Therapeutic adherence in primary care depressed patients: a longitudinal study

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Introduction. Lack of adherence has been associated to lower efficacy of anti-depressant treatment, increasing the risk of recurrence and persistence of clinical symptoms. Patients with poor medication adherence have more concomitant medical illnesses and somatic symptoms. Furthermore, this increases use of healthcare services.

Method. Longitudinal and observational study on therapeutic adherence level in depressive outpatients treated in 3 Primary Care (PC) centers. Eight evaluations during 6 months were carried out in 29 patients over 18, with DSM-IV-TR major depression diagnosis. The purpose of the present study was to determine adherence level, to analyze socio-demographic factors and clinical profiles involved in adherence, and to observe the evolution of depressive symptoms.

Results. Good therapeutic adherence was observed in 72.4% of patients. Significant differences in the Drug Attitude Inventory (U=107.5; p=0.036) were found. This tool evaluates the perceived effect of the medication, with a better perception observed in adherent patients. In those patients a progressive reduction on the Hamilton Depression Scale was found over the course of six monthly follow-up visits, with clinical remission observed in month 4. The analysis of survival rate did not reveal any significant difference between the two groups [Log Rank (χ^2=1.610, p=0.205)].

Conclusions. The therapeutic adherence observed in this longitudinal PC study is high, and it is associated with an improvement in the illness. A better perceived effect of the treatment showed a significant connection to an improvement in symptoms of depression.

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Adherencia terapéutica en pacientes depresivos de atención primaria: un estudio longitudinal

Introducción. La falta de adherencia se asocia a una reducción de la eficacia del tratamiento antidepresivo, incrementando la probabilidad de recurrencias y la persistencia de los síntomas clínicos. Los pacientes con mala adherencia a la medicación presentan más enfermedades médicas concomitantes y más sintomatología somática y generan mayor uso de los servicios de salud.

Método. Estudio observacional y longitudinal del grado de adherencia terapéutica en pacientes con trastorno depresivo atendidos en 3 centros de Atención Primaria (AP). Se realizaron 8 evaluaciones a lo largo de 6 meses a un total de 29 sujetos mayores de 18 años, con diagnóstico DSM-IV-TR de Depresión Mayor. Se pretendía determinar el grado de adherencia al tratamiento, analizar los datos sociodemográficos y perfiles clínicos que intervienen en la adherencia y observar la evolución de la sintomatología depresiva.

Resultados. Un 72.4% de los pacientes mostraron una buena adherencia terapéutica. Aparecieron diferencias estadísticamente significativas en el *Drug Attitude Inventory* (U=107.5; p=0.036), instrumento que evalúa el efecto percibido de la medicación, con una mejor percepción en los pacientes con buena adherencia. En estos pacientes se produjo una reducción progresiva en la puntuación de la Escala de Hamilton en cada una de las 6 visitas de seguimiento, alcanzando remisión de síntomas en la evaluación del 4º mes. En el análisis de supervivencia no se observaron diferencias significativas entre ambos grupos [Log Rank (χ^2=1.610, p=0.205)].

Conclusiones. La adherencia encontrada en este estudio longitudinal en AP es elevada y se asocia a una mejoría en el curso de la enfermedad. Un mejor efecto percibido del tratamiento está significativamente relacionado con una mejoría en la sintomatología depresiva.

Palabras clave: Trastorno depresivo, Adherencia terapéutica, Atención primaria, Tratamiento antidepresivo

INTRODUCTION

Depression is one of the most prevalent (13.9–29%) mental illnesses treated in the Primary Care service (AP).[1-3] Primary Care physicians are increasingly treating patients with these emotional disorders.[4-6] The financial cost of depression is very high.[7] It is estimated that over 150 million people suffer from this mental condition at some point in their lives.[8] Furthermore, depression is the main cause of years lived with disabilities, with a 50% greater load in favor of women.[9] It is believed that by 2020 this will be the second most common cause of disability in the world.[10]

