Pharmacist interventions in depressed patients

Maria Rubio Valera

UNIVERSITAT DE BARCELONA

FACULTAT DE FARMÀCIA

DEPARTAMENT DE FARMÀCIA I TECNOLOGIA FARMACÈUTICA

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Dra. M Antònia March Pujol Dr. Antoni Serrano Blanco

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A mis padres, José y Carmeli,

que han sido los mejores maestros y me han hecho feliz,

mis logros son los suyos.

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Outline of this thesis

In *Chapter 1* the actual knowledge about the treatment for depression and the problem of non-adherence to pharmacological treatment is reviewed. *Chapter 2* is divided in 5 sections that present the 4 papers that constitute the methods and results of this thesis. In *Paper 1*, the randomized controlled trials evaluating the impact in adherence of pharmacist interventions in depressed patients are systematically reviewed and available evidence is synthesized. *Paper 2* describes the research protocol of the randomized controlled trial and accompanying cost-effectiveness analysis of the pharmacist intervention conducted in our setting. The effectiveness of the pharmacist intervention is presented in *Paper 3*. *Paper 4* presents the results of the economic evaluation conducted alongside the randomized controlled trial. In the *Section 5* of *Chapter 2*, complementary analyses that have not been published or submitted for publication are presented. The thesis is concluded with a general discussion and a summary of results (*Chapters 3 and 4*).

In *Annex I*, the PRODEFAR intervention that was evaluated in this thesis is presented. Finally, the papers that were published during the development of this thesis but that are not directly related to this thesis are presented in *Annex II*.

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Dicen que lo mejor se reserva para el final, en este caso es verdad. Quiero cerrar estos agradecimientos recordando a mis padres, a mi hermana y a Joan. Ellos me conocen mejor que nadie y me apoyan mejor que nadie. Me animaron a empezar esta tesis y me han animado cada vez que lo he necesitado, como hacen siempre. Los cuatro saben que son lo más importante para mí y que nada de lo que hago sería posible sin ellos.

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Contents

General abstract

Objectives

1. To systematically evaluate the effectiveness of pharmacist care compared with usual care (UC) on improving adherence to antidepressants in depressed outpatients.

2. To evaluate the effectiveness of a community pharmacist intervention (CPI) compared to UC in the improvement of adherence to antidepressants and patient wellbeing in a primary care population initiating treatment with antidepressants.

3. To evaluate the cost-effectiveness and cost-utility of a CPI in comparison with UC for depressed patients initiating treatment with antidepressants in primary care.

Methods

Objective 1: a systematic review and meta-analysis of randomized controlled trials (RCTs) that evaluated the impact of pharmacist interventions on improving adherence to antidepressants was conducted. RCTs were identified through electronic databases, reference lists were checked and experts were consulted. Methodological quality was assessed and methodological details and outcomes were extracted in duplicate.

Objectives 2 and 3: a RCT comparing patients with depressive disorder receiving a low intensity CPI (87) with patients receiving UC (92) was performed in Barcelona. The intervention consisted of an educational programme focused on improving knowledge about medication, making patients aware of the importance of compliance, reducing stigma, reassuring patients about side-effects and stressing the importance of carrying out general practitioners' advice. Measurements took place at baseline, and after 3 and 6 months. Adherence was continuously registered from the computerized pharmacy records. Non-adherence was defined as refilling < 80% of doses or having a medication-free gap >1 month. Secondary outcomes included clinical severity of depression (PHQ-9), health-related quality of life (HRQOL) (EuroQol-5D) and satisfaction with the treatment received.

Objective 3: direct and indirect costs were assessed using the Client Service Receipt Inventory. Unit costs were derived from official local sources. The time horizon was less than a year so costs were not discounted. Quality-Adjusted Life-Years (QALYs) were calculated using the EuroQol-5D Spanish tariffs.

Results

Six RCTs were identified in the systematic review; most of them were conducted in the USA. A total of 887 depressed patients who were initiating or maintaining treatment with antidepressants and who received pharmacist care (459 patients) or UC (428 patients) were included in the review. The most commonly reported interventions were patient education and monitoring, monitoring and management of toxicity and side effects, compliance promotion, provision of written or visual information and recommendation or implementation of changes or adjustments in medication. Overall, no statistical heterogeneity or publication

bias was detected. The pooled odds ratio, using a random effects model, was 1.64 (95% CI 1.24-2.17). Subgroup analysis showed no statistically significant differences in results by type of pharmacist involved, adherence measure, diagnostic tool or analysis strategy.

Results from the RCT showed that patients in the CPI group were more likely to remain adherent at 3 and 6-month follow-up but the difference was not statistically significant. No statistically significant differences were observed in clinical symptoms or satisfaction with the pharmacy service. However, patients in the CPI group showed greater statistically significant improvement in HRQOL compared to UC patients, both in the ITT and PP analyses.

Overall costs were higher in the CPI group than in UC patients, mainly because of differences in productivity losses. There were no statistically significant differences between groups in QALYs. From the societal perspective, the incremental cost-effectiveness ratio (ICER) for CPI compared with UC was €9,335 per extra adherent patient and €29,548 per extra remission of depressive symptoms. The incremental cost-utility ratio (ICUR) was €38,896 per QALY gained. If willingness to pay (WTP) is €50,000 per one extra adherent patient, per extra remission of symptoms or per QALY, the probability of the CPI being cost-effective was 0.71, 0.52 and 0.56, respectively.

From the healthcare perspective, the ICER was €862 per extra adherent patient and €2,729 per extra remission of depressive symptoms. ICUR was €3,542 per QALY gained. The probability of the intervention being cost-effective was 0.75 if WTP is €12,000 for an extra adherent patient and €40,000 for QALY gained. The probability of the CPI being cost-effective in remission of depressive symptoms was 0.55 for a WTP of €50,000.

Conclusions

A pharmacist intervention could be a good strategy to improve patients' adherence to antidepressants in primary care but evidence supporting the pharmacist intervention in depressed patients is still limited, especially in community pharmacies and outside the USA.

A low intensity CPI proved to be ineffective in improving patients' adherence to antidepressants or clinical symptomatology. However, it was effective in improving the patient's health-related quality of life. The CPI was not cost-effective in comparison with UC in the improvement of adherence, depressive symptoms and quality adjusted life years.

Further research needs to be carried out to produce a deeper understanding of the role of community pharmacists in the management of depressed patients in primary care.

Chapter 1

Introduction and objectives

1.1 Major depression

Depression is highly prevalent and one of the diagnoses that generates the greatest impairment in the patient and costs to society. Consequently, one of the main challenges in public health is to improve treatment of depression.

Major Depression is classified by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) as a Mood Disorder (1). The two main groups of mood disorders are distinguished based on whether the person has had a manic or hypomanic episode. As such, there are depressive disorders, of which the most researched is major depression, and bipolar disorders or manic depressions, which are characterized by intermittent episodes of mania or hypomania alternated with depressive episodes. Other less severe forms of depressive disorder are dysthymic disorder and depressive disorder not otherwise specified.

1.1.1 Characterization of the disorder and diagnostic criteria

Major depression is a condition characterized by episodes where the patient presents depressed mood and/or loss of pleasure in most activities. According to the DSM-IV-TR (1), to meet diagnostic criteria this state of mind must produce clinically significant distress or impairment in social, occupational or another important area for the person. The symptoms must be maintained most of the time, nearly every day, for at least two consecutive weeks and should not be explained by the physiological effects of a drug or medicine or physical illness or by the presence of grief.

For a diagnosis of major depression, the DSM-IV system requires at least five out of nine depressive symptoms be present, with at least one of them being: a) persistent sadness or low mood; and or b) marked loss of interests or pleasure. Other associated symptoms that must be present are: a) disturbed sleep (either not being able to sleep well or sleeping too much compared with usual); b) decreased or increased appetite and/or weight; c) loss of energy or a significant reduction in energy level; d) agitation or slowing of movements; e) difficulty concentrating or making decisions that used to be made fairly easily; f) feelings of worthlessness or excessive or inappropriate guilt; and or g) suicidal thoughts, intentions or acts.

These episodes can be recurrent and are categorized as mild (few symptoms in excess of the 5 required to make the diagnosis, and only minor functional impairment), moderate (symptoms and impairment between mild and severe), or severe (presence of most of the symptoms and marked impact on social or occupational functioning) (1;2).

1.1.2 The prevalence of depression

Mood disorders are highly prevalent in the general population, with major depression being the most prevalent mental disorder. Between 2001 and 2003 the World Mental Health Survey Initiative was conducted; the largest coordinated series of cross-national psychiatric epidemiological surveys ever undertaken (3).

The survey found that the country with the highest prevalence of mood disorders was the United States of America while the country with the lowest prevalence was Nigeria, with a 12-month prevalence in the range 0.8% against 9.6% in the USA (4) and lifetime prevalence ranging from 3.3% to 21.4% (5). Women had a significantly higher lifetime risk of major depressive disorder (6). Regarding the age of onset distribution for mood disorders, lifetime prevalence of mood disorders was consistently low until the early teens, when a roughly linear increase began that continued through late middle age, with a more gradual increase thereafter. The median age of onset of mood disorders ranged between the late twenties and the early forties in the World Mental Health Surveys (5). In Europe, it is estimated that a 12.8% of population will suffer at least one episode of major depression throughout life (7). In Spain, lifetime prevalence and 12-month prevalence of major depression can reach up to 9.6% and 4.0%, respectively (8).

In Spain, as in other countries, patients with mental health problems are frequently treated exclusively by a general practitioner (9-13). Furthermore, access to specialized care for patients with more severe symptoms is usually achieved through a referral from a general practitioner. Subsequently, after assessment and treatment in specialized care, patients with mental disorders are usually referred back to primary care for follow-up. That this happens is not surprising, in fact, in order to strengthen the health care systems maximizing low-cost effective and efficient health services, the World Health Organization has focused attention on the development of a primary care strategy to treat mental health problems (14).

Major depression is also a highly prevalent disorder in primary care and has been estimated to be present in between 6.3% and 14.3% of primary care outpatients worldwide (11;15-19). The largest epidemiological study conducted in Catalonia, the DASMAP study, showed a 12-monthprevalence of major depression in primary care attenders of 9.6%. The lifetime prevalence was 29.91% (11).

1.1.3 The burden of major depression

In addition to its high prevalence, depression has a high cost, both socially and economically (20). In 1996, the World Health Organization identified depression as the leading cause of disability if one took into account only the years lived with disability and projected that, by 2020, depression will be the second largest cause of disability in the world (21). In 2000, major depression was the fourth leading cause of disability in all Western societies, the third in Europe and the first in the United States. Thus, in Europe, major depression alone was responsible for 6% of the total disability generated by diseases. New WHO projections predicted that by 2030, depression will be the leading cause of disability in Western societies (22).

In 2006, mood disorders were shown to have the greatest impact on health related quality of life in Catalan primary care patients when compared to chronic physical conditions, such as chronic pain and cardiovascular disease, and anxiety disorders (23). Major depression showed the lowest health-related quality of life (24). When

quality-adjusted life-years losses associated with chronic medical conditions were estimated, mood disorders ranked second, only surpassed by chronic pain (24).

1.1.4 The costs of major depression

Due to its high prevalence and generated impairment, major depression is the mental disorder associated with the highest costs and, alone, accounts for 33% of the costs associated with mental disorders (25). This cost is generated both directly through consumption of drugs or use of services, and indirectly; such as those associated with absence from work or mortality (26). In 2005, it was estimated that the cost associated with mental disorders was approximately 3%-4% of gross domestic product in Europe (27).

In Catalonia, the annual cost of major depression in 2006 was 735.4 million Euros (28). The direct health cost amounted to 155.6 million Euros (21.2% of the total costs) with the total cost of pharmacological care (mainly antidepressants) at over 101 million Euros (13.7% of the total costs) and spending on primary care services of almost 41 million Euros (5.6% of total costs). Indirect costs accounted for the 78.8% of total costs. Indirect costs solely due to inability to work were estimated at almost 553 million Euros (75.1% of total costs) while costs due to premature mortality (suicide attributed to depression) amounted to nearly 27 million Euros (3.7% of total costs). Overall, the average annual cost of an adult with depression was close to 1,800 Euros.

As such, major depression is now considered a public health priority and great efforts are being done to improve the prevention, treatment and reduction of relapses in major depression.

Key points 1.1 Major depression

– Major depression is a disorder characterized by depressed mood and/or loss of pleasure in most activities that produces distress and/or impairment in social, occupational and other important areas for the person.

– Major depression is a highly prevalent disease in the general population as well as in primary care, where it is mostly managed and treated.

– Major depression causes significant impairment in social and occupational areas of functioning. It has been projected to be the leading cause of disability in Western societies by 2030.

– Due to its high prevalence and impairment, major depression results in high costs, mainly as a consequence of the inability to work but also because of the use of pharmacological care and services.

1.2 The treatment of major depression

In view of the scientific evidence, the need to treat major depression is not questioned. However, the treatment options are numerous and making the treatment decision is a complex process. A wide range of biological, psychological and social factors have a significant impact on the course of major depression (7;29-32). These factors, as well as personal past personal history, family history of depression and the patients' needs and preferences should be taken into account by the clinician when undertaking a diagnostic assessment and making decisions about care and treatment (2).

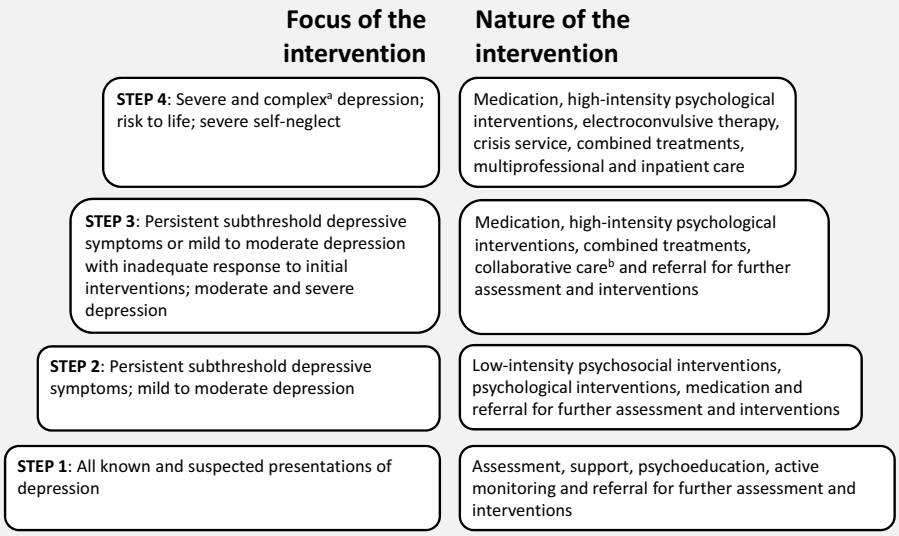
1.2.1 Treatment of depression according to clinical guidelines

The National Institute for Health and Clinical Excellence (NICE) suggests a stepped care model that organises the provision of services (2). It recommends beginning with the most effective and least intrusive interventions followed in a particular order that should be applied until an appropriate response is achieved (Figure 1.1).

A Spanish manual for the treatment of major depression, published with the support of the collegiate medical organization and prevailing at the time when this thesis was started, recommended the use of antidepressants, if possible, in combination with psychological therapy for the treatment of major depression (33).

In 2010, the first clinical guideline for the management of major depression adapted to the Catalan health system was published (34). The Catalan guideline

Figure 1.1 The stepped care model (Extracted from NICE CG 90) (2)

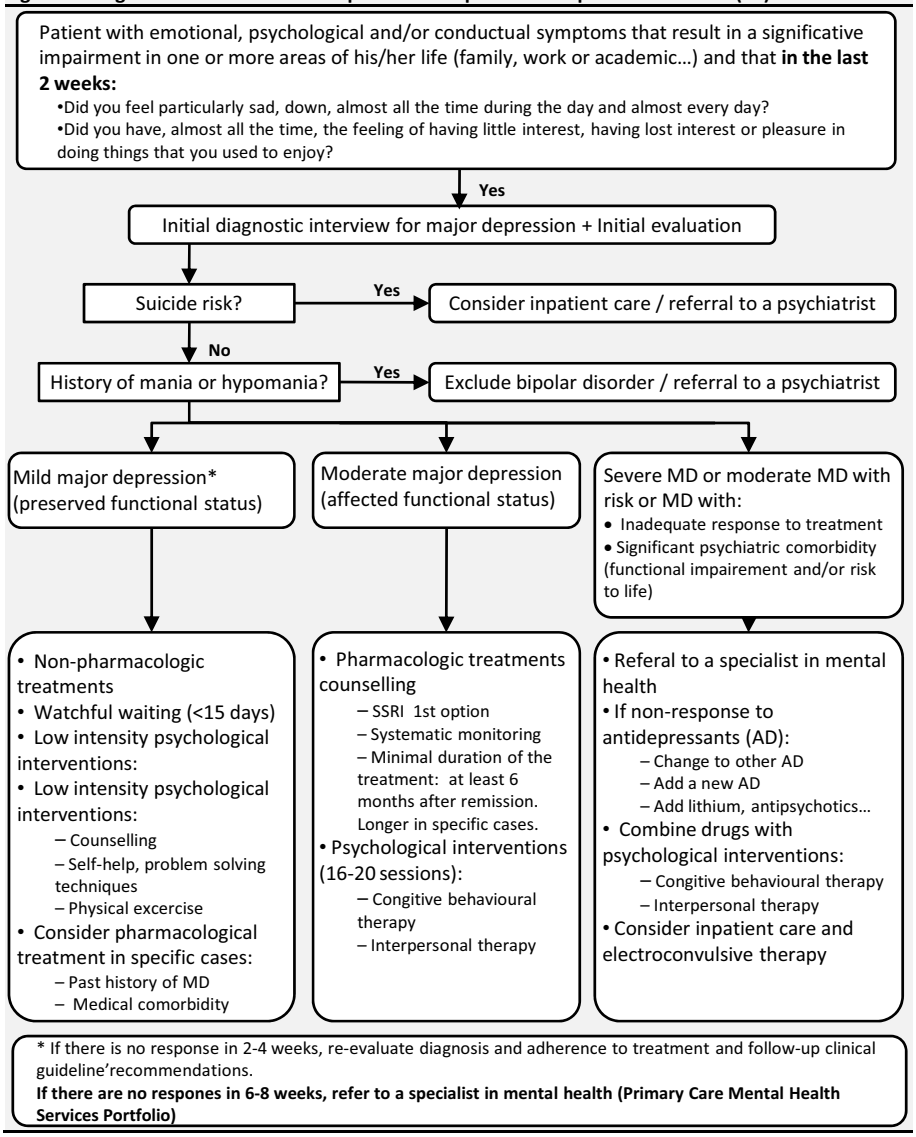


[a] Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors.
[b] Only for depression where the person also has a chronic physical health problem and associated functional impairment.

was based on the stepped care model suggested by the NICE clinical guideline for major depression and adapted taking into account the differences between the English and the Catalan health systems. As with the English guideline, the Catalan clinical practice guideline for the management of major depression in the adult population suggests an algorithm that clinicians should take into account to identify, diagnose, treat and monitor patients (Figure 1.2).

Although a systematic review concluded that antidepressants have only a modest clinical advantage over placebo in patients with mild to moderate symptoms, they

Figure 1.2 Algorithm of the healthcare process of depression adapted to Catalonia (34)



are still recommended in patients with severe depression (35). According to the guidelines, in patients with mild to moderate major depression, pharmacological treatment is only indicated when the patient has a past history of moderate or severe depression or in patients with subthreshold depressive symptoms that have been present for a long period (at least 2 years) or when subthreshold depressive symptoms or mild depression persists after other interventions. On the other hand, in patients with moderate to severe major depression, pharmacological treatment is indicated (alone or in combination with a high-intensity psychological intervention such as cognitive behavioral therapy).

1.2.2 The pharmacological treatment of depression

There are four main types of antidepressant drugs: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake selective inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs).

When an antidepressant drug is considered appropriate, clinical guidelines suggest beginning the treatment with an SSRI (2;33;34). TCAs and MAOIs, despite being the first types of antidepressant on the market, have a worst side effect profile and, currently, are the least used; usually reserved for cases in which the patient does not respond to other treatments.

In Spain, as in other European countries, almost 70% of individuals with a mood disorder received psychotropic drug treatment (either alone or in combination with psychological treatment) (36;37). In fact, the most commonly given treatment for primary care patients with recognized mood disorders is pharmacological treatment (11;12;38;39). In 2006, psychotropic drugs were prescribed to 66.9% of primary care attenders in Catalonia who met the DSM-IV criteria for a mood disorder, mainly anxiolytics and antidepressants (40).

In patients with severe or persistent symptoms, a referral to specialized care is indicated. However, it is estimated that only 42% of primary care attenders with a mood disorder consulted a mental health specialist in mental health (unpublished work but available upon request).

1.2.3 Treatment concordance with clinical guidelines and non-adherence

Adherence to practice guideline recommendations is important since they include the best available scientific evidence for the management of major depression. In fact, greater adherence to practice guidelines for major depression in primary care has been shown to be significantly associated with the presence of fewer depressive symptoms (41).

Treatment adequacy takes into account various factors associated with the appropriate use of antidepressant drugs, including kind of prescribed drug, minimum daily dosage, duration of treatment, and follow-up sessions with the prescribing practitioner. Some of these factors depend almost exclusively on the

practitioner while in others the patient's beliefs and attitude are key determinants of adherence to these recommendations.

Although previous published studies systematically report that patients treated in a specialised setting are more likely to receive adequate treatment, the largest and most recent epidemiological study conducted in Europe shows that no significant differences exist in treatment adequacy when comparing specialized care with primary care in Spain (9).

However, percentages of treatment concordance with clinical guidelines are still low in primary care in Catalonia, ranging between 21% and 25% (42). This low rate of concordance with clinical guidelines could not be explained by the kind of drug prescribed, the dose, or the duration of treatment as pharmacological treatment in major depressive episodes was mostly prescribed as recommended; 99% of Catalan primary care patients with major depression received one of the recommended antidepressants and 93% at a minimum usual daily dosage. The two main reasons for the low concordance between real practice in Catalonia and the recommendations made by clinical guidelines were the high ratios of patient discontinuation of treatment and the low number of follow-up sessions performed.

During the first 3 months of treatment (acute treatment phase) between 30% and 33% of patients stopped taking antidepressant medication and only 40% of patients received an adequate number of follow-up sessions. When considering a six-month period, between 41% and 44% of patients discontinued their treatment with antidepressant drugs and only 35% of patients received an adequate number of follow-up sessions (42).

Non-adherence has been widely described as one of the main problems related to pharmacological treatment of major depression. As described in the following section, rates of non-adherence to antidepressants can reach up to 75% (43-46), greatly affecting the treatment of major depression.

Key points 1.2 The treatment of major depression

– The Catalan guideline for the management of major depression suggests a stepped-care model similar to the NICE clinical guideline that recommends various treatments or interventions depending on the evolution of the depressive symptoms.

– According to clinical practice guidelines, antidepressant drugs are always indicated in patients with moderate to severe major depression and in patients with mild to moderate major depression if some criteria are met.

– In Spain and most European countries, the majority of patients with mood disorders are treated with psychotropic drugs.

– In Catalonia, the main reasons for low concordance of real practice with clinical guidelines are the low number of follow-up sessions and the high ratios of patient discontinuation.

1.3 Non-adherence

One main research priority, particularly in medicines for severe mental illness such as major depression, is to develop effective, efficient, achievable and equitable interventions that facilitate adherence to appropriate prescriptions (47).

1.3.1 Describing patient medicine-taking behavior

'Compliance', 'adherence' and 'concordance' are three terms related to medicine-taking behavior that are usually used as interchangeable although differences exist between them.

Compliance is defined as 'the extent to which the patient's behavior (in terms of taking medications, following diets, or executing other lifestyle changes) coincides with the clinical prescription' (48). Compliance does not involve the patient in the decision-making process and so the term adherence was introduced.

Adherence is defined as 'the extent to which a person's behavior (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider' (49) emphasizing the need for agreement and the patient's freedom to decide whether to adhere to the doctor's recommendations.

Finally, patient-centered models of medical treatment led to the introduction of a new term, concordance, which is a model of physician-patient relationship based upon mutual respect and involvement in treatment. Concordance describes not only patient behavior in relation to prescribed medication but also relates to the degree of consideration given to patient's perspective and its impact on the degree of agreement in decision-making. Consequently, it is a more complex term(47).

