the mean prescription is one prescription per month as the antidepressant treatment containers usually have 28 tablets and that the long-term medication prescriptions are administered every two months, a margin of two prescriptions was accepted to consider a patient as complier. The percentage of drug compliance was analyzed with its 95% confidence interval, globally and by groups of active ingredients. The relationship between being a complier and the rest of the variables was compared using the Chi Square and Students' T test or Mann-Whitney test, depending on the normality of the quantitative variables. A multivariate logistic regression analysis whose dependent variable was antidepressant treatment compliance (yes/no) was carried out. Independent variables included age, gender

Table 1	Demographic and clinical characteristics of the patients	
	Frequency (N=212)	%
Women	162	76.4
Under 65 years	112	52.8
Therapeutic groups		
SSRI	181	85.4
Duals (duloxetine/venlafaxine)	30	14.15
Tricyclics	18	8.5
Mirtazapine/mianserin	14	6.6
Others	14	6.6
Chronic condition recorded	143	67.5
Under treatment with other long-term drugs	179	84.4
They take anxiolytics	150	71.1
Seen in mental health Center	37	17.5

Table 2	Diagnostic distribution of depressive disorders. Some patients had more than one diagnoses	
	N	%
F32. Depressive episodes	185	80
F33 Recurrent depressive episodes	17	7.4
F34.1 Dysthymia	7	3
F41.2 Mixed anxious depressive disorder	18	7.8
F43 Reactions to serious stress and adjustment disorders	4	1.7

and the clinical variables that were significant in the bivariate analysis.

RESULTS

The 212 patients included in the study came from two primary care teams in Barcelona. Mean age was 63.2 years (SD=15.27). Demographic and clinical characteristics are described in Table 1. All the patients had been diagnosed of depressive disorder (see table 2 for distribution of diagnoses). A total of 66.5 % were under treatment with a single antidepressant 24.1% with two antidepressants and 8.1% with three or more antidepressants. The antidepressants used most were selective serotonin reuptake inhibitors (SSRI) (table 2). During the treatment, 71.1% of the subjects took anxiolytics (benzodiazepines or hypnotics) as treatment concomitant to the antidepressants (the duration of the anxiolytic treatment was not evaluated). The percentage of

patients with chronic condition recorded was: 50.5% hypertension, 38.7% dyslipidemia, 11.8% diabetes, 6.1% osteoporosis, 5.2 % chronic obstructive pulmonary disease and 2.4% ischemic heart disease. A total of 68.5% of the patients had one or more chronic conditions and 84.4 % of the patients were receiving long-term treatment with one or more drugs. The patients were attended by primary care teams with a mean of 11.48 visits per years (SD =10.6) and 50% of the patients made 9 or more visits. Follow-up was made by 17.5% of the patients in the mental health center and the rest were attended by the primary care team. The patients who were seen in the mental health made a mean of 5.47 visits/year (SD =7.20) and 50% had 3 or more visits. The percentage of non-adherent patients was 34% [95% CI (27.3-40.5)]. The non-compliers had a higher percentage of long-term drug treatment ($p=0.013$). No relationship was found between compliers and the rest of the variables studied (table 3). The multivariate analysis confirmed that having a prescription of any other long-term treatment increases the likelihood of being a poor complier of the antidepressant treatment, independently of age and gender of the patient (OR: 3.35; 95% CI: 1.18- 9.54). No differences in compliance were found according to the type of antidepressant prescribed or if concomitant treatment with anxiolytics was received. There was also no relationship between compliance and the rest of the variables studied. The compliance rates were analyzed in the SSRI-treated group of patients (see table 4). Among the complier patients, 82.2% were women versus 65.4% among the non-complier's ($p=0.015$). In this group, the non-compliers also had a higher percentage of treatment with other long-term prescription drugs ($p=0.006$). When the variables were adjusted among themselves with the multivariate analysis, the relationship between being a male and having lower compliance was confirmed (OR: 2.39; 95% CI: 1.12- 5.09) and having at least one long-term drug prescribed and being a poor complier (OR: 6.28; 95% CI: 1.37- 28.85).