Pharmacological and psychotherapeutic treatments form a part of the common management of depression. Pharmacological compliance and adherence form one of the basic pillars for the efficacy of currently available treatments.[11] For this reason there is an increasing interest in compliance with treatment among patients with mental illnesses.[12,13] Most publications have been based on samples of patients diagnosed with depressive or schizophrenic disorders referred to specialists.[12,14-19] Results show that patients take a low, or very low amount of their prescribed medication.[20,21] Lack of adherence has been linked to a drop in the efficacy of antidepressant treatment, thus increasing the probability of recurrence[22,23] and the persistence of clinical symptoms.[24-26] Patients with poor adherence to medication present more concomitant clinical illnesses and a greater prevalence of somatic symptoms.[12] Furthermore this increases use of healthcare services.[27]

Studies completed in depressive patients in PC are highly heterogeneous and, therefore difficult to compare.[28-31] Several factors have been suggested to explain the lack of adherence to prescribed treatment: being aged under 40 years, feeling dissatisfied with attention received from one's doctor,[31-32] having a first episode of depression vs recurrent depression,[18] negative beliefs or attitudes regarding certain side-effects of medication,[30,33] psycho-educational issues,[28] personality traits,[34] doctor-patient relationship and frequency of PC consultations.[35] Only 3 longitudinal studies have been published to date that assess adherence to antidepressant medication in face to face PC visits.[25,30,32]

This paper aims to determine the degree of therapeutic adherence in severely depressed PC patients, to analyze the socio-demographic factors and clinical profiles involved in the adherence process, and to observe the evolution of symptoms of depression in adherent and non-adherent patients.

METHODOLOGY

Observational and longitudinal study of the degree of therapeutic adherence in patients with depressive disorders treated at three PC medical centers in Mallorca.

The study involved doctors from all 3 centers. The study included each doctor's first 10 patients with a main diagnosis of a first episode of Severe Depression or Recurrent Severe Depression, through an open interview based on the DSM-IV-TR criteria,[36] with a total score on the Hamilton Depression Rating Scale of 17 or more, and who were initiating treatment with anti-depressant drugs at that time. Patients with clinical or psychological alterations that may limit their ability to understand and/or answer questions and completed questionnaires, and patients already under treatment with anti-depressant drugs at the time of the baseline evaluation were excluded from the study.

Eight assessments were conducted; screening, baseline assessment, and six monthly follow-up assessments.

Written informed consent was obtained from all participants in the study. The study was approved by the Balearic Islands Autonomous Community Ethics Committee.

Tools

- Socio-demographic and clinical variables questionnaire to collect the following socio-demographic and clinical information: age, gender, level of education, socio-economic level, civil status, cohabitation status, employment status, main DSM-IV-TR diagnosis and code, comorbidity with other psychiatric disorders (DSM-IV-TR), age of onset of the illness, number of previous episodes of depression, current and previous pharmacological and psychological treatment including anti-depressant treatment initiated at that time, total number of admissions to hospital and number of suicide attempts.
- Hamilton Depression Rating Scale, HDRS.[37] The 17-item Spanish version[38] assesses the severity of the depressive condition (inclusion criterion) and patient symptomatic profile. Inclusion criterion: total score of 17 points or more. Remission of depressive symptoms was defined as having obtained an HDRS score of 7 or less.[39,40]

- Simplified Medication Adherence Questionnaire, (SMAQ) (Spanish version validated by Knobel et al.[41]). This is based on the Morisky Scale[42] and presents high rates of sensitivity (72%) and specificity (91%), consisting of 6 questions posed directly to the patient regarding their medication taking habits. It includes a semi-quantitative question that indicates the percentage of therapeutic compliance. For this study, an adherent patient was defined as one obtaining a SMAQ score of over 85% at visits 1 to 6.
- Drug Attitude Inventory (DAI):[43] a self-assessment tool for the perceived effect of medication. There are two versions: a 30-item questionnaire asking for true/false answers, and a short, 10-item version[44], the one used in this study. A higher score denotes a more positive attitude to medication.
- Beliefs about Medicines Questionnaire, BMQ,[45] Spanish version;[46] designed to assess patient beliefs about their medication. This consists of a General BMQ to evaluate patient beliefs about medication in general (8 items) with two 2 subscales (*Abuse and Damage*) and a specific BMQ (10 items) to evaluate the patient's opinion about his/her specific treatment, also with 2 subscales (Perceived *Need* for the medication and *Concern* about its consequences).
- Revised NEO Personality Inventory (NEO PI-R):[47] this assesses personality in the general population. Five dimensions or factors are examined (Openness, Responsibility, Extroversion, Neuroticism and Friendliness); each factor comprises six scales or facets, measured using 8 items each, making a total of 240 questions to be answered. Spanish adaptation by Cordero el al.[48]