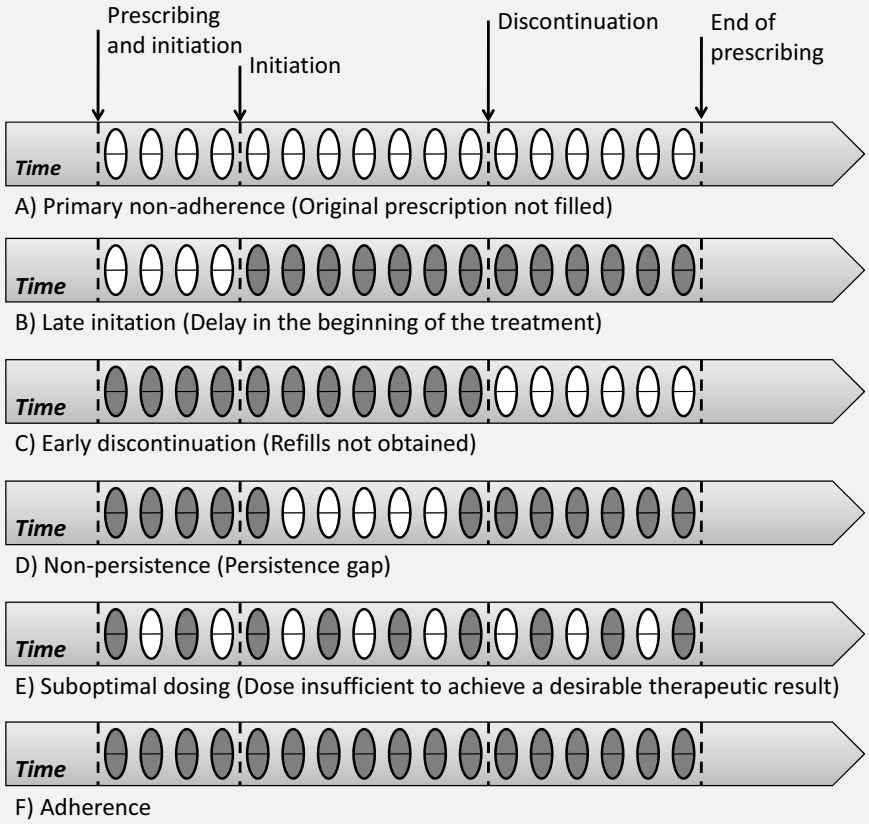
A fourth term that is related with treatment adherence is persistence. Persistence describes the degree of continuity in the medication-taking process. In a more practical way, persistence has been described by some authors as the act of continuing the treatment for the prescribed duration and could be defined as the period of time from initiation to discontinuation of therapy (50).

Throughout this thesis, the term adherence will be used to describe patient medication-taking behavior.

1.3.2 Types of non-adherence to medications

Medication-taking is a complex process and, consequently, differing patterns of usage will lead to different types or categories of non-adherence. Depending on the time and type of deviation from the agreed treatment plan, we can categorize medication non-adherence as: primary non-adherence (non-initiators), late initiation, early discontinuation, non-persistence (presence of persistence gaps) or suboptimal dosing (Figure 1.3).

Figure 1.3 Classification of non-adherence depending on the medication-taking pattern



From another point of view, we could classify non-adherence by whether it is intentional or unintentional non-adherence. Unintentional non-adherence could be motivated by limited patient capacity or resources as well as by environmental problems. Intentional non-adherence could be more influenced by the patient's beliefs, attitudes and expectations.

1.3.3 Factors associated with non-adherent behavior

In an attempt to develop strategies to improve adherence to medication, there has been much effort made to identify factors associated with non-adherence. These factors could be grouped into the following categories (51;52): A) Patient characteristics, B) Disease characteristics, C) Treatment factors, D) Interpersonal factors and, E) Social and organizational settings.

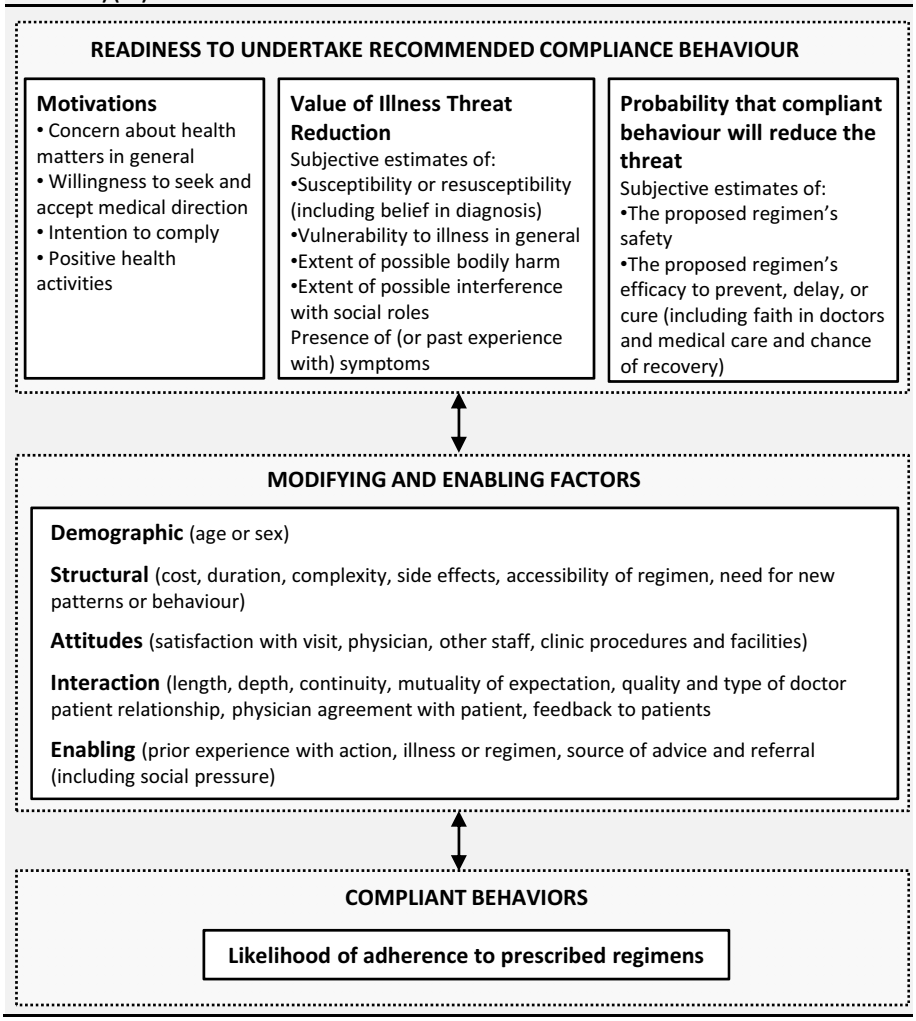
A) Patient characteristics

The patient is the most important part of the process since he/she is the one that ultimately will take the medication or discontinue the treatment. Many personal and social characteristics of the patient are described in the literature as associated

with non-adherence but patient's health beliefs seem to be the most relevant factor (51;53;54).

Adherence, as health-related behavior, is very affected by the patient's health concepts and beliefs (53). According to the "Model for predicting and explaining adherent behavior" by Becker and Mainman (Figure 1.4), the degree to which a person adheres to medication advice depends upon perceived disease severity and susceptibility to the disease, the perceived benefits of the treatment recommended and the patient's motivations (54). All these are affected by modifying and enabling factors.

Figure 1.4 Adapted model for predicting and explaining adherent behavior (Adapted from Becker and Mainmann) (54)



In depression, patients' perceptions about the illness (i.e. recognizing that depression is a medical illness and a chronic condition), beliefs about treatment (i.e. concerns about becoming addicted or the appearance of side effects; beliefs about the need for treatment or beliefs that depression should not be treated by medication) and attitude towards medication (i.e. self-confidence in one's capacity to managing side-effects or expectations of improvement due to treatment)have been associated with non-initiation of treatment with antidepressants and long term non-adherence to antidepressants (53;55-67).

Among patients' demographic characteristics, older age has systematically been associated with higher degrees of adherence and women are usually more adherent than men (43;46;57;65;68-77). Cognitive and memory impairment or forgetfulness are also related to non-adherence to antidepressants and it is reported by patients as one of the main reasons for non-adherence (55;57;62;67;68).

Several other patient demographic characteristics, such as educational level, working status, marital status or ethnicity, are reported to affect adherence to antidepressants (55;65;70;71;74;76-83). At the same time, contradictory results have been observed in some of the studies that found other demographic characteristics, and not the ones above, to be associated with adherence (72;74;77;82;83) and others did not even find any sociodemographic characteristic, apart from age in some of the studies, associated with non-adherent behavior (59;60;62;64). Consequently, it is not possible to ascertain whether these characteristics are really associated with non-adherence or not.

If the patient is socially isolated or his/her environment supports non-adherent behavior, he/she will be less adherent to medical treatment (51). Other social characteristics, such as low income or lack of economic resources are associated with non-adherence (68;78). In Catalonia, for example, the risk of non-adherence was higher in immigrants (84). Lack of social and family support are key factors associated with non-adherence, especially in chronic treatments (51;67).

B) Disease characteristics

The characteristics of the disease can also affect the behavior of the patient in relation to the treatment. In general terms, in both physical and mental conditions, adherence is poorer when the disease is associated with social stigma, when the prognosis is poor, when the disease is chronic, comorbid or asymptomatic or when severity of symptoms complicate adherence (51).

In the case of depression, patients presenting less severe symptoms or those that present non-specific symptoms are less likely to adhere to treatments with antidepressants (62;64;66;69;79;83). For example, van Geffen and colleagues reported that patients who consulted their GP for a non-specific rather than for a mental-related problem were more likely to decline or prematurely discontinue antidepressant treatment (70). These less severe or non-specific symptoms could make the patient perceive that he/she is not ill, affecting his/her beliefs about the

disease (66) or they may give a low value to the threat reduction achieved with the treatment. Adherence has been reported to be higher when the patients have previously taken an antidepressant because of a prior depressive episode (62;71;85).

Social stigma is very high in mental health. Patients who perceive a higher level of stigma related to depression are more likely to be non-adherent to antidepressant drugs (66;67). In the case of medication such as antidepressants, which are associated with a lot of social stigma, difficult dosage schedule that coincide with the patients' work schedule has been reported as a social side effect of the drug that prevents adherence(55).

Finally, other comorbid mental disorders, such as substance abuse, are associated with lower degrees of adherence (43;68;71;86).

C) Treatment factors

Many factors associated with the process of acquisition, preparation, consumption, and follow-up of the treatment, as well as the positive and negative consequences of it, are associated with non-adherence (52). Among others, we highlight complex treatment regimens, long-term treatment, lack of improvement or effectiveness, side-effects and lack of follow-up or supervision by professionals.

Complex treatment regimens (drug administration route or schedule) that highly disrupt the patients' everyday lives or that affect their social life are associated with non-adherence (43).

Most clinical guidelines suggest that continuation of treatment with antidepressants should be maintained for at least 6 months after remission of symptoms (87). Three common causes for earlier discontinuation are the appearance of side effects, the patient's perception of lack of efficacy and the patient's belief that he/she is already cured (55;57;61;62;67;74;76;79;88). However, Warden and colleagues observed that the patient's pre-treatment concerns about continuing antidepressant treatment in the presence of side-effect signals challenges completion of treatment even when the patient does not develop side effects (71). Moreover, discussing the possible side effects of the treatment and clearly stating that the treatment has to continue for at least 6 months even when symptoms decrease have been shown to improve patient adherence to antidepressants (56;80;89;90). This suggests that the problem of non-adherence is more associated with the patient's perceptions and beliefs about medication, as well as their knowledge about medication, than with possible side effects or the long term nature of the treatment.

Finally, follow-up sessions with the patients should be conducted to evaluate their progress. Adequate patient supervision is associated with increased rates of adherence (43;80;81).

D) Interpersonal factors

The physician's attitude, patient-physician relationship and patient satisfaction with the therapeutic relationship have been found to be associated with adherence (67;70;91).

Several studies have pointed out that physician attitudes towards antidepressant medication as well as the physician-patient relationship are key factors in enhancing adherent behavior (67;77;89). Low adherence to antidepressants is associated with a poor doctor-patient relationship (67;77). Adherence to medication is higher when the physician takes time to explain the expected duration of treatment and possible adverse effects (80;89).

Involving patients in the treatment decision process also affects posterior adherence to treatment. Wooley and colleagues found that patients who felt uninvolved in treatment decisions were more than twice as likely to discontinue antidepressants (92). In a study examining the association of patient treatment preferences with treatment initiation, adherence and clinical outcomes, Raue and colleagues reported that treatment initiation was associated with stronger treatment preferences and expectations of improvement from the assigned treatment, while no association of initiation with any sociodemographic or clinical variable was observed in this study (63).

Nevertheless, Madsen and colleagues observed that a collaborative provider style enhanced antidepressant adherence among more reactant patients whereas a less collaborative style was more beneficial when treating non-reactant patients (91).

Adherence to antidepressants improves when patient-clinician communication focuses on the patients' personal beliefs about how to best manage their depressive symptoms, which often conflict with medical models of treatment. Therefore, it seems clear that to improve adherence, the medical model needs to move towards an even more patient-centered model in which control is shared between doctor and patient.

E) Social and organizational setting

As we pointed out in the previous section, the amount of time the physician takes to explain the expected duration of treatment and possible side effects is associated with treatment adherence (89). However, the time that the physician can devote to the patient, especially in primary care, rarely depends on him/her and mainly depends on the organization of the practice or even health system directives.

Horgan reported that health plan features had a significant relationship with performance on antidepressant medication management, including obtaining good rates of adherence(93).

The setting and characteristics of the health center and practice (i.e. metropolitan or urban versus rural area) also affect patient adherence (94). Physicians with a

proportion of at least 50% of older patients in their practice were less likely to be associated with premature discontinuation but practicing mainly in metropolitan or urban regions increased the likelihood of suboptimal duration (94).

The practices that favour the inclusion of a psychiatrist or a psychologist in patient diagnosis or establishment of treatment or follow-up can obtain better rates of adherence. Patients attending mental health specialist appointments or receiving psychotherapy, or those followed-up by a psychiatrist, seem to be more accepting of treatment and more adherent (68;94-96). Yet, other studies found that adherence was not significantly affected by prescription from a psychiatrist or a non-psychiatrist (75).

1.3.4 Measuring adherence

As we will see, non-adherence has important consequences for the patient and interventions need to be developed to improve it. To do so, it is necessary to have an accurate measure of the degree of patient adherence. With it we can identify, in general terms, which drugs or diseases are more susceptible to non-adherence and which interventions show the highest effectiveness in improving adherence.

The methods for measuring adherence can be classified into two groups: direct and indirect measures. Table 1.1 summarizes the most relevant direct and indirect tools that can be used to measure adherence and briefly describes the benefits and drawbacks of each of these methods.

Direct methods include biological assays that facilitate the levels of the drug in the organism and direct observation of the patient's medication ingestion; for example, when the administration of the treatment has to be done by a professional (i.e. drugs that need to be injected or hospitalised patients).

These methods are considered to be standard tools for measuring adherence. However, they are costly, time consuming and not easily executed in ambulatory care. Although direct methods are considered to be more standard, they are not exempt of bias. Biological assays, for example, may be biased by the "white coat adherence".

Indirect methods, on the other hand, are easier to execute and used more frequently, although some of these methods are criticized for producing biased information. Indirect methods include self-reported adherence, pill count, electronic devices, and pharmacy refill records.

1.3.5The magnitude of non-adherent behavior

Despite efforts to improve patients' adherence to antidepressant drugs, studies conducted all over the world in the last 5 years still show high rates of non-adherence or early discontinuation.

More than 4% of primary care patients receiving a first-time prescription for a second-generation antidepressant did not fill the prescription (non-initiators)

(55;64;70). Previous studies found even greater rates (up to 15%) of patients that never started taking the medication (80).

Table 1.1 Benefits and drawbacks of direct and indirect methods for measuring adherence

Tool	*Definition*	*Benefits*	*Problems*
Direct methods			
Biological assay	The levels of the drug in the organism can be measured in a biological sample	Standard tool	Costly and sometimes painful Time of dose uncertain Assay noise and sample handling White coat adherence
Directly observed therapy	The medication-taking is directly observed by a professional(when the administration of the treatment has to be done by a professional (i.e. injections or hospitalised patients))	Standard tool Exact information about time and dose	Costly External validity Not swallowing Ethical issues
Indirect methods			
Questionnaire (self-reported)	Information directly reported by the patient or caregivers (i.e. parents for a paediatric patient) by means of a validated questionnaire.	Economical Information on reasons for non-adherence Possible information on number of pills	Biased data (forgetting, intentional misrepresentation) Needs to be validated Non-standard; Investigator variability
Diary (self-reported)	Information about medication-taking is directly reported by the patient or caregivers (i.e. parents for a paediatric patient) by means of a daily diary.	Economical Information on number of pills and days pills missed Information on reasons for non-adherence	Biased data (forgetting, intentional misrepresentation) Needs to be validated Non-standard
Medication Event Monitoring System (MEMS®)	Microelectronic devices record each time that the patient opens the device to take the medication.	Standard tool Difficult to consistently bias the measure Rich time series data	Costly No data on number of pills taken (underestimation of adherence) Biased data (intentional misrepresentation)
Pill Count	Counting the number of remaining pills in the container and the time passed since the acquisition of the medication.	Economical Information on number of pills taken Standard tool	Bias information (investigator miscount, patient improves drug taking or gets rid of pills just before the visit of the clinician)
Pharmacy records	Filled prescriptions are recorded by the electronic register in the pharmacy service or community pharmacy	Economical Information on number of pills refilled Standard tool Patient unaware of adherence control	Forgetting Refilling of prescriptions without ingestion

Among patients who initiated treatment with antidepressants, a wide range of early discontinuation rates (during the first month) have been reported, with persistence rates ranging from over 60% to around 96% after 1 month (44;70;79;82;85;97). In Catalonia, early discontinuation of antidepressants was reported to be around 40% in the period 2003-2009 (46;84).

During the first 3 months of treatment with antidepressants, treatment discontinuation ranged from 25% to over 60% (43;44;62;68;74;93;98) while in a 6-month period, adherence can be dramatically reduced, with rates of non-adherence over 75% (43-46), as was observed in Catalonia (46).

However, some studies conducted outside Catalonia reported high rates of adherence, i.e. adherence over 70% after 6 months of treatment (64;69).

1.3.6 The consequences of non-adherence

Treatment adherence to antidepressants is essential to achieve remission, restore previous level of functioning and prevent reoccurrence of depression.

Outcomes in depression severity are worse in patients who poorly adhere to antidepressant medication (69;99;100). In both acute and treatment continuation phases, a higher incidence of short-term disability was associated with antidepressant medication non-adherence, thus resulting in costs for employers (98).

Observational studies that evaluated the impact of adherence to antidepressants on prevention of relapse or recurrence led to contradictory results. Melfi and colleagues concluded that patients who discontinued antidepressant drug treatment early had a higher risk of relapse or recurrence than those who followed treatment guidelines (101). Later studies following the same methodology used by Melfi confirmed this result (102;103). However, Gardarsdottir and colleagues found the methods used in previous studies to be subject to bias (104). When they applied a more robust method of analysis to their data, they found that no protective effects exist in longer treatments with antidepressants. This study was not free of bias itself so future research must demonstrate whether an association truly exists between adherence to antidepressants and prevention of relapse/recurrence of depression in a natural uncontrolled setting.

However, when randomized controlled trials are considered to evaluate the prevention of relapse by antidepressants, the results point to a positive effect of antidepressant drugs (105;106) showing that treatment with antidepressants for sufficient time (i.e. at least 6 months after remission) can generate long term benefits for the patient in terms of preventing relapse. A systematic review considering 31 randomized controlled trials that compared antidepressants with placebo concluded that continuing treatment with antidepressants reduces the risk of relapse when compared with treatment discontinuation (105). A more recent review suggested that continuing antidepressant treatment reduced the relapse rate by more than half (106).

The most fatal conclusion of depression is suicide. An extensive review of observational studies concluded that new generation antidepressants reduce the risk of completed or attempted suicide when prescribed to adults or the elderly (107). Contradictory results were reported by Sokero and colleagues who found that suicidal behavior does not seem to be associated with poor adherence to antidepressant treatment (108).

Non-adherence not only weakens the effectiveness of antidepressants and increases the risk of relapse, but also leads to higher costs (26). Adherence to antidepressants reduces healthcare utilization. Liu and colleagues, for example, reported that adherence to antidepressants is associated with reduced hospitalisation and emergency room visits (109).

Furthermore, the cost of treatment for non-adherent patients or those who discontinue treatment is higher than for patients who adhere to or persist with the treatment (44;100;110-112).

Key points 1.3 Adherence to antidepressants

– The extent to which a person's behavior corresponds to agreed medical recommendations, or adherence, can be intentional or un-intentional and be classified as primary non-adherence, late initiation, early discontinuation, non-persistence or suboptimal dosing.

– Factors associated with non-adherence are patient or disease characteristics, treatment or interpersonal factors and social and organizational settings; the patients' health concepts and beliefs being a fundamental component affecting non-adherence.

–Several direct and indirect methods for measuring adherence are available. However, all methods are subject to bias to some extent so we cannot completely rely on any method to monitor it.

– In the last 5 years, rates of non-adherence to antidepressants have been shown to be still high, ranging from 25% to over 60% during the first 3 months and with rates of non-adherence to antidepressants that surpassed 75% after 6 months.

– High rates of non-adherence to antidepressants can limit the effectiveness of the treatment and increase the risk of relapse or recurrence, increasing the costs of the treatment for depression.

1.4 Interventions to improve adherence to antidepressants

1.4.1. Overall interventions

Bollini and colleagues (2006) systematically reviewed the recommendations provided by previous reviews on how to improve patient adherence to pharmacological treatment of depression (113). After reviewing the literature they identified 9 categories of recommendations that were the most frequently cited. The most common recommendations are listed below:

1) Patient education about the disease and the treatment;
2) Improvement of patient-physician empathy/alliance;
3) Education of the family about the disease and treatment;
4) Standardization of clinical management strategies (standardized approach to drug taking and monitoring);
5) Simplification of the treatment plan;
6) Informing patients about side effects, monitoring them and reassuring patients about treatment;
7) Facilitating behavioral feedback in relation to the medicine taking routine;
8) Use of SSRI as opposed to older generation antidepressant to minimize side effects.
9) Training the physician to improve their skills with respect to dealing with depressed and non-adherent patients.

The most commonly recommended interventions were patient education and improving patient-physician empathy/alliance, while the interventions most frequently based on evidence were patient education and management of side effects. Other recommendations not listed above were encouraging patient self-care or using a multidisciplinary team to help the patient.

Programs to improve the quality and effectiveness of antidepressant pharmacotherapy in primary care could be divided into those directed at physicians (physician education programs, academic detailing, and audit and feedback programs) and those involving direct intervention with patients (patient education programs, outreach programs to increase the frequency of follow-up care, use of care managers or other care extenders and introduction of specialty consultation) (114).

A number of randomized controlled trials have been conducted evaluating the effectiveness of interventions to improve the treatment of depression in primary care. In most cases, these trials considered complex interventions such as multifaceted, case management, collaborative care interventions or even stepped care interventions. In order to synthesize the evidence generated by these studies, systematic reviews of the evidence have been conducted (114-117).

These reviews reported failure of interventions targeting the health care provider only (114;118-120). Physician education or training interventions were inexpensive

but did not report robust or lasting changes in quality of treatment or patient outcomes and similar results were observed when physician reminders or feed-back systems were evaluated (114).

Trials providing direct interventions with patients showed better results, especially when they included as elements of the intervention systematic patient education, an active follow-up and improved access to appropriate specialty consultation (114;118).

Interventions relying solely on educational strategies, such as educational leaflets, failed to demonstrate any improvement in medication adherence although the satisfaction with treatment and the attitude towards medication of patients did improve (114;118). However, brief counseling programs delivered face-to-face or by telephone by trained nurses led to significantly greater medication adherence (114).

In general, more intensive interventions and those with a larger number of elements involved show greater success in improving both adherence and clinical outcomes. Multifaceted interventions that integrate mental health specialists into primary care settings have been shown to be successful in improving both antidepressant adherence and depression outcome (115;116;118).