DISCUSSION

There are a variety of methods that make it possible to analyze the grade of compliance.²¹ The method used in this study is based on the registry of prescriptions dispensed to patients in the pharmacy. This registry is reliable, and has easy and rapid access from the management program of the e-CAP (primary health care team) clinical record in the usual clinical practice in the consultation. This is a novel indirect, objective measurement method²⁸ with null possibility of manipulation by the patient. It is easy and clear for the professional to interpret, the questions all being differential regarding the other measurement methods of compliance. On the other hand, it is not possible to assure that the medication withdrawn from the pharmacy was finally administered, this fact being the principal limitation of the method. It is also not possible to take into account the drugs

Table 3		Comparison between complier and non-complier patients		
		Cumplidores (total=140)	No cumplidores (total=72)	p
Gender	Women	78.6%	72.2%	0.302
	Men	21.4%	27.8%	
Age (years)	Under 65	54.3%	50.0%	0.554
	65 and over	45.7%	50.0%	
Chronic disease recorded	None	35.0%	27.8%	0.228
	One or more	65.0%	72.2%	
Long-term treatment with other drugs	No	20.0%	6.9%	0.013
	Yes	80.0%	93.1%	
They take anxiolytics	No	27.1%	32.4%	0.427
	Yes	72.9%	67.6%	
Seen in mental health center	No	85.0%	77.8%	0.190
	Yes	15.0%	22.2%	

withdrawn and pharmacies outside of Catalonia, as they do not share the same prescription registry computer system. In this study, complier is considered to be that patient who withdrew 100% of the drugs prescribed from the pharmacy during the year, accepting a variation of ± 2 prescriptions due to the measurement method.

In this study, one third of the patients were classified as non-compliers. This is slightly lower than in other studies that have evaluated antidepressant treatment compliance with other methods, although the results have been very variable and have varied from 10 to 60%.^{23, 29, 30} It is very likely that compliance has been overestimated because it has not been possible to assure that the medication was taken once withdrawn from the pharmacy. There are many direct and indirect methods to measure compliance, but most of them are difficult to apply in the daily clinical practice. This novel method, in spite of its limitations, offers true, reliable information and rapid access from the patient clinic. In spite of these limitations, according to the existing literature, this method has been shown to be valid to analyze treatment adherence, given that it evaluates the grade of compliance similarly to other methods and is adequately related with the clinical results.³¹

Treatment compliance in this study seems to also be slightly superior to other chronic medical diseases that vary

Table 4		Comparación entre pacientes cumplidores y no cumplidores, en los que tomaban ISRS		
		Compliers (total=129)	Non-Compliers (total=52)	p
Gender	Women	82.2%	65.4%	0.015
	Men	17.8%	34.6%	
Age (years)	Under 65	53.5%	48.1%	0.510
	65 and over	46.5%	51.9%	
Chronic disease recorded	None	32.6%	30.8%	0.862
	One or more	67.4%	69.2%	
Long-term treatment with other drugs	No	20.2%	3.8%	0.006
	Yes	79.8%	96.2%	
They take anxiolytics	No	29.7%	25.0%	0.527
	Yes	70.3%	75.0%	
Seen in mental health center	No	87.6%	80.8%	0.236
	Yes	12.4%	19.2%	

from 30 to 50%.^{32, 33, 34} Many studies have tried to determine the causes of low compliance in patients with depression. One of the factors postulated as being a determining factor when improving compliance is the profile of drug side effects.³⁵ In this study, better treatment compliance has not been found with SSRIs regarding treatment with other antidepressants, possibly due to the limited number of patients being treated with other antidepressants (tricyclics, etc.) that have not made it possible to find differences.

As was to be expected, no differences were found in regards to drug compliance among the different SSRIs, as well as in patients who received concomitant and selective treatment. Multiple drug treatment with other long-term drugs has been found to be a factor determining adherence, it being the only clinical factor related with compliance in this study. These results agree with other studies published.^{27, 36} The number of daily dosages of antidepressant drugs taken was not analyzed, a question that has been demonstrated to be important when improving compliance,³⁷ although most of the SSRIs are administered as a single daily dose.

It also was not possible to observe any difference in regards to compliance among patients who received follow-up by Primary Care or by the Mental Health Center, on the contrary to other studies.²⁹ On the other hand, adherence

was similar, regardless of the number of visits made to the MHC, so that we observed that a more frequent follow-up does not ensure better compliance nor does low compliance seem to generate more visits.