Patients meeting the inclusion criteria were invited by their doctors to take part in the study. They signed the informed consent document, and all relevant socio-demographic data and details of medical history were collected. They also completed the HDRS, DAI, NEO PI-R and BMQ inventories and questionnaires. The patients were assessed longitudinally on eight occasions over the course of six months: screening, baseline assessment and six monthly follow-up visits, using HDRS and SMAQ.

Statistical analysis

The spread of data for our study did not meet the conditions required for statistical normality, therefore non-parametric data analysis was used.

The data were analyzed using the statistical software package SPSS 19.0. Univariant analyses were completed for the differences between adherent and non-adherent patients using the χ^2 and Mann-Whitney U tests.

A survival analysis was performed using the Kaplan-Meier method to assess the time elapsed from inclusion in the study until remission of depression in these patients.

RESULTS

A total of 29 patients completed the study. The sample consisted predominantly of women (82.8%), who were married (55.2%), with secondary school level studies or above (44.8%), who lived with their own family (69%). Average age of participants was 47.5 (SD=13.6).

Table 1 shows the socio-demographic characteristics of the sample. No significant differences were observed in any of the sociodemographic variables studied between adherent and non-adherent patients.

A total of 72.4% of patients showed good therapeutic adherence and 27.6% were non-adherent patients. Figure 1 shows the evolution of the percentage of adherence over the 6 months' duration of the longitudinal study, collected using SMAQ.

Statistically significant differences were observed on the Drug Attitude Inventory (U=107.5; p=0.036), a tool that assesses the perceived effect of medication, with a better perception of its effect in adherent patients (Table 2).

No statistically significant differences were observed on the Personality Inventory (NEO-PI) or the Beliefs about Medicines Questionnaire (BMQ) between the two groups of patients on any of the 4 subscales (*abuse* p=0.283, *damage* p=0.383, *need* p=0.219, *concern* p=0.096).

Similarly, no significant differences were observed with regard to adherence in patients suffering a first episode of depression (69%) or those suffering repeat episodes (31%) (U=77.0; p=0.670).

On the Hamilton Depression Rating Scale (HDRS), although initially all patients obtained a score of 17 or over (severe depression), it was observed that in patients with good adherence there was a progressive drop in the score on this scale at each of the 6 follow-up visits (Figure 2), unlike the pattern observed for non-adherent patients, whose scores on this scale were more variable. This progressive drop in score showed a statistically significant improvement in adherent patients in months 2 and 5 (p=0.035, p=0.028). It is also notable that adherent patients presented a remission of depressive symptoms (HDRS≤7) two months earlier than non-adherent patients, at the 4th follow-up visit. To analyze this information in further detail, a survival analysis (Kaplan-Meier method) was completed, although no significant differences were observed between the two groups [Log Rank (χ2=1.610, p=0.205)].

Table 1 Socio-demographic characteristics of the sample

	TOTAL n=29 Median (SD)	Adherent n=21 (72.4%) Median (SD)	Non-adherent n=8 (27.6%) Median (SD)
Sex			
male	17.2	23.8	0
female	82.8	76.2	100
Age	47.5 (13.6)	47.9 (14.6)	46.5 (11.4)
Civil Status			
single	20.7	28.6	0
married	55.2	47.6	75
separated	13.8	14.3	12.5
widowed	10.3	9.5	12.5
Level of Education			
None / primary	31	28.6	37.5
Secondary	24.1	13.8	37.5
Further education	44.8	37.9	25
Employment status			
employed	48.3	47.6	50
unemployed	51.7	52.4	50
Cohabitation			
Parental family	10.3	14.3	0
Own family	69	61.9	87.5
Alone	17.2	23.8	0
Others	3.4	0	12.5
Monthly income			
0-1200	41.4	38.1	50
>1200	58.6	61.9	50

DISCUSSION

In the present study, 72.4% of patients were found to be taking their medication correctly, a higher figure than that found in most papers published on adherence to anti-depressant medication in PC found to date,[28,30,32,49-52] except for the study by Tamburrino et al.[31] with 86% of patients adhering by month 4 of anti-depressant treatment.