Collaborative care is an intensified care program that incorporates patient education and shared care of the patient among the general practitioner, the psychiatrist or psychologist and non-medical specialists such as nurses (115;116). The scientific evidence strongly suggests that this type of intervention is effective in improving outcomes in depression (116;121;122).These studies reported increased levels of adherence to medication as well as better clinical outcomes and patient satisfaction (116;122).

1.4.2. Interventions conducted by pharmacists

The pharmacist is one of the most accessible health-care professionals and can play a decisive role in the management of ambulatory patients (123). A philosophy of pharmaceutical care (124), defined as “the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve the patient’s quality of life” and that involves cooperation with patients and other professionals with the aim of producing specific therapeutic outcomes for the patient has been tested in many physical chronic conditions with good results in terms of adherence and clinical outcomes (125-128).

Since 2003, attempts have been made to involve the hospital pharmacist and clinical pharmacy services as well as community pharmacists in the management of patients suffering from depression. Detailed information about the interventions dispensed by community pharmacy can be found in Chapter 2 (Paper 1). However, the results reported by studies evaluating a pharmacist intervention in depressed patients led to contradictory results in terms of improvement of adherence (129-134).

Bower and colleagues, in an attempt to identify active ingredients in collaborative care models for depression in primary care, used meta-regression to examine relationships between intervention content and outcome (121). Bower reported that interventions conducted by case managers with a specific mental health background were more effective in improving symptom outcomes than those conducted by case managers without a specific mental health background, such as pharmacists. However, no significant differences were detected when the outcome assessed was antidepressant use. Furthermore, in these analyses pharmacists were grouped with other health professionals so their specific contribution to the results is difficult to determine.

1.4.3 Economic evaluation of interventions to improve adherence

Even when an intervention proves to be effective, the costs associated with it have to be taken into account. Economic evaluations provide decision-makers with information on how to allocate the limited resources available for health care (135).

A review conducted by Gilbody and colleagues showed that enhancement of care, such as case management and collaborative care, mostly produce improved outcomes but is also associated with increased direct healthcare costs over the short term (136). On the other hand, educational strategies did not seem to lead to improved clinical outcomes and were associated with increased costs. These types of interventions, although cost-effective, are very intensive and their implementation in real practice could be complicated by the complex nature of the intervention.

In the case of interventions conducted by pharmacists, to the best of our knowledge, only one study has been conducted to evaluate the cost-effectiveness of a pharmacist intervention to improve adherence to antidepressants (137). This study, conducted by Bosmans in The Netherlands, concluded that coaching and education by pharmacists, compared with usual care, is not likely to be cost-effective as a means of increasing adherence to antidepressants (137). However, the study considered a small sample size both in the main analysis (N=88) and in the per protocol analysis (only 26 patients in the intervention group). This could have hindered the detection of significant differences in costs. Moreover, this study did not include quality adjusted life years (QALYs) as a measure of effectiveness, thus limiting comparison with other therapies and therapeutic areas (135).

Key points 1.4 Interventions to improve adherence to antidepressants

– Several recommendations have been made to improve the treatment of depression, patient education and the improvement of the patient-physician alliance being the most commonly reported.

– Programs relying exclusively on the health care provider or on educational strategies do not improve depressive outcomes. Patient education, together with active follow-up and improved access to care, showed the best results.

– Collaborative care models that incorporate patient education and shared care of the patient among the general practitioner and other specialists (commonly a psychiatrist or psychologist) are effective and cost-effective in improving outcomes in depression.

– Community pharmacists can cooperate with the primary care team to deliver interventions to improve patient adherence and clinical outcomes but little is known about the effectiveness and cost-effectiveness of these interventions.

1.5 Research questions and objectives

To summarize, major depression is a highly prevalent disorder associated with high burden, disability and costs. The effectiveness of antidepressant drugs can be limited by the high rates of non-adherence. Non-adherence to antidepressants is affected by many factors; the patients' health concepts and beliefs being the most important. Many interventions addressed to depressed patients have been tested, with collaborative care models shown to be effective and cost-effective in improving outcomes in depression. Community pharmacists can cooperate with the primary care team to deliver interventions to improve patient adherence and clinical outcomes but little is known about the effectiveness and cost-effectiveness of these interventions.

The general objective of this thesis is to provide an insight into the impact of pharmacist care on the improvement of adherence, as well as in patient wellbeing and minimization of costs of depressed patients in primary care. The following specific research questions will be addressed:

1. Does the available evidence support the implementation of pharmacist care to improve adherence to antidepressant medication?

2. Is a pharmacist intervention conducted in Spain effective in the improvement of adherence to antidepressants and patient wellbeing?

3. Is a pharmacist intervention conducted in Spain cost-effective in the improvement of adherence to antidepressants and patient wellbeing?

Consequently, the specific objectives of this thesis are:

1. To systematically review randomized controlled trials evaluating the impact of pharmacist interventions on outpatients with regard to improvement of adherence to antidepressants when a depressive disorder was being treated.

2. To evaluate the effectiveness of a community pharmacist intervention compared to usual care in the improvement of adherence to antidepressants and patient wellbeing in a primary care population initiating pharmacological treatment after being diagnosed with depression by their general practitioner.

3. To evaluate the cost-effectiveness and cost-utility of a community pharmacist intervention in comparison with usual care for depressed patients initiating treatment with antidepressants in primary care.

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Chapter 2

Methods and results

Chapter 2

Paper 1

Effectiveness of Pharmacist Care in the Improvement of Adherence to Antidepressants: A Systematic Review and Meta-Analysis

Maria Rubio-Valera
Antoni Serrano-Blanco
Jesús Magdalena-Belío
Ana Fernández
Javier García-Campayo
Marian March Pujol
Yolanda López del Hoyo

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Abstract

Background

Pharmacists can play a decisive role in the management of ambulatory patients with depression who poorly adhere to antidepressant drugs.

Objective

To systematically evaluate the effectiveness of pharmacist care on improving adherence to antidepressants in depressed outpatients.

Methods

A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted. RCTs were identified through electronic databases (Medline, Central, ISI web of knowledge and CSIC database) from inception to April 2010, reference lists were checked and experts were consulted. RCTs that evaluated the impact of pharmacist interventions on improving adherence to antidepressants in depressed patients in an outpatient setting (community pharmacy or pharmacy service) were included. Two reviewers independently extracted data using a pre-specified tool with a third consulted to resolve any disagreements. Methodological quality was assessed and methodological details and outcomes were extracted in duplicate.

A random-effects model was used to pool odds ratios and 95% confidence intervals. Heterogeneity was measured using I^2 and tested for statistical significance using a Cochran Q test. Subgroup analyses (pharmacist setting, main adherence measure, clinical diagnosis or validated diagnostic instrument, and analysis strategy [intent to treat or per protocol]) were used to explore heterogeneity. To assess the sensitivity to individual trials, the leave-one-out analysis was performed. Egger test and funnel plot were used to assess the potential impact of publication biases.

Results

Six RCTs were identified that had been conducted, between 1998 and 2005, in the USA (4 studies), Australia and The Netherlands. A total of 887 patients with an established diagnosis of depression who were initiating (658 patients) or maintaining (229 patients) pharmacological treatment with antidepressant drugs and who received pharmacist care (459 patients) or usual care (428 patients) were included in the review. In 3 of the studies, interventions were conducted by community pharmacists and, in the other 3, by pharmacists in a pharmacy setting of a hospital or primary care centre. The most commonly reported interventions were patient education and monitoring, monitoring and management of toxicity and side effects, compliance promotion, provision of written or visual information and recommendation or implementation of changes or adjustments in medication. Overall, no statistical heterogeneity or publication bias was detected. Pooled odds ratio, using a random effects model, was 1.64 (95% CI 1.24-2.17). There was considerable clinical heterogeneity and methodological variation between trials but

subgroup analysis showed no statistically significant differences in results by type of pharmacist involved, adherence measure, diagnostic tool or analysis strategy.

Conclusions

These results suggest that pharmacist intervention is effective in the improvement of adherence to antidepressants. However, the number of studies identified was small, there was considerable clinical and methodological heterogeneity and sample sizes of the individual studies were small. Consequently, we would recommend more research in this area, specifically outside the USA.

Effectiveness of Pharmacist Care in the Improvement of Adherence to Antidepressants: A Systematic Review and Meta-Analysis

Maria Rubio-Valera, Antoni Serrano-Blanco, Jesús Magdalena-Belío, Ana Fernández, Javier García-Campayo, Marian March Pujol, and Yolanda López del Hoyo

BACKGROUND: Pharmacists can play a decisive role in the management of ambulatory patients with depression who have poor adherence to antidepressant drugs.

OBJECTIVE: To systematically evaluate the effectiveness of pharmacist care in improving adherence of depressed outpatients to antidepressants.

METHODS: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted. RCTs were identified through electronic databases (MEDLINE, Cochrane Central Register of Controlled Trials, Institute for Scientific Information Web of Knowledge, and Spanish National Research Council) from inception to April 2010, reference lists were checked, and experts were consulted. RCTs that evaluated the impact of pharmacist interventions on improving adherence to antidepressants in depressed patients in an outpatient setting (community pharmacy or pharmacy service) were included. Methodologic quality was assessed and methodologic details and outcomes were extracted in duplicate.

RESULTS: Six RCTs were identified. A total of 887 patients with an established diagnosis of depression who were initiating or maintaining pharmacologic treatment with antidepressant drugs and who received pharmacist care (459 patients) or usual care (428 patients) were included in the review. The most commonly reported interventions were patient education and monitoring, monitoring and management of toxicity and adverse effects, adherence promotion, provision of written or visual information, and recommendation or implementation of changes or adjustments in medication. Overall, no statistical heterogeneity or publication bias was detected. The pooled odds ratio, using a random effects model, was 1.64 (95% CI 1.24 to 2.17). Subgroup analysis showed no statistically significant differences in results by type of pharmacist involved, adherence measure, diagnostic tool, or analysis strategy.

CONCLUSIONS: These results suggest that pharmacist intervention is effective in the improvement of patient adherence to antidepressants. However, data are still limited and we would recommend more research in this area, specifically outside of the US.

KEY WORDS: depressive disorder, meta-analysis, patient adherence, pharmacist services.

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Depression is a major health concern worldwide due to its high prevalence, patient impairment, and cost.[1-3] Since the first antidepressant was introduced in 1957,[4,5] pharmacologic treatment for depression has undergone a number of changes, but it is still the first approach for treatment of moderate and severe depression.[6] Despite efforts to improve adverse effect profile and tolerability of medication, adherence to antidepressant drugs is still poor.[7,8]

The pharmacist is one of the most accessible health-care professionals[9] and can play a decisive role in the management of ambulatory patients. Pharmaceutical care is described as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" and it involves cooperation with patients and other professionals, with the aim of producing specific therapeutic outcomes for the patient.[10] In physical conditions such as heart failure, asthma, diabetes, hypertension, and dyslipidemia, pharmacist interventions have been shown to improve patient well-being in terms of clinical improvement and adherence.[11-15]

Recently, pharmacist involvement in the management of patients suffering

Author information provided at end of text.

from mental health disorders has been increasing and studies have been carried out to evaluate the impact of pharmacist interventions in this population. In 2003, Finley et al.[16] conducted a systematic review examining the impact of clinical pharmacists on the care and outcomes of patients with mental disorders including, among other diagnoses, schizophrenia, depression, and behavioral disturbances. The pharmacist interventions described in the review included drug monitoring, treatment recommendations, patient education, drug management, and education to providers on prescribing patterns. The results of this work indicated a positive effect of pharmacist interventions in patients with mental health problems, although there were several sources of heterogeneity related to the study design, patient populations, measured outcomes, and treatment settings. Furthermore, since this review was published, more research has been conducted on this issue; therefore, these results need to be updated.

More recent systematic reviews have shown that multidisciplinary strategies for the management of patients with mental health problems in primary care have a positive effect on antidepressant use and depressive outcomes.[17-19] These studies concluded that interventions conducted by case managers with a specific mental health background were more effective in improving symptom outcomes than those conducted by case managers without a specific mental health background, such as pharmacists. However, no significant differences were detected when the outcome assessed was antidepressant use. Furthermore, in these analyses pharmacists were grouped with other health professionals, so their specific contribution to the results is difficult to determine. Overall, most of the literature in this field did not appear to show statistically significant differences between intervention and control groups and seemed to be inconclusive. We therefore conducted a meta-analysis to increase the power of the study and to try to improve effect size estimate.

In general, interventions conducted by pharmacists are usually focused on medication; consequently, adherence is the primary outcome in most of these studies. For this reason we decided to focus our review on adherence improvement. Furthermore, in patients with depression, it has been stated that there is a significant positive association between antidepressant use and improved depression outcomes.[17,18]

The objective of this study was to systematically review randomized controlled trials (RCTs) evaluating the impact of pharmacist interventions on outpatients with regard to improvement of adherence to antidepressants when a depressive disorder was being treated.

Methods

We followed the PRISMA guidelines for reporting meta-analyses.[20]

LITERATURE SEARCH

We performed a systematic review of the published literature for RCTs evaluating the impact of pharmacist interventions on the improvement of adherence to antidepressant pharmacologic treatment of outpatients with depressive disorder (major depressive disorder and dysthymic disorder) according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or International Classification of Diseases criteria. In order to identify all articles involving interventions intended to improve use of antidepressants, the databases were searched separately by 2 investigators (AF and MRV). Literature searches were completed from inception to April 2010, without language restrictions, through MEDLINE, the Cochrane Central Register of Controlled Trials database, the Institute for Scientific Information Web of Knowledge, and the Spanish National Research Council databases.

The search strategy used was: [("Pharmaceutical Services"[MeSH] OR pharmac* OR "pharmaceutical intervention" OR "pharmacy counsel*" OR "pharmacy-based coaching") AND ("Depressive Disorder"[MeSH] OR "depression" OR "Antidepressive Agents"[MeSH] OR "antidepressant*") AND ("Patient Compliance"[MeSH] OR "Treatment Refusal"[MeSH] OR "Patient Dropouts"[MeSH] OR adherence OR dropout OR compliance)].

Abstracts of all citations were obtained for study selection. Citation indices and reference lists of retrieved articles were checked for additional studies not identified in the original database search. Expert informants from the pharmaceutical industry and the School of Pharmacy (University of Barcelona) were consulted to retrieve grey literature (such as unpublished reports and conference abstracts).

STUDY SELECTION

Studies were screened for inclusion by reviewing the title, the published abstract, and the full article where necessary. First selection was made in duplicate (AFS and MRV). The final screening, which reviewed full text articles, was performed by 2 researchers (ASB and MRV). One of the researchers (ASB) was blinded to the names of the authors of the articles and the journals in which they were published. In the case of disagreement, a third researcher (AFS) was consulted.

We included RCTs with ambulatory patients diagnosed using a validated psychiatric interview or a clinical diagnosis for a mood disorder and who were initiating or maintaining treatment with antidepressants. No restriction by type of antidepressant medication was applied. Nor were restrictions imposed with respect to age, sex, or ethnicity. Interventions taken into account included educational messages and counseling, monitoring and medication dosage adjustment, and management of adverse effects. Our definition of interven-

tion excluded all research in which the pharmacist's role was focused only on the review of medication patterns (ie, detection of medication-related problems, such as drug interactions, without a subsequent intervention delivered to the patient to solve the problems). As the intervention should be applied directly to the patient, articles evaluating the effects of pharmacist intervention in institutions, physicians, or families were excluded. Articles were rejected if the study was conducted in an acute inpatient facility or hospital, or if it was a multidisciplinary model in which the role of the pharmacist was not well established. Nevertheless, there was no restriction regarding the setting in which the intervention was performed, so that community pharmacies or pharmacy services in hospitals or primary care centers were included. Regarding outcome measures, any measure evaluating adherence to medication was accepted, such as pharmacy records, electronic pill containers, and self-reported adherence.

QUALITY ASSESSMENT

The quality of the studies was assessed independently by YLH and MRV using the Jadad scale.[21] The Jadad scale is a 3-item scale that considers 3 features of a study: randomization, double-blinding, and flow of patients. Adequate description of allocation concealment was also evaluated, so total summed scores ranged from 0 to 7, with the higher scores indicating higher quality.[22-24] However, blinding of pharmacists and participants was not possible because of the type of intervention assessed in this meta-analysis; therefore, total scores ranged from 0 to 5. Inter-reviewer reliability for the quality of studies was measured by κ statistics (0.958).

DATA ABSTRACTION AND QUANTITATIVE DATA SYNTHESIS

By using a standardized abstraction form, 2 reviewers (MRV and YLH) independently extracted key features of the characteristics, methods, and outcomes of articles that met the inclusion criteria. Key features included study design, period of study, setting, sample size, number of pharmacists, intervention components, the main outcome measures reported by the authors, and results and analysis strategy (ie, per-protocol or intent-to-treat). In the case of disagreement, a third reviewer (JGC) also checked the data and agreement was reached. Inter-reviewer reliability was measured by κ statistics (0.910).

Dichotomous and continuous measures of the outcome were extracted. For continuous data, the standardized mean difference (SMD) was computed with a 95% confidence interval. A random effects model was used to calculate pooled odds ratios and 95% confidence intervals. Statistical heterogeneity was assessed employing the Cochran Q test and I^2 statistic. Publication bias was assessed using the funnel plot and Egger test.

To assess the possible effects of clinical heterogeneity in the meta-analysis results, subgroup analyses were performed according to the setting of the pharmacist doing the intervention (community pharmacies or pharmacy services in hospitals or primary care centers), main adherence measure (pharmacy records, electronic pill container, or self-reported adherence), and type of diagnosis used for inclusion (only clinical or with a validated diagnostic instrument). Those subgroup analyses were pre-specified. Moreover, subgroup analyses were performed according to the analysis strategy (intent-to-treat or per-protocol) as a means of assessing its effect on the results of the meta-analysis. Analyses were performed using Comprehensive Meta-Analysis, version 2, software (Biostat, Englewood, NJ).

Results

LITERATURE SEARCH AND STUDY SELECTION

The electronic search strategy identified 438 potentially relevant papers, while 7 additional studies were retrieved via the manual search of citation indices and reference lists. In all, 50 were duplicated titles indexed in multiple databases and were excluded. Of the 395 remaining studies, 367 were excluded by reviewing title and abstract (221 described other interventions, the population in 78 was not depressed patients, 63 were not RCTs, and 5 did not evaluate adherence) and 22 were excluded by reviewing full-text articles (7 did not evaluate adherence, 7 were not RCTs, 6 described other interventions, and 2 were only descriptive) (Figure 1). In addition, correspondence was conducted with the corresponding author of 1 article describing study methods that matched

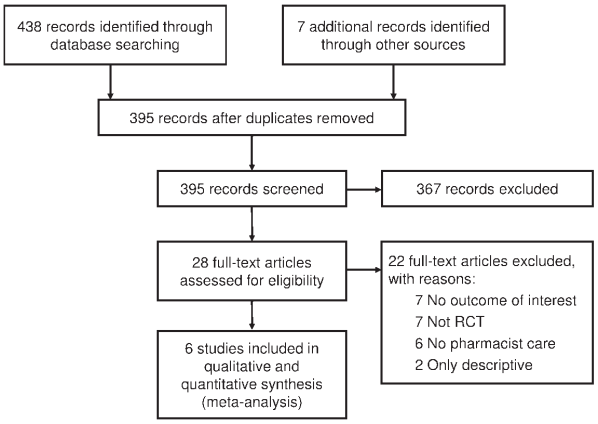

Figure 1. Flow diagram of studies screened, assessed for eligibility, and included in the review. RCT = randomized controlled trial.

Table 1. Characteristics of Studies

Reference	Country	Setting (pharmacists, n)	Key Components of Pharmacist Intervention	Main Adherence Measure (other adherence measures)	Main Diagnostic Procedure	Baseline Level of Depression by Group (measurement tool)	Main Analysis Strategy	Randomized Patients (N)	Number of Women (%)	Mean Age	Follow-up (months)	Quality
Finley (2003)[26]	US	PS (2)	Medication education, depression education, adherence promotion, obtaining patient clinical history, monitoring drug efficacy and toxicity, recommendation for changes in medication to the physician, advising about other available treatment options, providing written information	Pharmacy records (self-reported)	Clinical	Intervention = 18.7 Control = 18.3 (BIDS)	ITT	125 Intervention = 75 Control = 50	106 (85)	54	6	4
Adler (2004)[27]	US	PS (5)	Medication education, depression education, adherence promotion, obtaining patient medication history, monitoring drug efficacy and toxicity, facilitating communication with the physician	Self-reported (pharmacy records)	VDI	Intervention = 23.2 Control = 23.2 (mBDI)	PP	384[a,b] Intervention = 202 Control = 182	364 (72)[c]	42[c]	6	5
Capoccia (2004)[28]	US	PS (2)	Medication education, depression education, adjustment of medication dosage and time of dose, change or discontinuation of antidepressants, monitoring and management of adverse effects, provision of medication refill authorizations, facilitating the access to patient assistance programs and appointments with mental health service providers	Self-reported	VDI	Intervention = 1.83 Control = 1.75 (SCL-20)	ITT	74 Intervention = 41 Control = 33	42 (57)	39	12	2
Brook (2005)[29]	Netherlands	CP (19)	Medication education, depression education, adherence promotion, monitoring and management of adverse effects, providing written and visual information[d]	Electronic pill container (pharmacy records)	Clinical	Intervention = 3.1 Control = 2.8 (SCL-13)[d]	ITT	135 Intervention = 64 Control = 71	95 (70)	43	6	3
Rickles (2005)[30]	US	CP (14)	Medication education, depression education, adherence promotion, monitoring and management of adverse effects, contact with prescriber if needed, monitoring patient progress	Pharmacy records (self-reported)	VDI	Intervention = 28.9 Control = 27.0 (BDI-II)	PP	63 Intervention = 31 Control = 32	53 (84)	38	6	5

Crockett (2006)[31]	Australia	CP (32[e])	Medication education, monitoring patient progress, providing written and visual information	Self-reported	Clinical	Intervention = 23.0 Control = 21.7 (K10)	PP	106[f,g] Intervention = 46 Control = 60	84 (79)[f]	46[f]	2	2

BDI-II = Beck Depression Inventory (range 0-63); BIDS = Brief Inventory for Depressive Symptoms (range 0–42); CP = community pharmacy; ITT = intent-to-treat; K10 = 10-question screening scale of psychological distress (range 10-50); mBDI = modified Beck Depression Inventory (range 0-63); PP = per protocol; PS = pharmacy service; SCL-13 = 13-item Hopkins Symptom Checklist (range 1-5); SCL-20 = 20-item Hopkins Symptom Checklist (range 0-4); VDI = validated diagnosis instrument.

[a]Two hundred thirty-four of the randomized patients were initiating treatment with antidepressants and 150 were already taking antidepressants at the time of inclusion.

[b]Five hundred thirty-three patients (intervention = 265, control = 268) were randomized, but information was given only for the 384 who completed the 6-month assessment.

[c]Information from the 507 patients who completed the initial intervention.

[d]Data extracted from Brook et al. (2003).[32]

[e]Number of pharmacies; number of pharmacists was not reported.

[f]One hundred nineteen (intervention = 51, control = 68) patients were randomized, but results were reported for the 106 patients who completed the 2-month assessment.

[g]Twenty-seven patients had been on antidepressant medication for less than 1 month at the beginning of the study.

our criteria for selection. Results at 6-month follow-up were published, but no results were reported after that time.[25] Even though we received a response from the author, data were unavailable.