One of the limitations of our study is the fact that the patients were classified into two categories, without considering the different grades of compliance. This facilitated the interpretation of the results, but did not make it possible to differentiate between patients who had not withdrawn any prescription from those who had withdrawn 75%. On the other hand, no analysis was made regarding at what point of the treatment the abandonment or noncompliance occurred, nor the severity of the depression. When collecting data of patients with at least three months of treatment, early dropouts were ruled out.

The results of this study show that multiple drug treatment is a factor influencing antidepressant treatment adherence and primary care, similar to other studies.²⁶ Multiple drug treatment is common in elderly patients as occurs in this sample (mean age 63 years). This indicates the need to develop strategies that improve antidepressant treatment compliance, especially in this population segment in order to improve the clinical course of these patients.

For this reason, it is necessary to intensify certain strategies aimed at improving compliance in both primary care and specialized care, these strategies being education to the patient on their disease, informing on the most frequent adverse effects on which tolerance will be developed, involving the caregivers and family, above all in elderly patients, using calendars, use of dose reminders for the pills, and other strategies that have demonstrated efficacy in some studies.^{38, 39}

CONCLUSIONS

One third of the patients receiving antidepressant treatment do not adequately comply with the drug treatment, according to the accountability of the drugs withdrawn in the pharmacy. Strategies must be developed to improve drug treatment compliance, especially in the population with multiple drug treatment.

REFERENCES

- Gabilondo A, Rojas-Farreras S, Vilagut G, Haro JM, Fernandez A, Pinto-Meza A, et al. Epidemiology of major depressive episode in a southern European country: results from the ESEMeD-Spain project. *J Affect Disord.* 2010;120(1-3):76-85.
- Haro JM, Palacin C, Vilagut G, Martinez M, Bernal M, Luque I, et al. [Prevalence of mental disorders and associated factors: results from the ESEMeD-Spain study]. *Med Clin (Barc).* 2006;126(12):445-51.