Results published on adherence in Primary Care cover a wide range of values as a result of the different methods used to define, implement and assess therapeutic adherence, making it difficult to complete a more detailed comparison of our results with those previously obtained in other studies,[25,30,32] as our study consists of a longitudinal design with face to face assessment over the course of 6 months. For example, some studies have completed a retrospective analysis of therapeutic adherence, based on prescription details: according to this data only one in five patients adhered to anti-depressant treatment over the four-month study. Chronic polymedicated chronic patients presented better compliance.[52]

A significant problem of assessment arises in studies on therapeutic adherence. No single measurement strategy has been considered ideal; a combination of methods is the best approach to assessing adherence habits.[53] Some papers use clinical criteria; Others are based only on questions posed directly to the patient. Questionnaires constitute one of the most commonly used procedures, given the simplicity with which they reflect patient behavior, using easily applicable direct questions. Their main disadvantage is that they tend to overestimate levels of compliance. Observation of adherence to medication completed by trained staff is probably one of the most reliable methods, found in hospital environments. Testing for the presence of medication in blood and urine samples is an expensive and complex method, as it requires laboratory analysis. Electronic devices

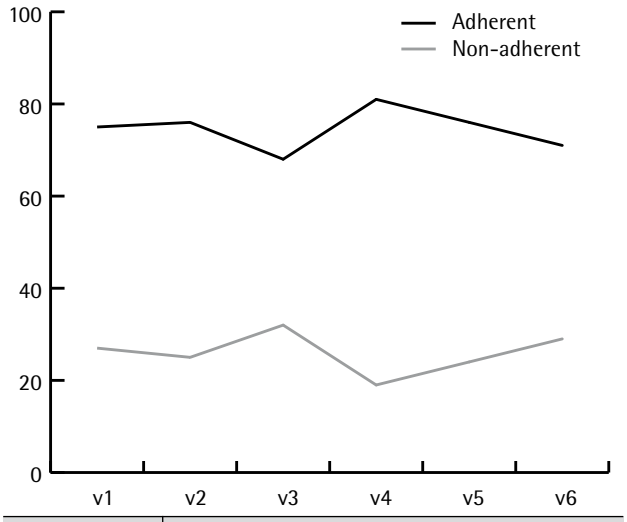

Figura 1 — *Evolution of adherence in both groups (%). Simplified Medication Adherence Questionnaire (SMAQ). Author: Maria J Serrano*

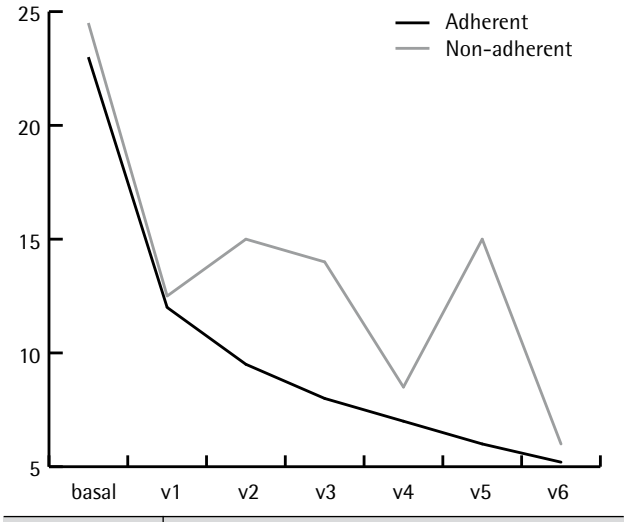

Figure 2 — *Evolution of severity of depressive symptoms. Scores obtained on the Hamilton Depression Rating Scale (HDRS). Author: Maria J Serrano*

for the measurement of compliance or control of use, such as the Medication Event Monitoring System (MEMS) are considered less intrusive and more practical than direct observation, but their high cost rules out general use of this method for outpatients. Furthermore, the patient opening a container at certain times of day can in no way guarantee that the drug has been taken. The scales used for the assessment of compliance with treatment in mental health patients therefore address three general areas: awareness of the illness or *insight*, attitude to drugs, and tolerability (in particular regarding the side effects of medication). It must be considered that most of these tools have been created specifically for the assessment of adherence in Schizophrenia.[54]