CHARACTERISTICS AND METHODOLOGIC QUALITY OF THE INCLUDED STUDIES

We identified 6 studies for inclusion in the analysis that assessed pharmacist interventions in patients initiating or maintaining a treatment with antidepressant medication (Table 1).[26-31] Overall, 1049 subjects were randomized, 527 (50.2%) of whom were randomized to an intervention group and 522 (49.8%) to a control group. However, because of per-protocol analyses in some studies, results are reported for only 887 patients (84.9% of randomized patients), 459 (51.7%) belonging to the intervention group and 428 (48.3%) to the control group. Most of the studies (4 of 6) were carried out in the US,[26-28,30] while the others were performed in the Netherlands[29] and in Australia.[31] The studies were carried out between 1998 and 2005 and the publication years ranged from 2003 to 2006. There were no significant baseline differences in sociodemographic characteristics between the control and intervention groups. However, in 3 of the studies, baseline differences related to antidepressant medication[27,30] and clinical characteristics[28] were reported. In the study by Rickles et al.,[30] intervention participants were more likely than control participants to have a history of psychotropic medication use (41.9% vs 15.6%; $p < 0.05$). In the study by Adler et al.,[27] intervention participants were more likely to have first used antidepressants more than a year before the initial questionnaire (56.1% vs 45.2%; $p < 0.05$). Finally, in the study by Capoccia et al.,[28] more patients in the intervention group had been diagnosed with major depression at baseline than those in the control group (21% vs 9%; $p < 0.05$). However, in the case of the articles by Adler et al.[27] and Capoccia et al.,[28] statistical analyses were controlled for prior experience with antidepressants and baseline Structured Clinical Interview for DSM Disorders score, respectively, to minimize bias.

All patients had an established diagnosis of depression and were initiating (n = 658; 74.2%) or maintaining (n = 229; 25.8%) pharmacologic treatment with antidepressant drugs. In the study by Brook et al.,[29] only patients taking nontricyclic antidepressants were considered for inclusion and in the study by Finley et al.,[26] 96% of control patients and 88% of intervention patients were prescribed selective serotonin reuptake inhibitors. A total of 3 different methods of assessing adherence to antidepressants were defined; self-reported adherence,[26-28,30,31] pharmacy records,[26,27,29,30] and electronic pill container.[29]

In 3 of the 6 studies,[27,28,30] depression was diagnosed by means of validated diagnostic instruments based on DSM-IV criteria, including the Primary Care Screener for Affective

Disorders, the Primary Care Evaluation of Mental Disorders, and the Beck Depression Inventory II. Baseline severity of depression was reported as being moderate to severe based on different measures (Beck Depression Inventory; Hopkins Symptom Checklist, Brief Depression Inventory, and K10).

While the follow-up period ranged from 2 to 12 months, in 4 of the studies it was 6 months.[26,27,29,30] Where possible, data from 6 months were used to perform the analysis.[26-30] Community pharmacists applied the intervention in 3 of the studies,[29-31] and pharmacists from a pharmacy service of a primary care setting performed it in the other 3 studies.[26-28]

In 1 case,[29] information about the intervention was extracted from a previous publication related to the study.[32] In all 6 studies the intervention included patient education and monitoring. Other common interventions were monitoring and management of toxicity and adverse effects,[26-30] adherence promotion,[26,27,30,31] and provision of written or visual information.[26,29,31] In 2 of the studies[26,28] in which the intervention was conducted by a clinical pharmacist, the pharmacist could recommend or conduct changes or adjustments in medication.

Methodological quality ranged from 2 to 5 on the Jadad scale, and 4 of the studies scored 3 or more.[26,27,29,30] The most commonly absent item was an adequate description of concealment of allocation.

Intent-to-treat analyses were conducted in 3 of the 6 studies.[26,28,29] In the study by Adler et al.,[27] although it was stated that an intent-to-treat analysis was conducted, not all randomized patients were included in the analysis—only those with any 6-month data. That is to say, 533 patients were randomized, but information was given only for the 384 who completed the 6-month assessment. According to the Consolidated Standards of Reporting Trials (CONSORT) guidelines,[33] in order to preserve fully the huge benefit of randomization, intent-to-treat analysis should include all randomized participants in the analysis, who should all be retained in the group to which they were allocated. Using this conservative definition of the intent-to-treat approximation analysis, we decided to classify the Adler et al.[27] study in the group of studies that conducted per-protocol analysis.[27,30,31]

In 2 of the studies, some of the included patients were already on antidepressants at the time of enrollment.[27,31] The study by Adler et al.[27] reported results of patients initiating and maintaining treatment with antidepressants at the time of enrollment, while the information in the study by Crockett et al.[31] was presented in aggregated form, making it impossible to discern who was being initiated and who was being maintained on medication. For our meta-analysis, results from all patients were included, regardless of whether patients were initiating or maintaining pharmacologic treatment. In the study by Capoccia et al.,[28] adherence information at 6-months of follow-up was used. In the study by Finley et al.,[26] 2 different ways of reporting adherence were employed: the Mean Possession Ratio and the percentage of adherent patients. In our meta-analysis, the percentage of adherent patients at 6 months was used.

META-ANALYSIS

No significant heterogeneity was found between the included studies (Cochran Q = 2.677; df = 5; p = 0.750; I^2 <0.001; τ^2 <0.001). The pooled odds ratio demonstrated a significant benefit from pharmacist interventions in the improvement of adherence to antidepressant pharmacologic treatment (1.639; 95% CI 1.236 to 2.174; p < 0.001) (Figure 2).

When we compared the effectiveness of pharmacist intervention in depressed patients, after grouping by setting of pharmacy where the intervention was implemented (community pharmacy or pharmacy service), type of diagnosis (clinical or validated psychiatric instrument), type of adherence measure (pharmacy records, electronic pill container, or self-reported), and analysis strategy (per protocol or intent-to-treat), we observed that there were no significant differences, as confidence intervals from different subgroups clearly overlapped (Figure 3).

The funnel plot of standard error against the natural logarithm of the odds ratio (Figure 4) and the Egger test for assessing bias (p = 0.460) suggested that there was little publication bias in the selection of studies.

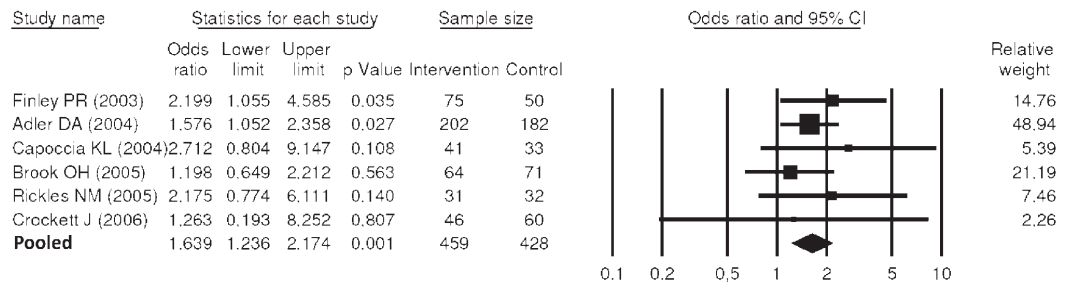

Figure 2. Meta-analysis results.

The effect of removing 1 study each in turn was assessed and showed that statistically significant results did not depend on any of the individual studies. Cumulative meta-analysis was also performed, proving that the pooled estimate is robust over time.

Discussion

The results of our meta-analysis suggest a positive effect of pharmacist interventions on antidepressant use in terms of patient adherence. These results are similar to those reported on collaborative care by Bower et al.[17] that found a positive effect of collaborative care on patient adherence to antidepressants (OR = 1.92; 95% CI 1.54 to 2.39). Subgroup analysis showed no significant differences between groups when grouping by setting of pharmacy in which pharmacist conducted the intervention, type of diagnostic procedure, type of adherence measure, or analysis strategy used.

These results should be interpreted with the following limitations in mind. Firstly, although a significant improvement in patient adherence to antidepressant medication was identified, it is unclear whether this will result in an improvement in depressive symptoms. However, previous studies have reported a positive association between improved antidepressant use and depressive symptoms, suggesting that the effects of collaborative care on symptoms of depression may be mediated through changes in adherence to antidepressants.[17,18]

Secondly, the RCTs included were different in some methodologic approaches, such as the pharmacy setting in which the pharmacist performed the intervention, type of intervention performed, and type of diagnostic measures. In this respect, studies that considered different outcome measures were used, which could limit internal validity. Although no statistical heterogeneity was detected, the Cochran Q test has low power when the number of studies included in the meta-analysis is small and the I^2 statistic also suffers from large uncertainty in this situation.

In a similar way, the power of the Egger test for assessing bias can also be affected by the low number of studies included.

Thirdly, a 6-month follow-up period is a short time when referring to antidepressant treatment, which should be continued for at least 6 months after remission of an episode of depression.[6] However, it is well known that dropout occurs mostly at the beginning of treatment with antidepressants.[7] Even though a short follow-up period could have influenced the effect sizes of pharmacist intervention versus controls, the 2-month trial by Crockett et al.[31] did not alter the results, as we confirmed in the robustness of analysis.

Fourthly, most studies were conducted in the US and the results may not generalize to other contexts. Finally, some baseline differences of the compared groups were identified in 3 of the studies,[27,28,30] which could introduce bias. However, in 2 of these studies,[27,28] statistical methods to adjust for the baseline differences were used to minimize bias, while the third study[31] reached the highest score on

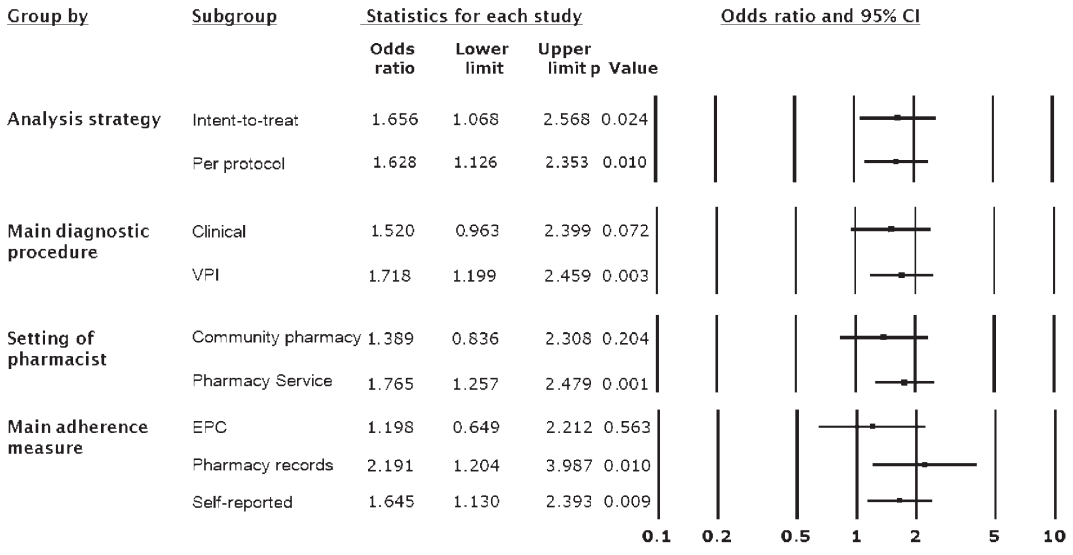

Figure 3. Subgroup analyses by setting of pharmacist implementing the intervention, type of diagnosis, main adherence measure, and strategy of analysis. EPC = electronic pill container; VPI = validated psychiatric instrument.

the Jadad scale and described an adequate randomization process and allocation concealment.

In spite of these limitations, this study is, to the best of our knowledge, the first published systematic review and meta-analysis of pharmacist intervention in patients with depression. Analysis proved that the pooled estimate was robust and suggested that there was little publication bias.

Our review indicates that pharmacist interventions in the care of outpatients treated with antidepressants can significantly improve patient adherence to medication. Patient education and monitoring, along with monitoring and management of adverse effects and adherence promotion, were the most commonly reported interventions in both pharmacy service and community pharmacy. Two of the studies conducted in a pharmacy service also allowed pharmacists to recommend or conduct changes or adjustments in medication. However, no significant differences were found in terms of improvement of patient adherence to antidepressants when subgroup analyses were conducted by setting of pharmacist involved in the intervention.

Our review also indicates that the data generated from the published RCTs on pharmacist interventions in patients with depression are limited. Only 6 studies have been identified, implying that the power of some of the statistics used may be limited and it is possible that we have not been able to detect existent heterogeneity between studies or publication bias. Therefore, we would recommend more research in this area, mainly outside the US, to provide definite answers to the question we explored.

Maria Rubio-Valera MSc, PhD Candidate, Research and Development Unit, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain; Associated Clinical Group, Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria, RedIAPP, Spain

Antoni Serrano-Blanco MD PhD, Head of the Research Group in Health Services and Health Outcomes, Research and Development Unit, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona; Mental Health Group, Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria

Jesús Magdalena-Belío MSc, General Practitioner, Letux Health Centre, Letux, Zaragoza, Spain; Mental Health Group, Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria

Ana Fernández PhD, Postdoctoral Researcher, Research and Development Unit, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona; Mental Health Group, Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria

Javier García-Campayo MD PhD, Senior Lecturer, Department of Psychiatry, Miguel Servet University Hospital, University of Zaragoza, Spain; Mental Health Group, Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria

Marian March Pujol PhD, Professor, Estades en Pràctiques Tutelades Unit, School of Pharmacy, University of Barcelona

Yolanda López del Hoyo MSc, Assistant Lecturer, Department of Psychology and Sociology, University of Zaragoza; Mental Health Group, Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria

Correspondence: Ms. Rubio-Valera, mrubio@pssjd.org

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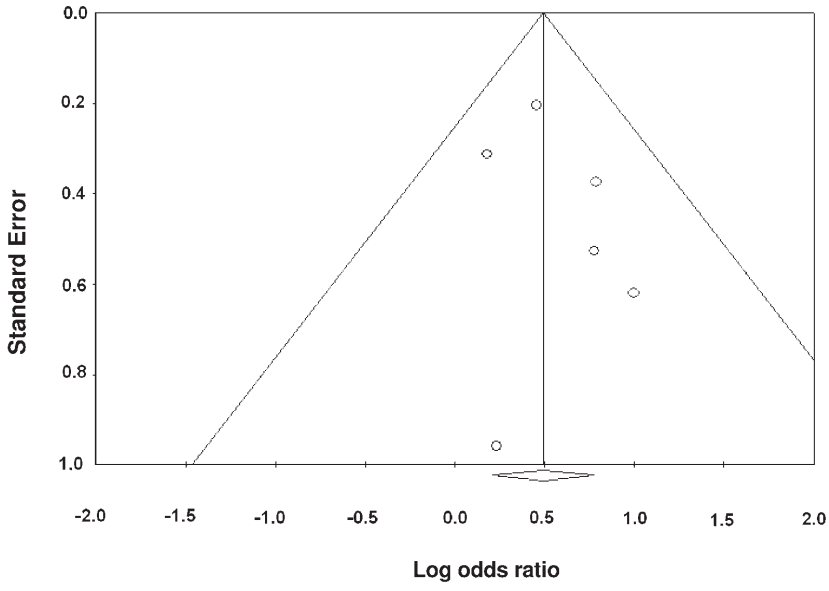

Figure 4. Funnel plot of standard error by log odds ratio.

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Efectividad de la Atención del Farmacéutico en la Mejora de la Adherencia a los Antidepresivos: Revisión Sistemática y Meta-Analisis

M Rubio-Valera, A Serrano-Blanco, J Magdalena-Belío, A Fernández, J García-Campayo, M Pujol, y YL del Hoyo

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EXTRACTO

TRASFONDO: Los farmacéuticos pueden jugar un rol decisivo en el manejo de los pacientes ambulatorios con depresión que no se adhieren adecuadamente a la medicación antidepresiva.

OBJETIVO: Evaluar de forma sistemática la efectividad de la intervención farmacéutica en la mejora de la adherencia a los antidepresivos en pacientes ambulatorios con depresión.

MÉTODOS: Se realizó una revisión sistemática y meta-análisis de ensayos clínicos aleatorizados (ECAs). Los ECAs fueron identificados mediante búsqueda en bases de datos electrónicas (MEDLINE, Central, ISI web of knowledge, y CSIC) desde su origen hasta abril de 2010, además se revisaron las listas de referencias y se consultó a expertos. Se seleccionaron aquellos ECAs que evaluaban el impacto de intervenciones llevadas a cabo por farmacéuticos para mejorar la adherencia a los antidepresivos en pacientes deprimidos en el entorno ambulatorio (farmacias comunitarias o servicios de farmacia). Dos investigadores puntuaron la calidad de los estudios y extrajeron los datos sobre las características del estudio y los resultados.

RESULTADOS: Se incluyeron seis ECAs. Un total de 887 pacientes con un diagnóstico establecido de depresión que iniciaban o mantenían un tratamiento farmacológico con medicación antidepresiva y que recibieron una intervención farmacéutica (459 pacientes) o el tratamiento habitual (428 pacientes) fueron incluidos en la revisión. Las intervenciones más frecuentemente descritas fueron la monitorización y educación del paciente, el control y manejo de la toxicidad y los efectos secundarios, la promoción del cumplimiento, la provisión de información visual o escrita y la recomendación o implementación de cambios y ajustes en la medicación. En general, no se detectaron heterogeneidad estadística ni sesgos de publicación. La odds ratio agregada, utilizando un modelo de efectos aleatorios, fue de 1.64 (95% CI 1.24 y 2.17). Los análisis de subgrupos no detectaron diferencias estadísticamente significativas en los resultados en función del tipo de farmacéutico involucrado, la medida de adherencia, la herramienta diagnóstica, o la estrategia de análisis.

CONCLUSIONES: Estos resultados sugieren que la intervención del farmacéutico es eficaz en la mejora de la adherencia a los antidepresivos. Sin embargo, estos datos aún son limitados y recomendaríamos más investigación en este campo, especialmente fuera de los E.E.U.U.

Traducido por Maria Rubio-Valera

L'Efficacité des Interventions du Pharmacien sur l'Amélioration de l'Adhésion aux Antidépresseurs: Revue Extensive et Méta-Analyse

M Rubio-Valera, A Serrano-Blanco, J Magdalena-Belío, A Fernández, J García-Campayo, M Pujol, et YL del Hoyo

Ann Pharmacother 2011;45:39-48.

RÉSUMÉ

HISTORIQUE: Les pharmaciens peuvent jouer un rôle important dans le suivi des patients dépressifs en milieu ambulatoire et qui sont peu adhérents à leur traitement antidépresseur.

OBJECTIF: Évaluer de façon rigoureuse l'efficacité des interventions du pharmacien sur l'amélioration de l'adhésion au traitement antidépresseur chez des patients ambulatoires et déprimés.

MÉTHODOLOGIE: Une revue systématique et une méta-analyse des études cliniques randomisées et contrôlées ont été faites. Les études ont été identifiées à l'aide d'une recherche dans des bases de données informatisées (MEDLINE Central, ISI, CSIC) (début-avril 2010); les références bibliographiques identifiées par cette recherche ont été incluses si pertinentes et des experts ont été consultés. Les études portant sur l'impact des interventions du pharmacien sur l'amélioration de l'adhésion au traitement antidépresseur chez des patients déprimés en milieu ambulatoire (pharmacie communautaire ou service externe de pharmacie) ont été incluses dans cette analyse. La qualité de la méthodologie était un critère recherché et des précisions sur la méthodologie et la mesure des résultats ont été mises en évidence.

RÉSULTATS: Six études ont été retenues. Un total de 887 patients ayant un diagnostic établi de dépression chez lesquels un traitement antidépresseur était débuté ou dans une phase de maintien avec des médicaments antidépresseurs, et chez qui des interventions du pharmacien ont été faites spécifiquement (459 patients) ou non (428 patients), ont été inclus dans cette revue. Les interventions les plus fréquemment rapportées étaient: information au patient et suvi, suivi et gestion des effets indésirables et de la toxicité, promotion de l'adhésion au traitement, fourniture d'information et de recommandations écrites et implantation de modifications ou d'ajustements de la médication. En somme, aucune hétérogénéité statistique ou biais de publication n'a été détecté. Les rapports de cote, mis en commun en utilisant un modèle des effets du hasard, étaient de 1.64 (IC 95%, 1.24-2.17). L'analyse des sous-groupes n'a montré aucune différence statistiquement significative dans les résultats, que ce soit par type de pharmaciens impliqués, par moyens utilisés pour faciliter l'adhésion, par outils diagnostiques ou stratégie d'analyse.

CONCLUSION: Ces résultats suggèrent que l'intervention du pharmacien est efficace pour améliorer l'adhésion au traitement antidépresseur. Cependant, les données sont encore limitées et les auteurs recommandent plus de recherche sur ce sujet, surtout à l'extérieur des États-Unis.

Traduit par Denyse Demers

Chapter 2

Paper 2

Community pharmacist intervention in depressed primary care patients (PRODEFAR study): randomized controlled trial protocol

Maria Rubio-Valera
Antoni Serrano-Blanco
Pere Travé
M Teresa Peñarrubia-María
Mar Ruiz
Marian March Pujol

BMC Public Health 2009, 9:284

Abstract

Background

Treatment of depression, the most prevalent and costly mental disorder, needs to be improved. Non-concordance with clinical guidelines and non-adherence can limit the efficacy of pharmacological treatment of depression. Through pharmaceutical care, pharmacists can improve patients' adherence to antidepressants and wellbeing. The aim of this study is to evaluate the effectiveness and cost-effectiveness of a community pharmacist intervention developed to improve adherence to antidepressants and outcomes of primary care patients with depression.

Methods/design

A randomized controlled trial, with 6-month follow-up, comparing patients receiving a pharmaceutical care support programme in primary care with patients receiving usual care.

The total sample comprises 194 patients (aged between 18 and 75) diagnosed with depressive disorder in a primary care health centre in the province of Barcelona (Spain) and that are prescribed an antidepressant. Subjects will be asked for written informed consent in order to participate in the study.

Randomization is generated at the patient level by a computerized random-number generator following a permuted block design (bocks of 10 patients with a ratio of 1:1). Concealment of allocation is assured by using numbered, opaque, sealed envelopes containing patient assignment. Blinding is not possible. Diagnosis will be confirmed using the SCID-I.

The intervention consists of an educational programme focused on improving knowledge about medication, making patients aware of the importance of compliance, reducing stigma, reassuring patients about side-effects and stressing the importance of carrying out general practitioners' advice.

Measurements will take place at baseline, and after 3 and 6 months. Main outcome measure is compliance with antidepressants. Secondary outcomes include; clinical severity of depression (PHQ-9), anxiety (STAI-S), health-related quality of life (EuroQol-5D), satisfaction with the treatment received, side-effects, chronic physical conditions and sociodemographics. The use of healthcare and social care services will be assessed with an adapted version of the Client Service Receipt Inventory (CSRI).

Data will be primarily analyzed according to the intention to treat principle (ITT), including all participants with valid data regardless of whether they did or did not receive the intervention. In addition, results will be analyzed according to the on-treatment principle. Cost-effectiveness analysis will be performed taking into account direct and indirect costs and incremental cost-effectiveness ratios will be calculated.

Discussion

This trial will provide valuable information for health professionals and policy makers on the effectiveness and cost-effectiveness of a pharmaceutical intervention programme in the context of primary care.

BMC Public Health

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Study protocol

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Community pharmacist intervention in depressed primary care patients (PRODEFAR study): randomized controlled trial protocol

Maria Rubio-Valera*[1,2], Antoni Serrano-Blanco[1,2], Pere Travé[3,4], M Teresa Peñarrubia-María[2,5], Mar Ruiz[1] and Marian March Pujol[3]

Address: [1]Sant Joan de Déu – Serveis de Salut Mental, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain, [2]Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria RedIAPP (RD06/0018/0017), Spain, [3]Estades en Pràctiques Tutelades Unit, School of Pharmacy, University of Barcelona, Barcelona, Spain, [4]ABS Just Oliveres, DAP L'Hospitalet, Àmbit Costa de Ponent, Institut Català de la Salut, L'Hospitalet, Spain and [5]ABS Bartomeu Fabrés Anglada, DAP Baix Llobregat Litoral, Àmbit Costa de Ponent, Institut Català de la Salut, Gavà, Spain

Email: Maria Rubio-Valera* - mrubio@sjd-ssm.com; Antoni Serrano-Blanco - aserrano@sjd-ssm.com; Pere Travé - ptrave.cp.ics@gencat.cat; M Teresa Peñarrubia-María - 32829mpm@comb.es; Mar Ruiz - mruizfalques@gmail.com; Marian March Pujol - marianmarch@ub.edu

* Corresponding author

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Abstract

Background: Treatment of depression, the most prevalent and costly mental disorder, needs to be improved. Non-concordance with clinical guidelines and non-adherence can limit the efficacy of pharmacological treatment of depression. Through pharmaceutical care, pharmacists can improve patients' compliance and wellbeing. The aim of this study is to evaluate the effectiveness and cost-effectiveness of a community pharmacist intervention developed to improve adherence and outcomes of primary care patients with depression.