3. Aragonès E, Piñol JL, Labad A, Masdéu RM, Pino M, Cervera J. Prevalence and determinants of depressive disorders in primary care practice in Spain. *In J Psychiatry Med.* 2004;34(1):21-35.
4. World Health Organization. (2008). *The Global Burden of Disease: 2004 Update.* In W. H. Organization (Eds.)
5. Sobel R, Markov D. The impact of anxiety and mood disorders on physical disease: The worried not-so-well. *Current Psychiatry Reports.* 2005;7(3):206-12.
6. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 200;160(14):2101-7.
7. Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry.* 1991;52(suppl5):28-34.
8. Nutt DJ. Rationale for, barriers to, and appropriate medication for the long-term treatment of depression. *J Clin Psychiatry.* 2010;71Suppl E1:e02.
9. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet.* 2003;361(9358):653-61.
10. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol.* 2008;22(4):343-96.
11. Furukawa TA, Cipriani A, Barbui C, et al. Long-term treatment of depression with antidepressants: a systematic narrative review. *Can J Psychiatry.* 2007;52(9):545-52.
12. Kok RM, Heeren TJ, Nolen WA. Continuing treatment of depression in the elderly: a systematic review and meta-analysis of double-blinded randomized controlled trials with antidepressants. *Am J Geriatr Psychiatry.* 2011;19(3):249-55.
13. National Institute for Health and Clinical Excellence. Depression: the treatment and management of depression in adults (update). 2009. (Clinical guideline 90.) www.nice.org.uk/CG90
14. Grupo de Trabajo sobre el Manejo de la Depresión Mayor en el Adulto. Guía de Práctica Clínica sobre el Manejo de la Depresión Mayor en el Adulto. Madrid: Plan Nacional para el SNS del MSC. Agencia de Avaluación de Tecnologías Sanitarias de Galicia (avalía-t); Guías de Práctica Clínica en el SNS: avalía-t 2008; No2006/06.
15. Sherbourne CD, Schoenbaum M, Wells KB, Croghan T. Characteristics, treatment patterns, and outcomes of persistent depression despite treatment in primary care. *Gen Hosp Psychiatry.* 2004;26(2):106-14.
16. Bosworth HB, Voils CI, Potter GG, Steffens DC. The effects of antidepressant medication adherence as well as psychosocial and clinical factors on depression outcome among older adults. *Int J Geriatr Psychiatry.* 2008;23(2):129-34.
17. Wade AG, Häring J. A review of the costs associated with depression and treatment noncompliance: the potential benefits of online support. *Int Clin Psychopharmacol.* 2010;Sep;25(5):288-96.
18. Akerblad AC. Response, remission and relapse in relation to adherence in primary care treatment of depression: a 2-year outcome study. *Int Clin Psychopharmacol.* 2006 Mar;21(2):117-24.
19. The expert consensus Guideline Series: Adherence problems in patients with serious and persistent Mental illness. *J Clin Psychiatry.* 2009;70(4):1-48.
20. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand.* 2002;105:164-72.
21. Nogués X, Sorli ML, Villar J. Instrumentos de medida de adherencia al tratamiento. *An Med Interna (Madrid)* 2007;24:138-41.
22. Montejo AL, Menchón JM, Carrasco JL, Franco M, Martín Carrasco M, Moriñigo A. Guía de evaluación y mejora del cumplimiento en el tratamiento a largo plazo del trastorno depresivo mayor. *Actas Esp Psiquiatr* 2010;38(Suppl. 2):1-27.
23. Pompili M, Serafini G, Del Casale A, Rigucci S, Innamorati M, Girardi P, et al. Improving adherence in mood disorders: the struggle against relapse, recurrence and suicide risk. *Expert Rev Neurother.* 2009 Jul;9(7):985-1004.
24. Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Patient adherence in the treatment of depression. *Br J Psychiatry.* 2002 Feb;180:104-9.
25. Olfson M, Marcus S, Tedeschi M, Wan GJ. Continuity of Antidepressant Treatment for Adults With Depression in the United States. *Am J Psychiatry* 2006;63:101-8.
26. Martín MJ, García-Toro M, Campoamor F, Pareja A, Aguirre I, Salvá J, et al. Use of antidepressant treatment. Patients' perception. *Actas Esp Psiquiatr.* 2009;37(5):276-81.
27. Zivin K, Kales HC. Adherence to depression treatment in older adults: a narrative review. *Drugs Aging.* 2008;25(7):559-71.
28. Bambauer KZ, Adams AS, Zhang F, Minkoff N, Grande A, Weisblatt R, et al. Physician alerts to increase antidepressant adherence: Fax or fiction? *Arch Intern Med.* 2006;166(5):498-504.
29. Stein MB, Cantrell CR, Sokol MC, Eaddy MT, Shah MB. Antidepressant adherence and medical resource use among managed care patients with anxiety disorders. *Psychiatr Serv.* 2006;57(5):673-80.
30. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Med Care.* 2006;44(4):300-3.
31. Baena-Díez JM, Gómez-Fernández C, Vilató-García M, Vázquez-Lazo EJ, Byram AO, Vidal-Solsona M. [A prescription register incorporated into computerized medical records for patients with hypertension: a new instrument to evaluate medication adherence.]. *Aten Primaria.* 2011 Jul;43(7):336-342
32. Coca A. Control de la hipertensión arterial en Atención Primaria en España: Resultados del estudio CONTROLPRES 2003. *Hipertensión.* 2005;22:5-14.
33. García-Reyes M, López-Torre J, Ramos E, Alcarria A, Fernández C, López MA. Cumplimiento terapéutico en pacientes con enfermedades cardiovasculares. *Med Clin (Barc).* 2002;118:371-5.
34. Clark LT. Improving compliance and increasing control of hypertension: needs of special hypertensive populations. *Am Heart J.* 1991;121(2):664-9.
35. Tai-Seale M, Croghan TW, Obenchain R. Determinants of antidepressant treatment compliance: implications for policy. *Med Care Res Rev.* 2000;57(4):491-512.
36. Hansen DG, Vach W, Rosholm JU, Søndergaard J, Gram LF, Kragstrup J. Early discontinuation of antidepressants in general practice: association with patient and prescriber characteristics. *Fam Pract.* 2004;21(6):623-9.
37. Nemeroff CB. Improving antidepressant adherence. *J Clin Psychiatry.* 2003;64(Suppl.18):25-30.
38. Katon W, Robinson P, Von Korff M, Lin E, Bush T, Ludman E, et al. A multifaceted intervention to improve treatment of depression in primary care. *Arch Gen Psychiatry.* 1996;53(10):924-32.
39. Vergouwen AC, Bakker A, Katon WJ, Verheij TJ, Koerselman F. Improving adherence to antidepressants: a systematic review of interventions. *J Clin Psychiatry.* 2003;64(12):1415-20.