Early research on factors affecting adherence focused more on demographic aspects and other patient characteristics, and on the treatment prescribed, leaving aside factors relating to patient attitude and expectations, or doctor-patient relations.[35,55] In this study, adherent patients show a more positive attitude and a better perception of the positive effect of medication than non-adherent patients. However, with regard to beliefs about medication, the results reflect those of Russell and Kazantzis,[51] who also assessed this relationship in the PC setting and did not find any connection to adherence, except on the subscale for *Concern*, which is the only one in the present study to show significance, although in other PC studies differences have been observed regarding adherence.[30]

Table 2 — **Drug Attitude Inventory Scores**

	median	SD	Mann-Whitney U
Non-adherent	14.57	2.99	U=107.5
Adherent	17	1.72	**p=0.036**
Total	16.37	2.32	

The sample consisted of patients commencing anti-depressant treatment at the time of inclusion, and it was observed that adherent patients presented a remission of depressive symptoms (HDRS≤7) two months earlier than non-adherent patients, on the 4th follow-up visit, reflecting earlier remission than found in other longitudinal studies in PC.[25-57] However, the personality factors examined in this study, unlike other studies which identified a connection between adherence and Cluster B personality disorders,[34] did not seem to predict adherence in any way.

It has been shown that there is a greater probability of patients continuing to take medication during the first month of treatment if they have received specific educational messages: the importance of compliance, the possibility of a lack of perceptible symptomatic improvement during the first two to four weeks, the importance of persisting with treatment even if the expected improvement is not noticed and the importance of gradual withdrawal from medication under the supervision of a doctor.[49]

Given that PC services are an increasingly more common setting for the treatment of depression in patients, the need has arisen for improving the handling of the illness at the

start of treatment in order to obtain a response to therapy over a short period of time and thus generate a more positive perception of treatment among patients. Similarly, it is important to make use of the relationship between the PC doctor at the patient in order to provide personalized information about medication, its effects and therapeutic response.

Finally, it is important to stress that the results obtained show that patients with a higher level of therapeutic adherence are those who have a better perception of the effect of the medication, showing earlier remission than in patients who do not comply with the treatment prescribed.

STRENGTHS AND LIMITATIONS OF THE STUDY

The most important and primary strength of the study is its longitudinal design, with 8 assessments conducted in person by a trained researcher, in Primary Care consultations. Furthermore, the patients were starting anti-depressant treatment at the time of inclusion on the study.

The main limitation of the study is sample size, which conditions the extrapolation of data and the generalization of results. Objective measurements (biological samples, such as drug concentrations in the bloodstream) were not taken for the assessment of therapeutic adherence. The number of times the anti-depressant drug was taken each day was not analyzed, although most effective regimes in the treatment of depressive disorders allow for a single daily dose in authorized presentations.

CONCLUSIONS

As this is a longitudinal study we can consider that adherence in our study is high, and is related to a substantial improvement in the course of the illness. However, the analysis of factors associated with greater adherence to anti-depressant treatment shows that personality factors and beliefs surrounding medication do not influence therapeutic compliance. A greater perceived effect of treatment is nevertheless significantly connected to therapeutic adherence and patients thus experience an improvement in depressive symptoms.

Given that PC services are an increasingly more common setting for the treatment of depression in patients, the need has arisen for improving the handling of the illness at the start of treatment in order to obtain a response to therapy over a short period of time and thus generate a more positive perception of treatment among patients. Similarly, it is important to make use of the relationship between the PC doctor at the patient in order to provide personalized information about medication, its effects and therapeutic response.

CONFLICT OF INTEREST

There is no conflict of interest.

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