Methods/design: A randomized controlled trial, with 6-month follow-up, comparing patients receiving a pharmaceutical care support programme in primary care with patients receiving usual care. The total sample comprises 194 patients (aged between 18 and 75) diagnosed with depressive disorder in a primary care health centre in the province of Barcelona (Spain). Subjects will be asked for written informed consent in order to participate in the study. Diagnosis will be confirmed using the SCID-I. The intervention consists of an educational programme focused on improving knowledge about medication, making patients aware of the importance of compliance, reducing stigma, reassuring patients about side-effects and stressing the importance of carrying out general practitioners' advice. Measurements will take place at baseline, and after 3 and 6 months. Main outcome measure is compliance with antidepressants. Secondary outcomes include; clinical severity of depression (PHQ-9), anxiety (STAI-S), health-related quality of life (EuroQol-5D), satisfaction with the treatment received, side-effects, chronic physical conditions and socio-demographics. The use of healthcare and social care services will be assessed with an adapted version of the Client Service Receipt Inventory (CSRI).

Discussion: This trial will provide valuable information for health professionals and policy makers on the effectiveness and cost-effectiveness of a pharmaceutical intervention programme in the context of primary care.

Trial registration: NCT00794196

Background

One of the main challenges of public health is to improve the treatment of depression. In fact, major depressive episode is one of the most prevalent mental disorders, both in the general population [1-3] and in primary care [4], and is one of the five mental disorders that cause the highest impairment, even higher than the ones associated with chronic physical conditions [5-7]. Furthermore, it is the most costly brain disorder in Europe, accounting for 33% of the total cost [8]. Even though pharmacological treatment in major depressive episodes is mostly prescribed as recommended by Spanish primary care physicians, percentages of treatment concordance with clinical guidelines are low (between 21% and 25%) mainly because recommended follow-up sessions are not performed [9]. Moreover, adherence to antidepressant medication is poor [10], which could limit its effectiveness in clinical practice. The World Health Organization and the European Council have stressed the importance of including community pharmacists, considered the health professional most readily accessible to patients, as an active member of the multidisciplinary healthcare team with the aim of benefiting patients' health [11,12], including those suffering from mental disorders [13].

By means of pharmaceutical care, community pharmacists have been shown to improve patient wellbeing in chronic physical conditions such as diabetes mellitus [14] and hypertension [15].

Research has been done to evaluate the effect of pharmaceutical care among outpatients diagnosed with depression [16-21] but in only three of the studies was the intervention conducted by a community pharmacist [16-18] and only one of them took place in a European country [16]. This was the only study that reported cost analysis information [22]. The results provided by these studies are contradictory and still more research is needed in order to study this issue. The aim of this study is to evaluate the efficacy of a pharmaceutical care programme, compared with usual care, on the improvement of adherence to antidepressant drugs and patient wellbeing in a population with a diagnosis of depression treated in primary care under real practice circumstances. Programme cost-effectiveness will be also calculated.

Methods/design

We followed the CONSORT statement for reporting randomized trials [23].

6 month follow-up naturalistic randomized controlled trial with random allocation of participants into two alternative branches: 1) Usual medical and pharmaceutical care plus support programme in community pharmacy (intervention group), and 2) Usual medical and pharmaceutical care (control group) (Figure 1).

The evaluation of compliance and clinical improvement of participants will be carried out by individual assessment at baseline, 3 and 6 months after the beginning of the intervention.

The Clinical Research Ethics Committee of the Foundation Sant Joan de Déu (CEIC *Fundación* SJD) approved the study protocol (Reference Number: BECAFIS04/07). Participants are only allowed to enter the study after signed informed consent has been obtained.

Setting

Gavà is a city situated in the province of Barcelona (Catalonia, Spain) approximately 15 kilometres south of Barcelona city. With a total area of 30.9 square kilometres and a population of more than 45,000 inhabitants, the city has two primary care health centres (PCHCs) (Gavà-1 and Gavà-Doctor Bartomeu Fabrés Anglada) that provide medical care to the whole population of Gavà. Patients will be recruited at those PCHCs from October 2008 to October 2009. 23 general practitioners (GPs) from the PCHCs voluntarily participate in the study and deal with the identification and subsequent recruitment of the patients.

Altogether there are 14 community pharmacies in Gavà that were asked to participate in the study. In addition, there is a community pharmacy in the adjacent town of Viladecans located very near to one of the PCHCs that was also asked to participate. Two of the pharmacies (13%) refused to participate, one citing heavy workload and the other a lack of interest in the study. Finally, 13 pharmacies with a total of 34 pharmacists will be responsible for providing patients with the intervention and usual care during the 6 month follow-up period.

Enrolment, randomization and allocation

All patients initiating a treatment with any antidepressant due to a depressive disorder through medical prescription from a PCHC GP in Gavà, and who are aged 18–75, are candidates for inclusion in the study. The following patients will be excluded: those on antidepressant medication in the past 2 months, those who had an appointment with an specialist in mental health in the past 2 months, those with history of psychotic or bipolar disorders, those with history of drug abuse or dependency, those with cognitive impairment that prevents assessment interviews, and those attending a pharmacy not included in the study. The eligibility criteria are listed in Table 1.

Patients meeting the inclusion criteria are given the information about the study's aim and procedures during the

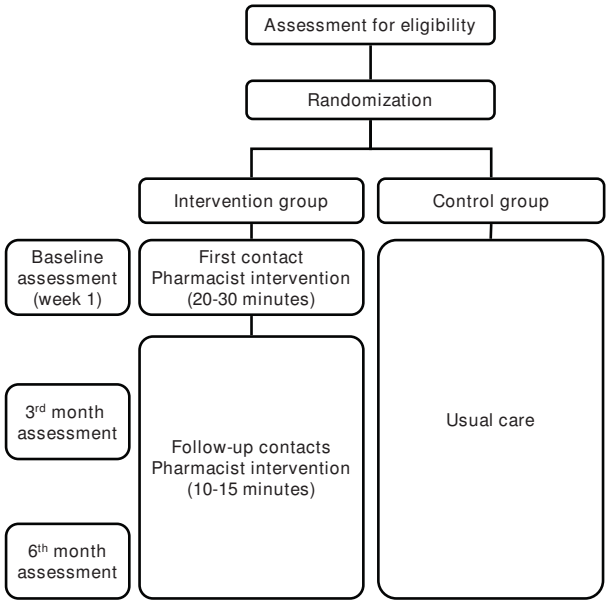

Figure 1
Study design.

medical visit and written informed consent is obtained. With the informed consent, the GP registers the patient's telephone number and PCHC clinical-history reference number. Within a week of the inclusion date, baseline assessment is performed at the PCHC by a trained psychologist.

Randomization was generated at the patient level by a computerized random-number generator following a permuted block design. Block size was of 10 patients with a ratio of 1:1. To assure the concealment of allocation, every GP receives a set of 10 sequentially numbered, opaque, sealed envelopes containing patient assignment. Envelopes were generated by an external investigator and details of the series are unknown to any of the GPs or pharmacists in the study. As patients are enrolled, the GP sequentially staples one of the envelopes to the prescription. When the patient gives the prescription to their community pharmacist, they open the envelope and create a patient study chart distinguishing between control and intervention group.

Blinding of participants and pharmacists is not possible because of the type of intervention. However, the assessment visits and data analysis are conducted by independent and blinded evaluators.

Intervention and usual care

Patients in the intervention group will receive the support programme in community pharmacy (PRODEFAR) every time they go to the pharmacy to pick up the medication or to ask for counselling in the course of the 6 months of the study. Pharmacists participating in the study received 8 hours of training about PRODEFAR prior to the study. The training followed a manual created for the study and is accredited by the Catalonian council of continuous pharmaceutical training (*Consell Català de la formació farmacèutica contínua*) (Reference Number: 09F00676).

PRODEFAR consists of a series of educational interventions focused on improving patients' knowledge of antidepressant medication, as well as making patients aware of the importance of compliance to the medication. Moreover, in patients with a sceptical attitude towards the medication, the intervention will aim to reduce stigma, reassure the patient about possible side-effects, and stress the importance of carrying out GPs' advice. First contact in the PRODEFAR is expected to take between 20 and 30 minutes, subsequent interventions are expected to take between 10 and 15 minutes.

Regardless of whether participants belong to the intervention group or not, they receive the usual pharmaceutical

Table 1: Eligibility criteria

Patients...
aged between 18 and 75,
initiating a pharmaceutical antidepressant treatment due to a depressive disorder through a medical prescription from a GP,
going to one of the participant community pharmacies,
that did not take antidepressant medication in the previous 2 months,
that have not had an appointment with an specialist in mental disorders in the previous 2 months,
with no history of psychotic or bipolar disorders,
with no history of drug abuse or dependency,
with no cognitive impairment that prevents assessment.

care as well as the treatment considered most appropriate by their physician. Patients receiving usual care get ordinary advice about medication when collecting it. Any concerns and questions addressed to the pharmacist are also answered.

Patients in the intervention group are asked to avoid conversations concerning the PRODEFAR with patients from the control group. The importance of this requirement is emphasised to patients from both groups at baseline assessment.

Measurements

Three assessment visits – at baseline, 3 and 6 months – are conducted by independent and blinded interviewers. Participants, pharmacists and GPs are not blinded. To limit bias, two trained psychologists conduct all the interviews. ASB and MRV were responsible for the interviewers' training. Table 2 shows the measures taken at each assessment study visit.

Clinical diagnosis is made using the research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [24,25]. Patients are interviewed in the modules of major depression (present and past), dysthymic disorder, anxiety disorder and adjustment disorder as defined according to DSM-IV criteria. Due to the pragmatic character of the study, GPs are blind to the DSM-IV diagnosis and patient inclusion and follow-up is performed according to their usual practice.

The primary outcome measure of our study is adherence to prescribed antidepressant medications, which is assessed through two methods:

1) pharmacy records: every time a patient buys their medication, the pharmacist registers the date of prescription, the date of dispensation and the number of pills dispensed. At 3 and 6 months from baseline, the patient is asked to present the stock of antidepressant medication and any surplus antidepressants following a GP recommended change in medication. To minimize bias, the patient is not told that the aim is to assess compliance. The pharmacist registers the stock of every medication and the percentage of medication intake is calculated by formula: (Number of doses removed/Number of doses prescribed)*100. Poor adherence is defined as taking less than 80% of the prescribed doses. There are two disadvantages of measuring adherence this way: the patient can remove pills but not take them, and this formula does provide information about the timing of the dose removal.

2) self-reported: adherence to prescribed antidepressant medications is assessed with the 4-item scale developed by Morisky et al [26]. The scale asks patients to respond "yes" or "no" to a set of 4 questions. A positive response to any question indicates a problem with adherence. Patients who respond "yes" to any of the items are categorized as non-adherent.

Clinical severity of depression is measured with the Patient Health Questionnaire 9-item depression module (PHQ-9) [27-29]. The PHQ-9 is a nine-item scale that assesses the depression symptoms of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Each of the nine items is scored from 0, not at all, to 3, nearly every day. The PHQ-9 can be used as a screening tool, with summed score ranging from 0 (no depressive symptoms) to 27 (all symptoms occurring daily). Summed scores of 0 to 4 correspond to minimal symptoms; 5 to 9 to mild symptoms; 10 to 14 to moderate symptoms, 15 to19 to moderately severe; and 20 to 27 to severe symptoms.

As mental disorders have been shown to be frequently comorbid in the general population in Spain, and the association between major depression and anxiety has been especially highlighted [4,30], it is recommended that comorbidity be taken into account when treating mental disorders. The State-Trait Anxiety Inventory (STAI) [31,32] is a 40 item self-report measure of state and trait anxiety. Total scores on the state subscale (STAI-S) (20 items) range between 0 and 60, with the higher scores indicating more severe state anxiety. STAI-S is administered in the present research to monitor comorbidity with depression and anxiety clinical severity.

Table 2: Measurement scheme

	Instrument	T0	T1	T2
Baseline measures				
Socio-demographics	Questionnaire	X		
Psychiatric diagnosis	SCID-I	X		
Chronic physical conditions	Check list	X		
Effect evaluation				
Compliance	Medication intake percentage		Continuous registration	
Compliance	MAQ		X	X
Severity of depression	PHQ-9	X	X	X
Health-related quality of life	EuroQOL-5D	X	X	X
Anxiety (state)	STAI-S	X	X	X
Side-effects	Check-list		X	X
Satisfaction	Armando PD questionnaire		X	X
Economic evaluation				
Direct and indirect costs	CSRI – adapted	X	X	X

T0 = Baseline, T1 = 3 months after baseline, T2 = 6 months after baseline.
SCID-I: Structured Clinical Interview Axis I DSM-IV; MAQ: Medication Adherence questionnaire; PHQ-9: Patient Health Questionnaire 9-item depression module; EuroQOL-5D: European Quality of Life Scale – 5 domains; STAI-S: State-Trait Anxiety Inventory (State subscale); CSRI: Client Service Receipt Inventory.

Health-related quality of life is evaluated using the Spanish version of the EuroQol-5D (EQ-5D) [33-35]. The EQ-5D questionnaire is a generic instrument of health-related quality-of-life. The first of the two parts records self-reported problems in one of five domains-mobility, self-care, usual activities, pain/discomfort and anxiety/depression-divided into three levels of severity corresponding to; no problems, some problems, and extreme problems, thus generating 245 possible health states [36]. Each state corresponds to a single index value referred to as the tariff. Value 1.000 is the best health state and value 0.000 corresponds to being dead, 82 of the 245 states have negative values, and are thus rated as being worse than dead [36]. The second part records the subject's self-assessed health on a Visual Analogue Scale (VAS); a vertical 20 cm line on which the best and worst imaginable health states score 100 and 0, respectively.

Satisfaction with the treatment received from the pharmacist is measured with the patient satisfaction questionnaire developed by Armando PD et al [37]. This instrument consists of 10 closed questions using a 5-point Likert scale from 1 (total disagreement) to 5 (strong agreement) and an open section to express comments.

Evident side-effects are assessed using a brief version of the UKU [38] considering the most common side-effects of antidepressants. Those side-effects are listed in Table 3. For each side-effect the intensity (Not present, mild, moderate, or severe), frequency (high or low) and causal relation with antidepressant drugs (yes, no, or unclear) is assessed.

Chronic physical conditions are assessed using a "yes" or "no" check-list of 28 illnesses with the potential to become chronic, and an open section for additional illnesses not considered by the authors of the list [39]. Physical conditions considered chronic are listed in Table 4.

Additionally, patients are asked for socio-demographic details including age, sex, marital status, living arrangements, education, employment and type of contract.

Economic evaluation

Client Service Receipt Inventory (CSRI) [40] is a questionnaire for collecting information about use of healthcare and social care services as well as other economic impacts. In our study, we adapted it to take into account the costs due to lost production as well as the cost of medicines, the costs of healthcare use and social care services, and the costs for patient in terms of travelling expenses and time lost. Patients are asked to give details of services and medicines that they have used during the previous 3 months due to depression or for other reasons. Services included hospital care, primary healthcare and social care, as well as the provision of aids, tests and medication. The length of stay is recorded for inpatient episodes, whilst the number of contacts with other services is recorded.

Sample size

To calculate the sample size it was taken into account that we needed to obtain a difference of at least 17 points in the percentage of medication intake [16]. A total of 194 patients are needed to conduct the study, assuming an alpha risk of 0.05 and a beta risk of < 0.20 and a 20% dropout rate.

Statistic analysis

Data collected will be analyzed using SPSS-WIN 17.0 and SAS 8.0 statistical analysis software and employs both quantitative and qualitative techniques. Firstly, comparability between the intervention and usual-care groups will be assessed at baseline to check differences.

Effect evaluation

Data will be primarily analyzed according to the intention to treat principle (ITT), including all participants with valid data regardless of whether they did or did not receive the intervention. In addition, results will be analyzed according to the on-treatment principle. Participants with documented deviations from the protocol (i.e. false inclusions, participants who did not receive the entire intervention or participants in either the intervention or the control group with incomplete follow-up data) will be excluded from the on-treatment analysis. The results of the ITT analysis will be compared with the results of the on-treatment analysis to assess whether protocol violations have caused bias.

Economic evaluation

In order to compare the two therapeutic programmes, a cost-effectiveness analysis will be performed. Direct costs will be calculated by adding the costs of the medication, the use of health-related services and the use of pharmaceutical-related services. According to the International Vademecum (Red Book) 2007–2009, the cost of medications will be calculated by determining the price per milligram during the study, including value-added tax, and multiplying it by the daily dose in milligrams and the number of days receiving such treatment. Costs derived from the use of health related services will be calculated considering OBLIKUE unitary cost database [41]. Costs of pharmaceutical related services will be calculated by multiplying the price of an hour of pharmacist attention by the time spent attending patient concerns and needs.

Indirect costs will be calculated considering the days on sick leave and multiplying them by the minimum daily wage in Spain. Finally, total costs will be calculated by adding direct and indirect costs.

Adherence to pharmacological treatment will be used to compare the benefits of each intervention. To determine which of the interventions is best for maximizing benefits, the incremental cost-effectiveness ratio (ICER) will be calculated. The ICER expresses the relation between the costs and effects of one intervention compared with another [42]. To address uncertainty in the ICER sampling distribution, non-parametric bootstrapping will be carried out [43]. Five thousand replications will be carried out for each treatment comparison.

As the duration of the study was only 6 months, neither costs nor outcomes were subject to discounting [42].

Table 3: Assessed side-effects

Asthenia/Lassitude/Increased Fatigability
Sleepiness/Sedation
Tension/Inner Unrest
Increased Duration of Sleep
Reduced Duration of Sleep
Increased Dream Activity
Tremor
Increased Salivation
Reduced Salivation
Nausea/Vomiting
Diarrhoea
Constipation
Stomach cramp
Orthostatic Dizziness
Palpitations/Tachycardia
Headache
Increased Tendency to Sweating
Weight gain
Weight loss
Diminished Sexual Desire
Sexual dysfunction

Discussion

The results of this study will provide valuable information for health professionals and policy makers on effectiveness and cost-effectiveness of a pharmaceutical intervention programme in patients with depressive disorders. In the case of proven effectiveness and cost-effectiveness, we would recommend implementing this management intervention into usual healthcare.

Below, design characteristics that involve potential threats to reliability and validity are described.

Firstly, the naturalistic nature of the study and the wide inclusion criteria generate a large inter-subject variability that can reduce the ability to detect differences. On the other hand, that may favour the generalization of the results of this study.

Secondly, two situations may cause contamination bias. Firstly, bias may occur due to the fact that participants of the usual care group share pharmacies with those on the intervention group. To limit this potential contamination

Table 4: Assessed chronic physical conditions

Chronic Allergy
Arthritis/Rheumatism
Bronchitis/Emphysema
Asthma
Diabetes
Migraine/Chronic headaches
Chronic Back Pain.
Chronic Neck Pain
Vascular Diseases
Heart attack/Angina Pectoris
Heart diseases
Stroke
Varicose veins
Hypertension
Peptic or Duodenal Ulcer
Hemorrhoids
Chronic constipation
Psychological problems/Depression
Cataract
Vision impairment
Hearing impairment
Thyroid Diseases (Hiperthyroidism/Hypothyroidism)
Nervous System Diseases (Multiple Sclerosis, Parkinsonian Disorders, Epilepsy...)
Cancer
Acquired Immunodeficiency Syndrome/HIV Infection
(If male) Prostatic Diseases
(If female) Menopause

bias, interviewers and pharmacists will remind patients not to share information about the appointments with their pharmacists or with other people participating in the study. Secondly, pharmacists participating will receive training in pharmaceutical care in depression which may encourage them to also apply the programme to the control group. In order to limit this bias, pharmacists will be asked to be especially careful not to contaminate the control group with pharmaceutical intervention.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ASB is the principal investigator and developed the original idea for the research. The study design was done by ASB, PT, MM and MTP. These authors, with the help of MRV and MRF, designed and planned the intervention that is going to be evaluated. ASB and MRV developed the statistical methods. All authors have corrected draft versions and approved the final version of the manuscript.

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Chapter 2

Paper 3

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

Maria Rubio-Valera
Marian March Pujol
Ana Fernández
M Teresa Peñarrubia-María
Pere Travé
Yolanda López del Hoyo
Antoni Serrano-Blanco

Submitted for publication

Abstract

Background

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.

Methods/design

Newly diagnosed primary care patients were randomized to usual care (92) or pharmacist intervention (87). Patients were followed up at 6 months and evaluated three times (Baseline, 3 and 6 months). Outcome measurements included clinical severity of depression (PHQ-9), health-related quality of life (HRQOL) (Euroqol-5D) and satisfaction with the pharmacy care. Adherence was continuously registered from the computerized pharmacy records. Non-adherence was defined as refilling less than 80% of doses or having a medication-free gap of more than 1 month.

To evaluate intervention effectiveness, two-level multilevel mixed-effects linear and logistic models were fitted where observations were clustered within patients. An intent to treat (ITT) strategy was used for the effectiveness analyses, including all participants as randomized regardless of whether they receive the intervention or had incomplete follow-up data. A second analysis was conducted according to the per protocol (PP) principle.

Number needed to treat (NNT) was calculated for the main outcome (adherence). For the continuous outcome variables showing statistically significant differences between groups, effect size (Cohen's d) was calculated.

Results

Overall, 11 (6%) patients never filled the medication (non-initiators) and a high proportion of patients that initiated medication dropped it at 3 (48.0%) and 6 month follow-up (57.0%). Patients in the intervention group were more likely to remain adherent at 3 (67.7% vs 83.3%) and 6 month (46.3% vs 67.3%) follow-up but the difference was not statistically significant. In the PP analysis, the same trend was observed and differences between groups were close to statistical significance (OR=3.44; p=0.055).

Patient satisfaction with the pharmacy service was high in both groups and both groups showed an improvement in mental health symptoms at 3 and 6 month follow-up. However, no statistically significant differences were observed between groups in clinical symptoms or satisfaction with the pharmacy service.

Patients in the intervention group showed greater statistically significant improvement in HRQOL compared to usual care patients both in the ITT and PP analyses. The overall improvement in the control and intervention group was 0.14

vs 0.25, respectively, in the ITT analysis and 0.16 vs 0.27 in the PP analysis. The effect size was small to medium in both the ITT and PP analyses (0.31 and 0.33 respectively).

Conclusions

The results of our study indicate that a brief intervention in community pharmacies does not improve depressed patients' adherence to antidepressants or clinical symptoms. Though not statistically significant, there was a clinically important improvement in the degree of adherence to antidepressants in the intervention group. This intervention helped patients to improve their HRQOL. Quality of life is a global measure of the patient's state and, in patients with this type of illness, feeling better is a very relevant result. As such, we believe that further research is necessary to evaluate the active components of the pharmacists' intervention and improve its impact on the patients' health related quality of life.

2.3.1 Background

It is estimated that almost 13% of Europeans will suffer major depression at least once in their life and that around 4% will suffer it within a year (1). Disability associated with depressive disorders is very high and it is projected that, by 2030, depression will be the leading cause of disability in Western societies and the second in the world, generating disability even greater than that caused by ischaemic heart disease or road traffic accidents (2). In addition, depression is associated with increased rates of suicide (3). This results in a high burden for patients and society and is costly to the system, mainly due to the patients' inability to work but also because of heavy service use, medication needs and premature death (4;5).

Consequently, it is necessary to improve the detection and prevention of depression, as well as its treatment, to minimize relapse and recurrence. Treatment with antidepressants for sufficient time (i.e. 6 months) is associated with decreased risk of relapse into depression, the treatment effect being greater in adherent patients (6). The effectiveness of pharmacological treatment is limited by the premature discontinuation of treatment and/or lack of adherence.

Low adherence to antidepressants has been systematically reported (7). In primary care, where mood disorders are commonly treated, high rates of patient discontinuation with antidepressant treatment is one of the main reasons for low concordance of real practice with clinical guidelines for depression (8). As a result, the development of effective and efficient interventions that facilitate adherence to appropriate prescriptions is a main research priority.

Community pharmacists (CPs) are easily accessible to patients and, being responsible for the provision of medicines, can be of great help in the implementation of interventions to facilitate adherence among ambulatory patients. A recent systematic review of randomized controlled trials evaluating the effectiveness of pharmacist intervention to improve adherence to antidepressants identified six studies addressing this issue (9). Although most of the individual studies had shown non-statistically significant results, when pooled, a statistically significant effect was observed favoring pharmacist intervention. However, the review included interventions conducted by pharmacists in different contexts (hospital service and community pharmacy) and sub-group analyses showed that, when pooled separately, studies comprising CPs 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 and that further research is necessary.

Only one of the studies identified by the systematic review had been conducted in a European country (10). In the per protocol analysis, Brook found that patients who received a CP intervention together with an informative videotape that emphasized the importance of adherence, showed better adherence with

antidepressant medication treatment. 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 CP intervention compared to usual care in the improvement of adherence to antidepressants and patient wellbeing in a population initiating pharmacological treatment after being diagnosed with depression by their general practitioner (GP).

2.3.2 Methods

2.3.2.1 Study Design

This was a six-month follow-up naturalistic parallel-group controlled trial with random allocation of participants into usual care and usual care plus CP intervention. A detailed description of the study protocol has been provided elsewhere (11).

2.3.2.2 Participant recruitment and randomization

Participants were recruited at 4 Primary Care Health Centers (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 the inclusion of patients, 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. Those patients who had taken any antidepressants or had had an appointment with a specialist in mental disorders in the previous 2 months; those with a history of psychotic, bipolar disorder or drug abuse; and those with cognitive impairment, were not considered for inclusion.

Spanish patients can choose any pharmacy in the country to fill their prescription and can switch from one to another in successive visits. Therefore, only patients that agreed to attend one of the participant community pharmacies were included in the study. Patients were asked to refill their antidepressant prescriptions at the same community pharmacy during the study.

GPs informed eligible patients about the study, invited them to participate and obtained signed informed consent. To assure concealment of allocation, every GP received a set of 10 sequentially numbered, opaque, sealed envelopes generated by an external investigator (MRV) containing patient assignment. Randomization was generated at the patient level by a computerized random-number generator following a permuted block design (1:1) with block sizes of 10. 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 control and intervention group. Blinding of participants and pharmacists was not possible but outcome assessors were blind to the allocation. Patients were asked to avoid conversations concerning the study with other participants.

2.3.2.3 Intervention

All the community pharmacies in Gavà and El Prat (15 and 24, respectively) were asked to participate in the study. Six of the pharmacies declined to participate, citing heavy workload (n=2) or lack of interest in the study (n=4). To homogenize the intervention across the various participating pharmacies, pharmacists received an 8 hour training session on the intervention focused on implementation and information-collection guidelines.Since patients freely decided where to buy their medication, only 24 of the 33 pharmacies that originally agreed to participate and had been trained for the study were approached and finally took part, including a total of 58 CPs. During the study, two pharmacies from Gavà dropped out of the study: one because the pharmacy was closed and one because the CP responsible for the study in the pharmacy no longer worked there.

Patients in the intervention group received the support programme (PRODEFAR) in community pharmacy when they went to the pharmacy where they received their first prescription of antidepressants to pick up the medication or to ask for counselling in the course of the 6 months. PRODEFAR consists of an educational intervention centred on improving patients' knowledge of antidepressant medication, as well as making patients aware of the importance of adherence to the medication. Moreover, 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 carrying out GPs' advice (see Annex I).

Patients were beginning treatment with antidepressives so the first contact was considered to be the most important. During the first visit, while the medication was being dispensed, the pharmacist provided the patient with information about the medicine and briefly discussed various aspects of the illness and its treatment. The aim was 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, asked how the patient was doing (improvement, appearance of side-effects, or queries).First contact in the PRODEFAR took a mean time of 14.4 minutes and subsequent interventions took a mean of 7.7 minutes.

Patients in the control group received usual care from their GP and CP. Usual care 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 contact in the usual care group took a mean of 7.8 minutes and subsequent visits a mean of 7.7 minutes.

2.3.2.4 Measurements

Three assessment visits (baseline, 3 and 6 months) were conducted by 8 trained psychologists. Patients were asked for socio-demographic details including age, gender, marital status, living arrangements, education and employment.

2.3.2.4.1 Antidepressant use

The primary outcome was adherence to prescribed antidepressants. Adherence was assessed using the computerized pharmacy records. Each time a patient bought medication in any pharmacy, the electronic computerized system registered all the information about the drug and added the information to the patient's clinical history.

Originally, the intention was for pharmacists to manually register the information on medication dispensed. However, the electronic system was much more reliable and easy to execute and was not affected by the mobility of the patients or the loss to follow-up. The medication possession ratio was calculated using the formula: (Number of doses refilled/Number of doses prescribed)*100. In addition, patient pharmacological information was reviewed for treatment gaps (medication-free periods during treatment).Poor adherence was defined as refilling less than 80% of the prescribed doses, a definition that has a reasonable balance between sensitivity and specificity (12) or having a treatment gap greater than one month (13).

2.3.2.4.2 Clinical severity of depression

Clinical severity of depression was measured with the Patient Health Questionnaire, 9-item depression module (PHQ-9) (14;15). Summed scores of the PHQ-9 range from 0 to 27 (0-4: minimal symptoms; 5-9: mild symptoms; 10-14: moderate symptoms; 15-19: moderately severe symptoms; 20-27: severe symptoms).

2.3.2.4.3 Health-related quality of life (HRQOL)

Health-related quality of life was evaluated using the Spanish version of the EuroQol-5D (EQ-5D) (16-18). The EQ-5D records self-reported problems in five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) into three levels of severity (no problems, some problems, and extreme problems). This generates 245 possible health states and each health state corresponds to a tariff or utility index with anchor points in 1 (best health state) and 0 (being dead) and negative values representing states that are considered worse than being dead (19).

2.3.2.4.4 Satisfaction with the pharmacist service

Satisfaction with the treatment received from the pharmacist was measured with a patient satisfaction questionnaire (20). This instrument consists of 10 closed questions using a 5-point Likert scale from 1 (total disagreement) to 5 (strong agreement) and an open section to express comments. Total scores range from 10 to 50 with higher scores indicating higher satisfaction.

2.3.2.4.5 Clinical diagnosis

When patients were recruited, clinical diagnosis was made by the GP and, at the baseline assessment, it was confirmed using the research version of the Structured

Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (major depression (present and past), dysthymic disorder, anxiety disorder and adjustment disorder) (21;22). Due to the naturalistic character of the study, GPs were blind to the DSM-IV diagnosis and patient inclusion, and follow-up was performed according to their usual practice. The protocol stipulated informing the GP only in the case that the patient's life was at risk.

2.3.2.4.6 Co-morbidities

Chronic physical conditions were assessed using a "yes" or "no" check-list of 28 illnesses with the potential to become chronic, and an open section for additional illnesses not considered by the authors of the list (23). Although checklist measures are imperfect, they provide useful information on chronic co-morbid conditions (24) and show moderate to high agreement with medical records (25).

2.3.2.5 Sample size calculation and data analysis

To detect a difference of at least 17 points in the percentage of medication intake (10), with a two-sided 5% significance level and a power of 80%, a sample size of 162 patients was necessary. Finally, since we used the patient's clinical chart to get the information, we did not have missing values for our main outcome.

Pre-treatment comparability between intervention and usual-care groups in baseline clinical characteristics and socio-demographic information was assessed applying the χ^2-test or Fisher exact test for categorical data, the Students t-test for continuous variables and the non-parametric equality-of-medians test for biased numerical data (i.e. number of comorbidities).

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 months and 6 months) as a within-participants repeated factor, and participants as a random factor with random intercepts and slopes for each participant. Models with variables not assessed at baseline (adherence and satisfaction) included only two time points (3 and 6 months).

An intent to treat (ITT) strategy was used for the effectiveness analyses, including all participants as randomized regardless of whether they receive the intervention or had incomplete follow-up data. When applying multilevel analysis to longitudinal data, there is no need to have a complete dataset (26). Moreover, it has been shown that applying multilevel analysis to deal with incomplete follow-up data is even better than applying imputation methods (26). Consequently, missing data was not imputed.

A second analysis was conducted according to the per protocol (PP) principle. Participants in the intervention group were excluded if they had never received the pharmacist intervention (they never bought medication or did it in a pharmacy not

engaged in the study). 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 multilevel mixed-effects 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 x group (control vs. intervention)' 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). When this interaction term was not significant (adherence, severity of depressive symptoms and satisfaction models), the model without the interaction term was used. A significant group effect was interpreted as an effect of treatment over the course of the study.

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 finally 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 at 3 and 6 months follow-up. For the continuous outcome variables showing statistically significant differences between groups, effect size (Cohen's d) was calculated by means of standardized mean difference between the two populations using the pooled standard deviation of the two groups at baseline. The effect size was categorized as small (0.2), medium (0.5) and large (0.8) (27).

All analyses were conducted with STATA 11.0.

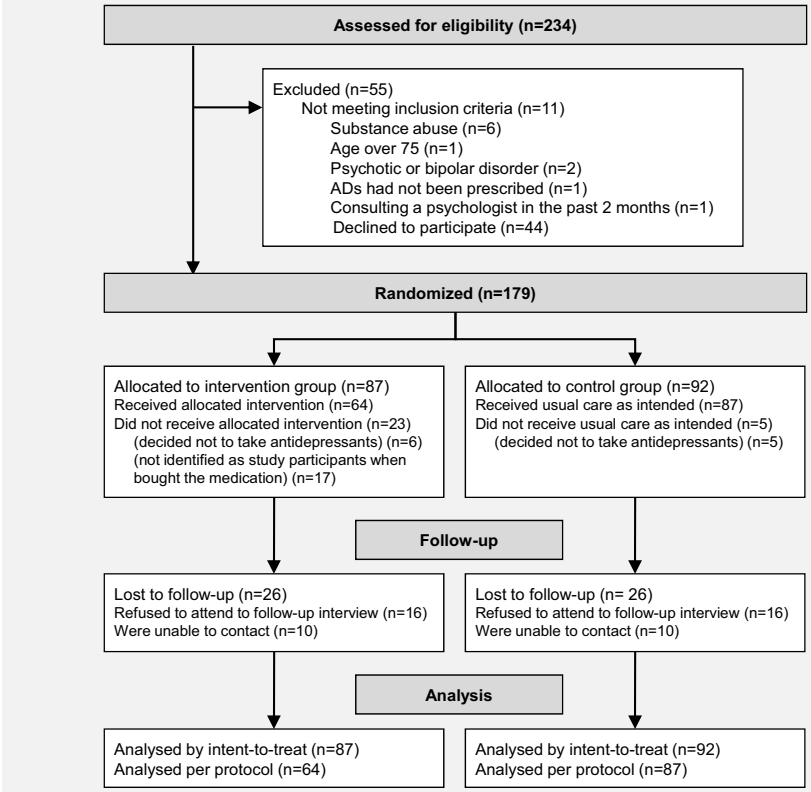
2.3.3. Results

2.3.3.1 Participants and drop-outs

Figure 2.3.1 shows the study flow chart. A total of 234 patients were referred by the GPs for the study. Finally, 179 patients were randomized to control (92) and intervention (87) groups and were evaluated at baseline and included in the ITT 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.

One-hundred and twenty (67%) patients completed the 3 assessment visits. Forty (23%) of the patients missed 1 of the 2 follow-up assessments. Seven (4%) and 33 (19%) of patients, respectively, missed the three month or six month follow-up assessments because they could not be contacted or they refused to attend. Finally, 19 (11%) participants were only evaluated at baseline (declined to participate or could not be reached).

Figure 2.3.1 Study flow chart



2.3.3.2 Baseline data

Table 2.3.1 shows the baseline characteristics of the participants in the control and intervention groups. 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 and the mean baseline severity of depression according to the PHQ-9 was 15.9 (corresponding to moderately severe symptoms).

Statistically significant differences existed in the proportion of women between the two groups; all the analyses were adjusted by gender. No other statistically significant differences existed between the 2 treatment arms.

2.3.3.3 Adherence to antidepressants

Table 2.3.2 shows the patients' probability of remaining adherent as well as the models-based mean satisfaction, severity of depression and health-related quality of life at 3 and 6 month follow-up in the control and intervention groups. Table 2.3.3 shows the regression models for adherence and satisfaction according to the ITT and PP strategies.

Table 2.3.1 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 2.3.2 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 ITT and PP analyses

	ITT			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, 85.1)	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)Π						
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

Π Values for male patients of age 45.5

Overall, 11 (6%) patients never bought the medication (non-initiators) and a high proportion of patients that initiated medication dropped it at 3 (48.0%) and 6 month follow-up (57.0%).

In the ITT analyses, patients in the intervention group seemed to be more likely to remain adherent both at 3 (67.7% vs 83.3%) and 6 month (46.3% vs 67.3%) follow-up (Table 2.3.2) but the trend did not reach statistical significance (OR=2.24; p=0.209) (Table 2.3.3). Number needed to treat was 5, indicating that 5 patients have to receive the intervention if one extra patient is to remain adherent to medication at 6 month follow-up (Table 2.3.2).

In the per PP analysis, the same trend was observed, with patients in the intervention group showing higher adherence both at 3 and 6 month follow-up (Table 2.3.2). Differences between groups in the PP analysis were close to statistical significance but did not reach it (OR=3.44; p=0.055) (Table 2.3.3). In order to prevent non-adherence in one patient, we need to implement the intervention in 5

Table 2.3.3 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)***			
	ITT		PP		ITT		PP	
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, 0.86)	0.209	3.44 (0.97,12.2)	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-married male 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).

patients.

2.3.3.4 Satisfaction with pharmacy service

Overall, patient satisfaction with the pharmacy service was high in both groups. No statistically significant differences were observed between groups at either 3 or 6 months (Tables 2.3.2 and 2.3.3).

2.3.3.5 Clinical severity of depression

Both groups showed an improvement in mental health symptoms at 3 and 6 month follow-up (Table 2.3.2). Table 4 shows the regression models for clinical severity of depression (PHQ-9) and HRQOL according to the ITT and PP analysis strategies.

No statistically significant differences in the severity of depressive symptoms were observed between the control and the intervention group in either the ITT or the PP analyses (Table 2.3.4).

Table 2.3.4 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)****			
	ITT		PP		ITT		PP	
Constant[&]	14.0 (12.3,15.6)	0.001	14.0 (12.3, 15.8)	0.001	0.67 (0.59, 0.74)	0.001	0.66 (0.58, 0.75)	0.001
Group								
Control	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								
Men	Reference		Reference		Reference		Reference	
Women	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								
3-months	Reference		Reference		Reference		Reference	
6-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
Depression baseline severity (PHQ-9)[ç]	ni		ni		-0.012 (-0.02–-0.01)	0.001	-0.01 (-0.02, -0.01)	0.001
Time x Group interaction								
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

2.3.3.6 HRQOL

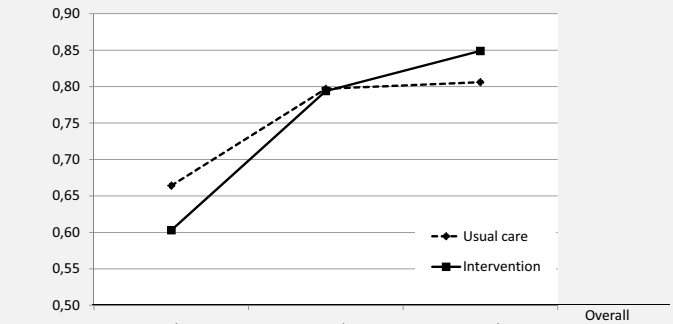
Figure 2.3.2 shows the multilevel based mean utilities (EQ-5D tariffs) in the control and intervention groups at baseline, 3 and 6 month follow-up, and the improvement at 6 month follow-up in HRQOL.

In both the ITT and in the PP analysis, a significant interaction was found between the time and the group in EQ-5D tariffs in favour of the intervention group (Table 2.3.4). The overall improvement (95% CI) in the control and intervention group was 0.14 (0.08, 0.21) vs 0.25 (0.18, 0.31), respectively, in the ITT analysis and 0.16 (0.09, 0.23) vs 0.27 (0.19, 0.35) in the PP analysis. The effect size was small to medium in both the ITT and PP analyses (0.31 and 0.33 respectively).

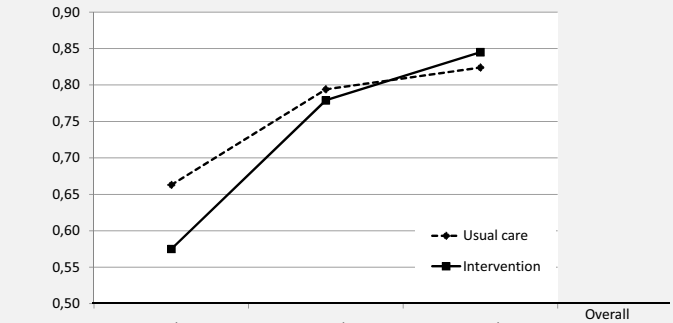
2.3.4 Discussion

A randomized controlled trial was conducted to evaluate whether a CP intervention designed to encourage adherence, reduce stigma, and help patients with

Figure 2.3.2 Multilevel based mean utility and overall improvement in the EQ-5D (95% CI) at 3 and 6 month follow-up for the ITT and PP analyses



ITT 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)

pharmacological treatment can help to improve adherence, symptoms and patient wellbeing in primary care patients initiating treatment with antidepressants.

Patients who received the intervention according to the intended protocol tend to have a higher probability of remaining adherent at 3 and 6 months than those who received usual care as intended. This result did not quite reach statistical significance (p=0.055). Though not statistically significant, this difference was clinically significant since the number of patients needed to treat was relatively small for an intervention that was easy to implement and not too time-consuming (pharmacists needed to implement the intervention in 4 patients in order to help one extra patient to remain adherent at 3 and 6 month follow-up).

In general, the results of our study are consistent with those previously published by Brook et al. 2005 and Rickles et al. 2006 (10;28). When they used the ITT analysis strategy, neither Brook nor Rickles found a statistically significant improvement in the group of patients who had received a pharmacist intervention in comparison with the usual care group. When analysing the data for the PP analysis, these studies did observe statistically significant differences in terms of adherence between groups. Both studies used a protocol definition that considered exclusively those patients that had received a minimum of 3 contact sessions with the pharmacist. Nevertheless, those patients who received one (or two) interventions and decided to abandon the medication may not have wanted to receive a second (or third) intervention session. Consequently, those patients in the intervention group who abandoned the medication during the first months may have been excluded from the PP analysis so increasing the difference between the groups. As such, there may be some difficulty in generalizing from this result.

In our case, the first contact with the patient was the most important. On this visit, the intervention was more intensive, while the meetings that followed consisted of reinforcement and review of the initial session. For this reason, we decided to be less strict with our protocol definition.

Despite having detected statistically significant differences in the degree of adherence to the antidepressive medication, none of the previous studies found statistically significant differences in clinical improvement, independently of whether the intervention was applied in the community pharmacy or pharmacy service (10;28-31). However, a powerful meta-regression based on collaborative care in depression showed a positive association between improved adherence and improvement in depressive symptomatology (32). The lack of difference in clinical improvement could be due to the fact that the relationship between it and 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 which influence the clinical course of depression. Another factor could be the appropriateness of the diagnosis, as only half the patients met major depression criteria according to the structured clinical interview. In this study, we opted for a pragmatic focus that was applicable to the clinical reality in primary care and, therefore, used the GP's clinical criteria with regard to the inclusion of patients

with depression. The analysis carried out on the subsample of patients with major depression according to the SCID did not show statistically significant differences between groups (data not shown but 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 regarding the behaviour of the subsample.

Contrary to that reported in previously by Capoccia and colleagues (30), statistically significant differences between groups were observed in HRQOL, indicating that patients who received extra care in their community pharmacy perceived their quality of life to be better.Effect size was small to moderate, which led us to question the clinical relevance of this difference. The difference could be due to a placebo effect, given that patients received more attention in the pharmacy and may feel that they are being helped in a better way, or because of desirability bias. Nevertheless, both groups showed very high levels of satisfaction with the pharmacy service with no statistically significant differences between groups.As a part of the intervention, the pharmacist discussed with the patient the nature of the treatment but also of the illness. 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. In our study, some 6% of patients diagnosed with depression according to the GP did not initiate treatment. These patients had agreed to participate in a study that attempted to improve the use of this medication and, as such, we concluded that the proportion of non-initiators would be much higher in normal practice. In fact, in previous studies, rates of non-initiation were found to reach 15% (33).

Unfortunately, if medication is not acquired, the role of the pharmacist is very limited. However, we believe that the reasons these patients have for not initiating treatment deserve to be studied in greater detail.

This study had a number of limitations that could represent a threat to its validity and may have restricted our capacity to detect differences. Firstly, as mentioned above, study enrollment may have been biased against patients who did not want to take antidepressants. However, the figures regarding the abandonment of treatment correspond to those found in other studies carried out in the same region (34). From this we conclude that our sample can be extrapolated to the primary care population.

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

Thirdly, the pharmacists who attended the control and intervention patients were the same, which could have led to some contamination. The pharmacists were asked to exercise great care and to register the intervention carried out on control

patients. A further source of contamination might have been the patients, who could have transmitted information among themselves. To minimize this possible contamination, patients were asked not to share information received with other participants.

Fourthly, only 74% of patients in the intervention group received at least one intervention in the pharmacy and this may have limited its impact.

The fifth limitation is related to the fact that patients were able to decide at which pharmacy they acquired their medication and could change pharmacy many times. Consequently, even those patients who received the intervention attended very few sessions. On the other hand, this leads us to believe that even with a single, relatively simple, although slightly more intense, intervention which is applied at the point of initiating the medication, we can obtain significant improvements in adherence and patients' quality of life; although this would require further exploration in the future.

We considered that another factor which may have affected our results, the sixth limitation, is the demotivation of participating pharmacists. As a result of the financial crisis, shortly after the study commencement, a series of economic adjustments were made which affected the viability of pharmacies in Catalonia (36-38). In addition, the low incidence of new cases that met inclusion criteria meant that the inclusion period had to be extended. These two factors, taken together, may have demotivated and/or exhausted our pharmacists and this may be reflected in the results. Nevertheless, 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. To begin with, patients may acquire the tablets but not take them. Furthermore, this measure does not provide us with information with respect to the time of taking the medication or non-adherence. It did, however, show relatively good agreement with electronic refill measures in previous studies, especially in depressed patients (39). Moreover, this measure did allow 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 antidepressive treatment. 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 (35). 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 antidepressive treatment 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 health-related quality of life. Quality of life is a global measure of the patient's state and, in patients with this type of illness, feeling better is a very relevant result. 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.

Future research should evaluate whether a single and more intensive intervention conducted in the community pharmacy is a good strategy to improve adherence and health-related quality of life in patients initiating treatment with antidepressants in primary care. 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.

2.3.5 References

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Chapter 2

Paper 4

Cost-effectiveness and cost-utility of a community pharmacist intervention compared to usual care in patients with depression: a randomized controlled trial

Maria Rubio-Valera
Judith Bosmans
Ana Fernández
Maite Peñarrubia-María
Marian March Pujol
Pere Travé
Juan Ángel Bellón
Antoni Serrano-Blanco

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Abstract

Background

Depression generates a high burden and costs for patients and society. Non-adherence to antidepressants is common, preventing depressed patients to fully benefit from treatment. Pharmacist's interventions improve adherence to antidepressants but further evidence is needed about the cost-effectiveness of such interventions.

Objective

To evaluate the cost-effectiveness and cost-utility of a community pharmacist intervention (CPI) in comparison with usual care (UC) in depressed patients initiating treatment with antidepressants in primary care.

Methods

The economic evaluation was conducted alongside a randomized controlled trial with 6 months follow-up. Patients were recruited in 4 primary care practices from two cities in Spain (October 2008-May 2011). Patients were eligible for inclusion if they were prescribed an antidepressant by the general practitioner (GP) because of a diagnosis of major depression. CPI patients received usual care by the GP and the CPI when they filled their prescriptions. The CPI consisted of an educational intervention focused on improving patients' knowledge of antidepressant medication, as well as making patients aware of the importance of compliance to the medication, reassuring the patient about possible side-effects, and stressing the importance of carrying out GPs' advice.

The main outcome, adherence to antidepressants, was measured using electronic pharmacy records. Non-adherence defined as having a medication possession ratio <80% or having an antidepressant gap >1 month. Secondary outcomes were Quality-Adjusted Life-Years (QALYs) and remission of depressive symptoms. These outcomes were assessed at baseline, 3 and 6 months through patient interview using the EuroQol-5D and the PHQ9.

Direct healthcare costs and indirect costs (sick leave) were assessed using the Client Service Receipt Inventory. Unit costs were derived from official local sources. The time horizon was less than a year so costs were not discounted.

Results

179 patients were randomized to UC (92) or CPI (87). Overall costs were higher in the CPI group than in UC patients. The largest part of the costs difference (90%) was due to differences in productivity losses.

There were no statistically significant differences between groups in adherence, QALYs or remission of depression.

From the societal perspective, the incremental cost-effectiveness ratio (ICER) for CPI compared with UC was €9,335 per extra adherent patient and €29,548 per extra remission of depressive symptoms. The incremental cost-utility ratio (ICUR) was €38,896 per QALY gained. If willingness to pay (WTP) is €50,000 per one extra adherent patient, per extra remission of symptoms or per QALY, the probability of the CPI being cost-effective was 0.71, 0.52 and 0.56, respectively.

From the healthcare perspective, the ICER was €862 per extra adherent patient and €2,729 per extra remission of depressive symptoms. ICUR was €3,542 per QALY gained. The probability of the intervention being cost-effective was of 0.75 if the WTP is €12,000 for an extra adherent patient and €40,000 for QALY gained. The probability of the CPI being cost-effective in remission of depressive symptoms was 0.55 for a WTP of €50,000.

Conclusion

A low intensity CPI addressed to improve the adherence and wellbeing of patients initiating a pharmacological treatment for depression was not cost-effective compared to UC and its implementation in real clinical practice is not recommended.

2.4.1 Introduction

Major depression is a highly prevalent disorder that generates a heavy burden both for the society and the public health system (1-3). WHO projections predict that major depression will be the leading cause of disability in Western societies by 2030 (2). Depression has a larger negative impact on health related quality of life than anxiety disorders or chronic physical conditions such as such as such as chronic pain and cardiovascular disease (2;4). Major depression also imposes a substantial financial burden on society through increased health care utilization and absenteeism from paid work (5).

The cost associated with mental disorders currently accounts for approximately 3%-4% of gross domestic product in Europe (6). Major depression, the mental disorder associated with the higher costs, makes up 33% of the costs associated with mental disorders (5). In Catalonia, a Spanish autonomous community with a population of over 7.5 million inhabitants, the annual cost of major depression in 2006 was 735 million Euros (7). Productivity loss (indirect costs) accounted for almost the 79% of total costs.

For patients with moderate to severe depressive symptoms, clinical guidelines recommend the use of pharmacological treatment (8;9). Almost 70% of patients with a mood disorder are prescribed psychotropic drugs, mainly antidepressants (10;11). Non-adherence to antidepressants is high, as shown by recently published studies that reported rates of non-adherence of over 75% after 6 months (12-14). These low adherence rates to antidepressants prevent patients to benefit fully from the effects of the treatment prescribed by their physicians increasing the risk of relapse and recurrence, and increasing costs (15;16).

A number of interventions aimed at improving patients' adherence to antidepressants have been evaluated, showing different results according to the type of intervention implemented (educational, behavioral, affective or provider-targeted) (17). Some efforts have concentrated on pharmacists, in their role of drug dispensers and specialists on medication (18-23). When results from these studies were pooled together, interventions implemented by pharmacists showed a positive effect on adherence to antidepressants (24).

Economic evaluations provide decision-makers with information on how to allocate the limited resources available for health care. However, only one study evaluated the cost-effectiveness of a pharmacist's intervention to improve adherence to antidepressants, concluding that coaching and education by pharmacists compared with usual care is not likely to be cost-effective as a means of increasing adherence to antidepressants (25). However the study considered a small sample size both in the main analysis (N=88) and in the per protocol analysis (only 26 patients in the intervention group). Besides, this study did not include quality adjusted life years (QALY) as a measure of effectiveness thus limiting comparison with other therapies and therapeutic areas (26).

The aim of the present study was to evaluate the cost-effectiveness and cost-utility of a community pharmacist intervention (CPI) in comparison with usual care (UC) for depressed patient initiating treatment with antidepressants in primary care.

2.4.2 Methods

The economic evaluation was conducted alongside naturalistic randomized controlled trial with 6 months of follow-up comparing a CPI with UC for patients prescribed a new antidepressant treatment by a general practitioner (GP). The study protocol was approved by the Fundació Sant Joan de Déu Ethics Committee. Patients signed an informed consent to participate. A detailed description of the study protocol has been provided elsewhere (27).

2.4.2.1 Study population

Participants were recruited in 4 Primary Care Health Centres (30 GPs) from two cities in the metropolitan area of Barcelona (October 2008-May 2011). Eligible patients were adults aged 18-75 initiating treatment with antidepressants because of a depressive disorder diagnosed by a GP; having had no prescription of antidepressants or appointment with a mental health specialist in the previous 2 months; having no history of psychotic, bipolar or drug abuse history; and having no cognitive impairment. In the baseline assessment, the diagnosis of depression was assessed using the research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (28;29) GPs were blind to the DSM-IV diagnosis and patient inclusion was performed according to their usual practice.

2.4.2.2 Randomization and concealment of allocation

Randomization was done at the patient level using a computerized random-number generator following a permuted block design. To ensure concealment of allocation, every GP received a set of 10 sequentially numbered, opaque, sealed envelopes generated by an external investigator containing patient assignment. When a patient was enrolled, the GP sequentially stapled one of the envelopes to the prescription. When the patient gave the prescription to the community pharmacist, the pharmacist opened the envelope. Blinding of participants and pharmacists was not possible due to the nature of the intervention. Pharmacists were asked to be careful not to use intervention elements in their contacts with the UC group. Patients were asked to avoid conversations concerning the study with other participating patients.

2.4.2.3 Interventions

Patients in the intervention group received the CPI when they went to the pharmacy to pick up their first prescription of antidepressants. A shorter version of the intervention was used as a reminder when patients refilled their prescriptions. The CPI consisted of an educational intervention focused on improving patients' knowledge of antidepressant medication, as well as making patients aware of the importance of compliance to the medication, to reassure the patient about

possible side-effects, and to stress the importance of carrying out GPs' advice. Also, in patients with a sceptical attitude towards antidepressants, the intervention aimed to reduce stigma. Pharmacists participating in the study were trained on how to implement the intervention.

Patients in the UC group received usual care from their GP and pharmacist.

2.4.2.4 Clinical outcome measures

2.4.2.4.1 Adherence to antidepressants

The primary outcome in this study, adherence to antidepressants, was measured using electronic pharmacy records. Every time the patient refills his/her medication the system automatically registers the information in the patient's clinical history. This method for assessing adherence provides a good estimate of adherence and has been recommended both in research and clinical contexts (30). Using pharmacy records a medication possession ratio over 6 months was calculated as: (Number of doses obtained from the pharmacy/Number of doses prescribed)*100. Also, continuity in the acquisition of medication was checked. Patients were considered to have a drug gap if there was a period of more than 1 month without medication. Poor adherence was defined as having a medication possession ratio < 80% or having an antidepressant gap larger than 1 month (31).

2.4.2.4.2 QALY and severity of depression

Secondary outcomes were QALYs and severity of depression. These outcomes were assessed at baseline, and 3 and 6 months of follow-up through patient interview.

Health-related quality of life was measured using the EuroQol-5D (32-34) and Spanish tariffs were used to estimate the utility of health states described by the patients (35). QALYs were calculated by multiplying the utility with the amount of time a patient spent in a particular health state. Linear interpolation was used for transitions between health states.

Severity of depression was assessed using the Patient Health Questionnaire 9-item depression module (PHQ-9) (36;37). The PHQ was used to classify patients as those presenting remission of symptoms and those not presenting it. Remission was defined as a 50% reduction or more in PHQ-9 scores (38).

2.4.2.5 Cost measures

2.4.2.5.1 Use of services

Cost data were collected from a societal perspective at baseline, 3 and 6 months. We used a modified version of the Client Service Receipt Inventory (CSRI) to collect information about use of health care resources and lost productivity with a three months recall period (39). Information about use of psychotropic drugs (antidepressants, anxiolytics and hypnotic-sedatives) was collected from computerized pharmacy records.

A secondary analysis was done from a health system perspective. For this analysis, we only considered costs due to the use of health care resources.

2.4.2.5.2 Unit costs

Direct healthcare costs comprised visits to publicly and privately funded primary and secondary care providers, home care, tests, and drugs. The Official Bulletin of the Catalan Government for 2009 was used to estimate the costs of publicly funded services (40). For privately funded services, we used the information provided by the Official College of Physicians of Barcelona (41).

Indirect costs consisted of the costs of absenteeism from paid work. Costs of work loss were calculated by multiplying the days on sick leave with the minimum daily wage in Spain according to the human capital approach (42).

Intervention costs were estimated using the patient study chart kept by the pharmacist. Every time that the patient bought his/her medication, pharmacist recorded in the patient's chart the minutes needed to dispense medication, in the UC group, and to implement the intervention and dispense the medication, in the CPI group. The time spent on each patient by the pharmacists was multiplied by the unit cost per hour of the community pharmacists.

The unit cost of the community pharmacists was calculated taking into account the pharmacists annum working time as well as general community pharmacy expenses, pharmacists salaries and salaries on costs, taxes and pharmacists annum working time (43). This information was extracted from a published annual report based on income tax return declarations from Spanish community pharmacies in 2009 (44).

In the CPI group extra costs were included to account for the time spent on the training by the pharmacists. Training costs were estimated by adding the tariffs of the Official College of Pharmacists from Barcelona for similar training courses with the time spent by the pharmacists on the training.

Table 2.4.1 shows the unit costs healthcare resources. Time horizon was less than a year so costs were not discounted.

2.4.2.6 Statistical methods

The main analyses were done according to the intention to treat principle (ITT). Sample size calculation was based on the primary outcome of the study, i.e. adherence to antidepressants. To observe an improvement of 17 points in the percentage of medication intake (19) and assuming an alpha of 0.05 and a power of 0.8 a total of 162 patients were necessary.

We explored baseline differences in the socio-demographic and clinical characteristics between the intervention and the control group applying the Students t-test for continuous variables, the χ^2-test or Fisher exact test for categorical data and the non-parametric equality-of-medians test for biased data.

Table 2.4.1 Unit costs for healthcare resources in Euros (year 2009 values)	
Type of utilisation	Unit costs
Costs in the public health care system	
General practitioner	36.0
Nurse	14.0
Psychologist	51.6
Psychiatrist	51.6
Other medical specialists	51.6
Hospital emergency visits	142.7
Hospital stay	277.6
Diagnostic tests	Range 3.7-329.0
Pharmacological treatment	Depending on type and dose
Social worker	36.0
Costs in the private health care system	
Psychiatrist	25.3
Psychologist	25.3
Medical specialist	25.3
General practitioner	25.3
Productivity losses	
Abstenteeism from work (Number or net days)	24.0
Intervention costs	
Cost of the intervention per hour	68.3[a]

[a]In the intervention group an extra 5 € were included to account for the time needed for the training of the pharmacists.

2.4.2.6.1 Missing data

Fifty-five percent of individuals had at least one missing clinical or cost variable. We cannot be certain about the reasons for the missing data, but no major discrepancy was found between imputed data and complete-case analysis so we are leaning towards its classification as missing at random. To avoid a loss in efficiency as well as bias, missing values were imputed using multiple imputation by chained equations using the predictive mean matching method. The imputation model was stratified by group and included important sociodemographic and prognostic variables associated with drop-outs and with the outcome variables. It has been suggested that the number of imputed databases has to be at least equal to the percentage of incomplete cases (45). Consequently, fifty-five imputed databases were created. To minimize the computational burden, 10 imputed databases were selected at random from the 55 imputed databases and were used for the analysis.

2.4.2.6.2 Costs and clinical analysis

The incremental costs and incremental effects between the CPI and UC group during the 6-month follow-up were modeled by generalized linear models. Generalized linear models were fitted with different distribution families (Gaussian, inverse Gaussian, Poisson and Gamma) and link functions (identity and log). Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to test the models.

The gamma distribution with identity link was the best fit for costs. For the QALYs models the Gaussian distribution with identity link was the one that best fitted. For adherence to antidepressants and remission of depressive symptoms, a binomial distribution with logit link was used. Sociodemographic and baseline clinical

variables considered to be relevant were tested in the models using likelihood ratio tests (p≤0.10). Variables that tested to be relevant were included in the generalized linear models. Unadjusted and adjusted analyses are presented.

The overall difference in mean costs and effects between the treatments was calculated using Rubin's rules (46) as the average of estimates from each of the 10 imputed datasets.

2.4.2.6.3 Cost-effectiveness and cost-utility calculations

We calculated the incremental cost-effectiveness ratio (ICER) by dividing the difference in costs between the treatments by the difference in effects. The ICER indicates the additional investment needed for the CPI to gain one extra unit of effect compared with UC. The incremental cost-utility ratio (ICUR) was calculated by dividing the incremental costs by the difference in QALYs.

2.4.2.6.4 Quantification of uncertainty

To estimate the uncertainty surrounding the cost differences, the ICER and the ICUR we used bootstrapping with 1000 replications in each imputed dataset. Due to the biased and skewed distribution of the costs, standard parametric techniques for calculating confidence intervals cannot be applied so the 95% confidence intervals around the mean cost differences were estimated using the bias-corrected and accelerated (BCa) confidence interval (47). Bootstrapping was performed on each imputed dataset and bias-correcting and acceleration constants were obtained from each dataset. The bias-correcting and acceleration constants were averaged and used to estimate the modified percentiles that were then applied to the combined density curve to estimate the 95% BCa confidence interval.

2.4.2.6.5 Generation of cost-effectiveness planes and cost-effectiveness acceptability curves

Bootstrapped cost effect pairs were then plotted on cost effectiveness planes and used to estimate cost effectiveness acceptability curves (CEACs). In the cost-effectiveness planes the X axis represents the difference in effects and the Y axis the difference in costs. Thus, differences in costs and effects between the CPI and UC can fall into one of four quadrants (Northeast quadrant: the intervention is more costly and effective than UC; Southeast quadrant: the intervention is less costly and more effective; Southwest: the intervention is less costly and effective and; Northwest: the intervention is more costly and less effective (26).

CEACs show the probability that a treatment is cost effective at a specific ceiling ratio, which is the amount of money society is willing to pay to gain one extra unit of effect (48).

All analyses were performed with STATA 12.0.

2.4.2.7 Sensitivity analyses

Four sensitivity analyses were conducted to assess the robustness of the results. Firstly, we did a cost-effectiveness analysis according to the per protocol (PP) principle. Patients in the CPI group who did not receive the intervention and patients in the UC group that did not attend to the community pharmacy, and consequently did not receive the UC by the pharmacist, were excluded from the per protocol analysis. Secondly, we did a complete case analysis without the data from the 52 patients who were lost to follow-up at 6 months. Thirdly, we conducted an analysis where the intervention costs were doubled. Finally, we carried out an analysis in which the cost for the absenteeism was calculated using the mean salary (52.3€ per day) instead of the minimum salary in Spain.

2.4.3 Results

Thirty-nine pharmacies (all pharmacies in the two cities) were asked to participate in the study. Six of the pharmacies refused to participate, citing heavy workload (n=2) or lack of interest in the study (n=4). Since patients can freely decide where to buy their medication, only 24 from the 33 pharmacies that accepted to participate and had been trained for the study were approached by study participants and finally participated in the study, including a total of 58 pharmacists. During the study, two pharmacies dropped from the study: one because the pharmacy was closed and one because the person responsible for the study within the pharmacy left.

Figure 2.4.1 shows the flow chart of the study. A total of 179 patients referred by the GP met the inclusion criteria, consented to participate and were randomized to the CPI (n=87) or UC group (n=92). Table 2.4.2 shows the baseline characteristics in intervention and control group. Most participants were women (75%), with mean age of 46.6 years. Fifty-one percent of the participants met DSM-IV criteria for major depression. Statistically significant differences existed in the proportion of women between the two groups. No other baseline differences existed between groups. Sixty-four (74%) and 87 (95%) patients in the CPI and UC group, respectively, received the intervention as allocated and were thus included in the PP analysis.

Complete outcome data on adherence was available for all participants. Sixty-two (71%) and 65 (71%) patients in the intervention and control group, respectively, attended the 6 months follow-up assessment and were included in the complete-case analysis. Patients with complete follow-up for clinical and costs data were higher educated and had lower rates of major depression according to SCID-IV at baseline than patients without complete follow-up clinical and costs data.

Table 2.4.2 Socio-demographic and clinical baseline characteristics of the sample

	Usual care (n=92)	*Pharmacist's intervention (n=87)*
Gender; % women (n)*	83.7% (77)	66.7% (58)
Age; mean (95% CI)	46.3 (43.3-49.2)	46.9 (44.0-48.6)
Marital status; % (n)		
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)		
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)
Others	–	2.3% (2)
Working status; % (n)		
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)
Others	–	2.3% (2)
NS/NC (Missing)		1.2% (1)
Major depression according to DSM-IV criteria; % (n)	50.0% (45)	52.3% (45)
Clinical severity according to PHQ-9; mean (95% CI)[a]	15.8 (14.6-16.9)	16.1 (14.7-17.4)
Number of co-morbidities; % of cases over the median (n)	37.0% (34)	40.2% (35)

*p<0.05

[a]PHQ-9 scores can range from 0 to 27, with scores of 15 to 19 corresponding to moderately severe symptoms

Figure 2.4.1 Flow-chart of the study

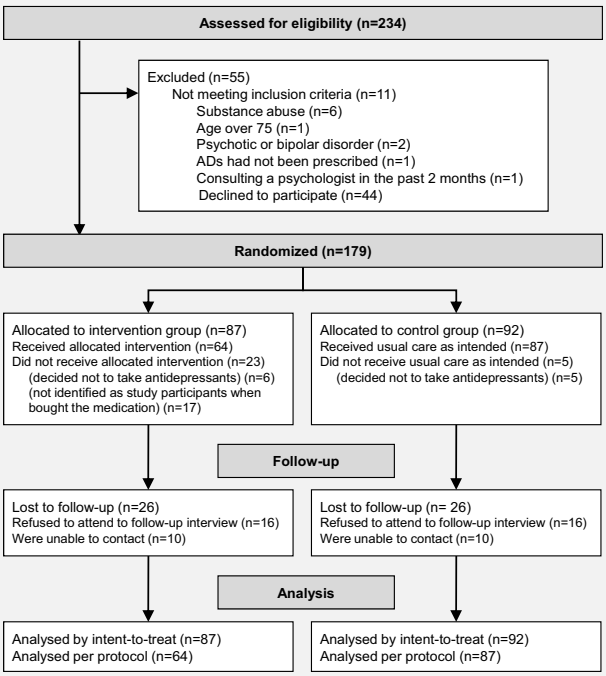


Table 2.4.3 Multiple imputed and pooled costs after 6 months follow-up in the usual care and intervention groups and mean differences between groups (95% CI) (unadjusted analysis)

Type of cost	*Usual care*	*Intervention*	*Mean differences*
Direct costs	409 (303, 515)	412 (322, 502)	3 (-134, 140)
Visits to primary and secondary care	185 (143, 228)	225 (165, 284)	39 (-27, 106)
Emergency visits and hospitalisation	113 (49, 176)	86 (39, 134)	-26 (-107, 54)
Diagnostic tests	61 (30, 92)	44 (26, 63)	-17 (-51, 16)
Medication costs	50 (38, 62)	57 (44, 69)	7 (-10, 24)
Intervention costs	16 (13, 20)	32 (27, 37)	16 (9, 22)
Indirect costs (sick leave)	342 (110, 573)	647 (351, 943)	306 (-95, 706)
Total costs	767 (499, 1035)	1091 (764, 1418)	324 (-97, 745)

2.4.3.1 Cost analysis and clinical outcomes

Table 2.4.3 lists unadjusted costs in the control and intervention groups during 6 months. Overall costs tended to be higher in the CPI group than in UC patients although not statistically significantly so. The largest part of the cost difference (over 90%) was due to the difference in indirect costs (productivity loss). The intervention costs were statistically significantly higher in the PCI group than in the UC group (Table 2.4.3).

In the main adjusted analysis, total costs in the CPI group were statistically significantly higher than in the control group (Table 2.4.4).

No statistically significant differences were observed between groups in clinical outcomes, neither in the unadjusted or adjusted analysis (Table 2.4.4), although outcomes were slightly better in the CPI group.

2.4.3.2 Cost-effectiveness and cost-utility analyses

Table 2.4.4 shows the cost-effectiveness analysis after 6 months follow-up.

2.4.3.2.1 Societal perspective

<u>Cost-effectiveness and cost-utility</u>

The bootstrapped cost-effectiveness pairs for the CPI effects on adherence were primarily located in the northeast (75%) and northwest (23%) quadrant, indicating that the costs in the CPI group were higher but that adherence did not differ between groups (Figure 2.4.2). The ICER for the CPI compared with UC was 9,335 indicating that €9,335 needs to be invested per extra adherent patient (Table 2.4.4).

Whereas costs were higher, the CPI group showed a very small improvement in the remission of depressive symptoms (at least a 50% reduction in PHQ-9 scores), resulting in a high ICER (€29,548 per extra remitted patient, Table 2.4.4).

Similar results were found for QALYs (Table 2.4.4). The CPI group showed both higher costs and a small increase in terms of QALYs compared with UC, but the effect difference was small, resulting in a large ICUR (€38,896).

Table 2.4.4 Mean pooled differences in total effects and costs at 6 months follow-up and results of cost-effectiveness and cost-utility analyses after 6 months follow-up for the main analysis and for the sensitivity analyses

	Sample size		*Outcome*	*Cost difference € (95% CI BCa)*	*Effect difference (95% CI)*	*ICER/ICUR*	*Distribution CE-plane*			
	I	*C*					*%NE*	*%SE*	*%SW*	*%NW*
Main analysis*	87	92	Adherence	336 (49, 737)	0.04 (-0.1, 0.1)	9335	75.2	1.6	0.4	22.9
			PHQ-9	336 (49, 737)	0.01 (-0.2, 0.2)	29548	53.7	1.2	0.8	44.4
			QALY	336 (49, 737)	0.01 (-0.02, 0.03)	38896	75.1	1.5	0.5	23.0
Main analysis (unadjusted)	87	92	Adherence	324 (-60, 727)	0.06 (-0.1, 0.2)	5625	73.9	3.9	1.3	20.9
			PHQ-9	324 (-60, 727)	0.01 (-0.2, 0.2)	31976	51.3	2.8	2.4	43.6
			QALY	324 (-60, 727)	-0.003(-0.03, 0.03)	-115778	40.2	2.3	2.9	54.6
Healthcare perspective*	87	92	Adherence	31 (-70, 181)	0.04 (-0.1, 0.1)	862	52.5	24.3	7.8	15.5
			PHQ-9	31 (-70, 181)	0.01 (-0.2, 0.2)	2729	37.2	17.7	14.4	30.8
			QALY	31 (-70, 181)	0.01 (-0.02, 0.03)	3592	51.8	24.8	7.3	16.1
Sensitivity analyses*										
Per Protocol analysis	64	87	Adherence	393 (27, 108961)	0.07 (-0.03, 0.2)	5553	87.4	2.1	0.3	10.2
			PHQ-9	393 (27, 108961)	-0.01 (-0.2, 0.2)	-52117	46.1	1.4	1.1	51.5
			QALY	393 (27, 108961)	0.01 (-0.02, 0.03)	58517	68.4	1.8	0.6	29.2
Complete cases	62	65	Adherence	241 (-34, 597)	0.02 (-0.1, 0.2)	11001	59.2	5.5	3.2	32.1
			PHQ-9	241 (-34, 597)	0.03 (-0.1, 0.2)	8559	58.6	5.6	3.2	32.7
			QALY	241 (-34, 597)	0.02 (-0.01, 0.05)	13363	82.9	8.0	0.8	8.4
Double intervention costs	87	92	Adherence	355 (73, 741)	0.04 (-0.1, 0.2)	9863	75.6	1.1	0.2	23.1
			PHQ-9	355 (73, 741)	0.01 (-0.2, 0.2)	31218	54.0	0.8	0.5	44.7
			QALY	355 (73, 741)	0.01 (-0.02, 0.03)	41094	75.5	1.0	0.3	23.1
Average salary for absenteeism	87	92	Adherence	647 (91, 324689)	0.04 (-0.1, 0.2)	18006	75.1	1.6	0.4	22.9
			PHQ-9	647 (91, 324689)	0.01 (-0.2, 0.2)	56992	53.7	1.2	0.9	44.3
			QALY	647 (91, 324689)	0.01 (-0.02, 0.03)	75022	75.0	1.6	0.4	23.0

*Models with costs as dependent variable adjusted for costs in the previous three months, baseline severity of depression and marital status. Models with adherence as dependent variable adjusted for age. Models with reduction of symptoms (20% or over reduction in PHQ-9) as dependent variable adjusted for comorbidities and presence of major depression. Models with quality adjusted life years (QALY) as dependent variable adjusted for age, baseline quality of life and marital status

Figure 2.4.2 Cost-effectiveness plane for adherence with antidepressant therapy (pharmacist intervention vs usual care) from the societal perspective. The central white dot indicates the point estimate of the incremental cost-effectiveness ratio

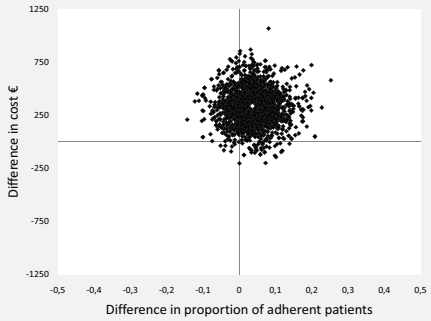
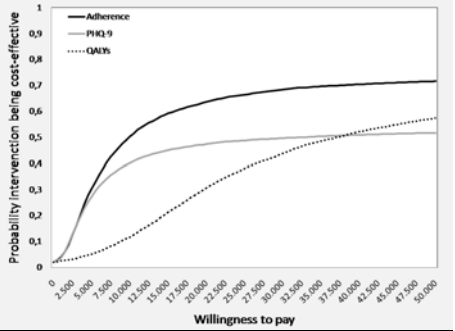


Figure 2.4.3 Cost-effectiveness acceptability curves for adherence with antidepressant therapy, remission of depressive symptoms (PHQ-9) and QALYs estimated using bootstrapping (societal perspective)



Cost-effectiveness acceptability curves

The CEACs (Figure 2.4.3) showed that the CPI was not likely to be cost effective compared with UC after 6 months. The probability of the intervention being cost-effective was 0.68 if the society is willing to pay €30,000 for one extra adherent patient, and of 0.71 for a willingness to pay (WTP) of €50,000.

In terms of remission of symptoms and QALY, if we take into account a WTP of €30,000 per extra remitted patient or QALT, the probability of the CPI is cost-effective in comparison with UC was 0.50 and 0.45, respectively and 0.52 and 0.58 if the WTP is set at €50,000.

2.4.3.2.2 Health system perspective

Cost-effectiveness and cost-utility

Since indirect costs were responsible for most of the difference in total societal costs between the groups, when the healthcare perspective was used the cost difference became much smaller. As a result the cost-effect pairs were more evenly distributed among the northern and southern quadrants in the CE plane (Figure 2.4.4). The ICER was €862 per extra adherent patient for the CPI compared with UC (Table 2.4.4).

Differences in both costs and number of remitted patients were small, resulting in an ICER of €2,729 per one extra remission of depression. The ICUR was also smaller using the health system perspective, being €3,592 per extra QALY.

Cost-effectiveness acceptability curves

From a health system perspective, the CPI was more likely to be cost effective after 6 months in comparison with UC than using a societal perspective (Figure 2.4.5).

Figure 2.4.4 Cost-effectiveness plane for adherence with antidepressant therapy (pharmacist intervention vs usual care) from the health care system perspective. The central white dot indicates the point estimate of the incremental cost-effectiveness ratio

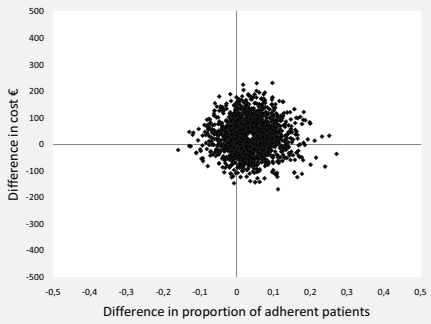
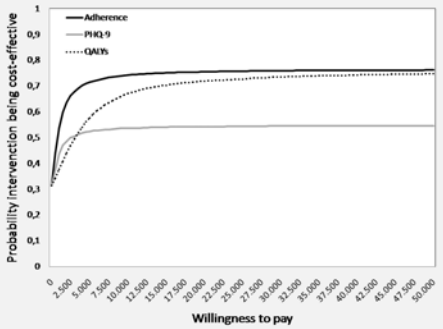


Figure 2.4.5 Cost-effectiveness acceptability curves for adherence with antidepressant therapy, remission of depressive symptoms (PHQ-9) and QALYs estimated using bootstrapping (health care system perspective)



The probability of the intervention being cost-effective is 0.75 if the willingness to pay is €12,000 for an extra adherent patient and €40,000 for an extra QALY. In terms of remission of symptoms, the maximum probability of CPI being cost-effective in comparison with UC (i.e. even if willingness to pay is an infinite amount of money) was 0.55.

2.4.3.3 Sensitivity analyses

Results of the sensitivity analyses were mainly in concordance with the main analyses and led to the same conclusions as the main analyses (Table 2.4.4).

In the PP analysis, costs differences were slightly larger than in the main analysis but effectiveness of the CPI was also larger in terms of adherence thus reducing the ICER (€5,553) and increasing the probability of CPI being cost-effective to 0.81 if WTP is €30,000. On the other hand, no difference in QALYs was observed in the PP analysis and consequently the ICUR increased (€58,517). The difference in the number of remitted patients in the PP was inverted, thus favoring the UC group. However the difference was still statistically non-significant and the effect was small so no relevant changes in the results were observed.

The complete case analysis showed smaller differences in adherence but the difference in costs was also reduced, not altering the results from the main analyses much.

Results of the sensitivity analyses in which the intervention costs were doubled or the average salary was used instead of the minimum salary did not differ from the main analysis.

2.4.4 Discussion

2.4.4.1 Main findings

The aim of the present study was to assess the cost-effectiveness and cost-utility after 6 months of a brief CPI compared to UC on the improvement of adherence, QALYs and clinical symptoms in primary care patients starting pharmacological treatment for depression.

The effectiveness analysis showed no statistically significant differences between groups in either adherence, depressive symptoms or QALYs. Total costs were higher in the CPI group, mainly as a consequence of increased costs in productivity losses. This had a considerable impact on the analyses conducted from a societal perspective. Cost-effectiveness planes and CEACs showed that, from the societal perspective, a brief CPI was not likely to be cost-effective in comparison with UC for any of the clinical outcomes used.

When the health system perspective was considered, the CEACs showed an increased probability (up to 0.75) of the CPI being cost-effective in terms of improvement of adherence and QALY. However, differences in costs and clinical effects were small, and the willingness to pay for an additional unit of effect should

be high to reach an acceptable probability of the CPI being cost-effective in comparison with UC.

2.4.4.2 Comparison with previous findings

Until now, to the best of our knowledge, only one study has been published on the cost-effectiveness of a pharmacist intervention for depression (25). Bosmans et al conducted a randomized controlled trial in The Netherlands in which a pharmacist intervention plus a take-home educational videotape were compared to UC for patients with depression initiating treatment with antidepressants. Bosmans and colleagues found no impact of the intervention on the improvement of adherence or clinical symptoms of depression. In their study, total costs were slightly higher in the intervention group but the difference was not statistically significant. As was the case in the present study, in the study by Bosmans et al indirect costs accounted for most of the difference in total costs between groups, although the difference between groups in indirect costs was not statistically significant.

Bosmans et al found little evidence supporting the cost-effectiveneness of a brief educative pharmacist intervention into clinical practice, which is consistent with the results observed in the present paper.

Schoenbaum and colleagues evaluated the impact of support medication adherence program that was implemented via the telephone by trained practice nurses (49). In this study, the Intervention group generated higher costs but differences were not statistically significant. No statistically significant differences in QALYs were observed between the intervention and UC groups and ICUR was €37,422 (adjusted to 2009 Euros). This result is in line with the results presented in the present paper showing that in terms of cost-utility, interventions implemented by community pharmacists are not cost-effective in comparison with UC when dealing with depressed patients who start antidepressant treatment.

2.4.4.3 Strengths and limitations

Economic evaluations are highly affected by sampling uncertainty. A possible limitation of this study is that sample size calculation was based on the main clinical outcome of the study, adherence to antidepressants. Therefore, the study could have been underpowered to detect differences in the cost-effectiveness analysis. However, to the best of our knowledge, our study has the largest sample size used to evaluate the cost-effectiveness of a pharmacist intervention in depressed patients.

Second, patients in the intervention and control group attended the same community pharmacies and that contamination of the control group could have occurred. This could have been prevented by performing a cluster randomization at the pharmacy level. To minimize the impact of this contamination, pharmacists were asked to be aware of contamination when attending patients in the UC

instead than at the patient level group and patients were asked not to share information with other patients participating in the study.

Third, the GPs that participated in the study could have had a special interest in the topic under study. Consequently, they could have conducted interventions to improve patients' adherence to antidepressants. Although this would have affected both UC and CPI groups, it could have limited the margin of improvement of the pharmacist intervention.

A fourth limitation is that some outcome measures (i.e. most of the information about healthcare utilization) were self-reported. Although the recall period was only 3 months, the information could have been affected by a recall bias. On the other hand, the recall bias should have affected equally both groups.

Fifth, a follow-up period of 6 months may be too short to be able to evaluate long term costs and effects of the intervention such as relapse of depression. Higher rates of adherence have been associated to a lower risk of relapse which could reduce the costs (15).

An important strength is that this was a naturalistic study with very wide inclusion criterion, which was conducted in two different populations and where the intervention was implemented by many different community pharmacists. This increases the generalisability of the results while this also could have introduced heterogeneity. Only half of the sample met DSM-IV criteria for major depression. Moreover, patients could decide whether to refill their prescription and move from one to another pharmacy in successive visits. Consequently, 26% of the patients in the intervention group did not receive the intervention as allocated. However, we think that this is representative of daily clinical practice and that this greatly improves the generalisability of the results.

Finally, the main clinical outcome, adherence to antidepressants, was measured using electronic pharmacy records. This method has two advantages: patients are unaware of the fact that their adherence to medication is being observed and information can be collected even when patients drop-out from the study, avoiding missing data for our primary outcome.

2.4.5 Conclusions

From a societal perspective, a brief CPI to improve adherence to antidepressants in patients initiating pharmacological treatment for depression was not cost-effective after 6 months follow-up when compared to UC. When the health care system perspective was considered, the CPI was more likely to be cost-effective but the CEAC showed that there was still substantial uncertainty surrounding the cost-effectiveness results and that the maximum probability of the CPI being cost-effective in comparison with UC was still low.

In view of the available evidence, we cannot recommend regular implementation this pharmacist intervention addressed to improve adherence to antidepressants

and conclude that low intensity pharmacist interventions are not cost-effective for depressed patients. The cost-effectiveness of more complex pharmacist's interventions needs to be evaluated before its implementation. In future studies, a longer follow-up period and the use of cluster randomization that limits contamination is recommended. Considering the uncertainty surrounding the costs in the sample size calculations is also necessary.

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Chapter 2

Section 5

Complementary analyses

Abstract

In this section of chapter 2, results that had not been submitted for publication but that can enrich the results and discussions of the present thesis are presented.

Objective

The aim of the present chapter is to evaluate the impact on the results of the systematic review on pharmacist interventions in depressed patients of the new evidence generated by the PRODEFAR study to evaluate the effectiveness of a pharmacist intervention in the improvement of adherence to antidepressants.

Methods

The quantitative synthesis of the systematic review presented in Paper 1 was updated using the information obtained in the randomized controlled trial presented in Paper 3. The ratio of adherent patients in each group was calculated using a chi-square test (unadjusted data) and was included in the quantitative synthesis of the evidence. A random effects model was used to calculate pooled odds ratios. Publication bias (funnel plot and Egger test) and statistical heterogeneity (Cochran Q test and I^2 statistic) were calculated. Subgroup analyses were conducted to assess clinical heterogeneity by analysis strategy; diagnostic procedure; type of pharmacist conducting the intervention; and adherence measure.

Results

After including the results of the PRODEFAR study, the pooled analysis showed a statistically significant effect of the intervention on adherence to antidepressants (odds ratio = 1.563; 95% CI 1.211 to 2.017; $p < 0.001$). Number needed to treat was 9, indicating that pharmacists need to provide the intervention to 9 patients in order to get an extra adherent patient. We did not observe significant heterogeneity between the included studies. In the subgroup analysis, no statistically significant differences were observed between subgroups. The subgroup considering interventions conducted by community pharmacists showed no statistically significant results.

Conclusion

A pharmacist intervention showed to be effective in the improvement of adherence to antidepressants in outpatients with depression.

2.5.1 Rationale

According to Professor Clarke, from The Cochrane Collaboration, "If a new clinical trial is to be justifiable both scientifically and ethically it should be designed in the light of an assessment of relevant previous research, ideally a systematic review. When its findings are reported, these should be set in the context of updated reviews of other, similar research" (1;2).

The aim of the present chapter is to evaluate the impact on the results of the systematic review on pharmacist interventions in depressed patients (presented in Chapter 2) of the new evidence generated by the PRODEFAR study that evaluated the effectiveness of a pharmacist intervention in the improvement of adherence to antidepressants (results presented in Chapter 4).

2.5.2 Methods

The quantitative synthesis of the systematic review presented in Paper 1 was updated using the information obtained in the randomized controlled trial presented in Paper 3.

In Paper 3, the results presented in relation to adherence were derived from the multilevel mixed-methods models and were expressed in terms of probability of remaining adherent after 6 months follow-up. To facilitate inclusion of the information about adherence in the meta-analysis, the ratio of adherent patients in each group was calculated using a chi-square test (unadjusted data).

This information, together with the sample size of each group, was included in the quantitative synthesis of the evidence.

Pooled odds ratios and 95% confidence intervals were calculated by means of a random effects model. And probabilities of remaining adherent in each group were used to compute the number needed to treat. The Cochran Q test and I^2 statistic were used to assess statistical heterogeneity. Publication bias was assessed using the funnel plot and Egger test.

Subgroup analyses were conducted to assess clinical heterogeneity. The sources of heterogeneity tested were: analysis strategy (intent-to-treat or per-protocol); diagnostic procedure used to evaluate depression in the included patients (validated diagnostic procedure or clinical); environment where the pharmacist is conducting the intervention (community pharmacy or pharmacy service); and main adherence measure (pharmacy records, electronic pill container or self-reported adherence).

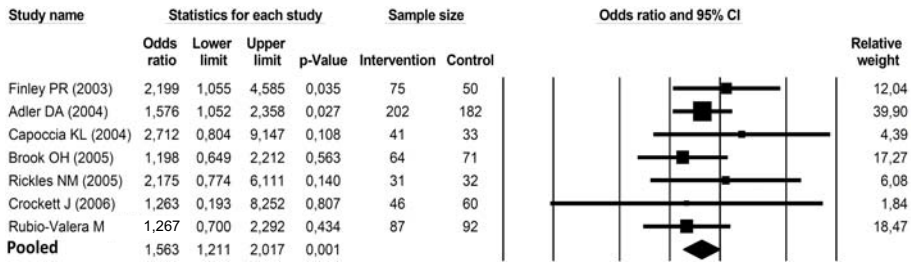
Analyses were performed using Comprehensive Meta-Analysis, version 2, software (Biostat, Englewook, NJ).

2.5.3 Results

2.5.3.1 Meta-analysis

After including the results of the PRODEFAR study (Paper 3), the pooled analysis showed a statistically significant effect of the intervention on adherence to antidepressants (odds ratio = 1.563; 95% CI 1.211 to 2.017; p < 0.001) (Figure 2.5.1). Number needed to treat was 9, indicating that pharmacists need to provide the intervention to 9 patients in order to get an extra adherent patient. We did not observe significant heterogeneity between the included studies (Cochran Q = 3.534; df = 6; p = 0.739; I^2 <0.001; t^2 <0.001).

Figure 2.5.1 Meta-analysis results



2.5.3.2 Sub-group analysis

No significant differences were observed in the effectiveness to improve adherence to antidepressants of the pharmacist intervention after grouping by analysis strategy, diagnostic procedure for depression, setting of the pharmacist who conducted the intervention or adherence measure used to conduct the analysis (Table 2.5.1).

With the exception of two subgroup analyses, all subgroup analysis showed that the pharmacist intervention had statistically significant effects or close to significance (as in the case of where the clinical diagnosis was used to assess depression [P-value = 0.057]). The two subgroup analysis that showed non-statistically significant results were the subgroup where the intervention was implemented by a community pharmacist or where adherence was measured with an electronic pill container (Table 2.5.1). The latter subgroup depended exclusively on one study that showed no-statistically significant results (3).

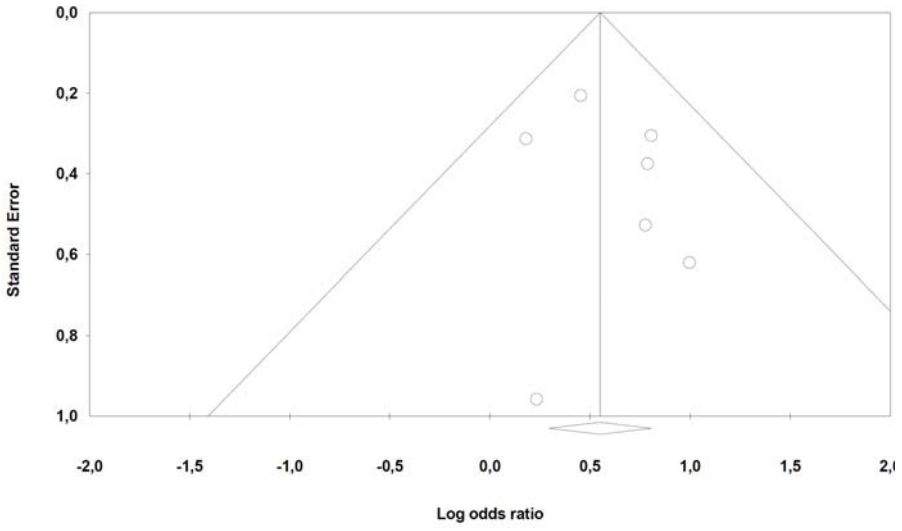
The funnel plot of standard error against the natural logarithm of the odds ratio (Figure 2.5.2) and the Egger test for assessing bias (p = 0.493) suggested that there was little publication bias in the selection of studies.

Table 2.5.1 Subgroup analyses by strategy of analysis, type of diagnosis, setting of pharmacist implementing the intervention and main adherence measure

Subgroup analysis	***Pooled results***			
	Odds ratio	*Lower limit**	*Upper limit**	*p-Value*
Analysis strategy				
Intent-to-treat	1.506	1.058	2.143	0.023
Per protocol	1.628	1.126	2.353	0.010
Main diagnostic procedure				
Clinical	1.420	0.989	2.039	0.057
VPI	1.718	1.199	2.459	0.003
Setting of pharmacist				
Community pharmacy	1.336	0.909	1.965	0.141
Pharmacy service	1.765	1.257	2.479	0.001
Main adherence measure				
EPC	1.198	0.649	2.212	0.563
Pharmacy records	1.662	1.091	2.532	0.018
Self-reported	1.645	1.130	2.393	0.009

*95% Confidence Interval
EPC = electronic pill container; VPI = validated psychiatric instrument.

Figure 2.5.2 Meta-analysis results



2.5.4 Discussion and conclusions

Discussion generated by these complementary analyses and conclusions drawn from them will be presented in Chapter 7 (General discussion) and Chapter 8 (Conclusions), respectively.

2.5.5 References

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Chapter 3

General discussion

3.1 Does the systematically reviewed evidence support the implementation of pharmacist care to improve adherence to antidepressant medication?

Based on the data presented in the present thesis (Chapter 2: Paper 1 and Section 5), we can affirm that the pharmacist is a professional qualified to improve adherence to medication in depressed patients. When compared to usual care, the probability of patients who received a pharmacist intervention remaining adherent was 0.61 vs 0.50 for the usual care group (OR = 1.56) resulting in a number of patients needed to treat of 9 (Section 5). These results are similar to the ones reported by previous systematic reviews that evaluated collaborative care interventions addressed to depressed patients (1;2). The selection criteria of these reviews were broad and covered collaborative care interventions that included various professionals (i.e. general practitioners, psychiatrists, psychologists, nurses or pharmacists). They reported that patients that received the collaborative care interventions had a probability of 0.65-0.66 of remaining adherent. This translates into a number needed to treat of 7 patients.

In view of these results, we can conclude that a pharmacist intervention could be a good strategy to improve patients' adherence to antidepressants in primary care.

3.1.1 Is it clinically relevant to improve adherence to antidepressants?

Pharmacists are experts in pharmacological treatment. For this reason, when pharmacists interventions addressed to patients with depression are designed, they are focused on the improvement of the management of medication, mainly in the enhancement of adherence to medication (3-7).

Adherence is an intermediate variable in the clinical process of recovery from depression. Therefore, improving adherence will only be valuable if it brings clinical benefits to the patient. However, we do not know how the improvement in adherence achieved by an intervention will affect the patient's clinical symptoms.

As pointed out in Chapter 1, adherence is, per se, a complex process that is influenced by many factors. Consequently, the translation of adherence into clinical benefits is a more complex process and it, in turn, is affected by many other factors.

The expectation that an improvement in adherence to medication will immediately be reflected in an improvement in clinical symptoms will only be reasonable if we accept that, at the very least, the diagnosis is correct, the selection of treatment is appropriate, the medication is effective, and the clinical course of depression is only affected by the medication prescribed. As we have seen, depression is a complex disease and both prognosis and treatment decisions are affected by a wide range of factors which are sometimes difficult to control.

In addition, non-adherence is sometimes motivated by clinical improvement. This makes it difficult, in a short-term period, to observe the impact of a pharmacist intervention addressed to improve adherence to antidepressants in the patient's depressive symptoms (8-10).

However, a positive association between improving adherence to antidepressant drugs and amelioration of depressive symptoms has been reported (1), suggesting that clinical improvement is mediated through changes in adherence to antidepressants. Moreover, adherence to antidepressants has shown to be associated with a reduction in relapse and costs (11-13).

Furthermore, results presented in Paper3 showed that a community pharmacist intervention (Annex I) was effective in the improvement of patient health related quality of life which is a measure of the global patient status.

3.1.2 Which type of pharmacist should take care of depressed patients?

Subgroup analysis presented in Paper 1 and Section 5 of Chapter 2 showed some differences between the interventions conducted by pharmacists in a community pharmacy (4-6) and those in a pharmacy service (3;7;14).

No statistically significant differences were found in terms of improvement of patient adherence to antidepressants when subgroup analyses were conducted. However, when pooled separately, the pharmacist intervention showed a statistically significant improvement in adherence to antidepressants when conducted by a pharmacist in the pharmacy service of a hospital or primary care center but not when it was performed in a community pharmacy. This is in agreement with the results of our study (Paper 3).

This result could be due to a lack of power to detect differences in the subgroup analysis of community pharmacist interventions or to the differences in the interventions implemented in the two settings, as explained below.

3.1.2.1 Limited power to detect differences

Several sources of heterogeneity existed in the studies conducted in the community pharmacy that were not present in the studies conducted in the pharmacy service.

Firstly, in community pharmacy studies, many different pharmacies participated. Since the characteristics of the community pharmacy (i.e. number of pharmacists, type and number of additional services offered in the pharmacy) can vary, the service provided may have differed from pharmacy to pharmacy. Only one pharmacy service was engaged in the study when the studies were conducted in hospitals or primary care health centers.

Similarly, the number of pharmacists conducting the intervention was also much smaller in the studies conducted in the pharmacy service compared with those conducted in community pharmacies. In the studies conducted in a pharmacy service, the number of pharmacists engaged in the study ranged from 2 to 5. On the other hand, in the studies conducted in community pharmacies, the number of pharmacists implementing the intervention ranged from 14 to almost 60. Consequently, even patients that attended the same pharmacy could have been attended by different pharmacists.

The researchers implementing the studies conducted in a community pharmacy setting tried to minimize the impact of this source of bias by training the community pharmacists. Nonetheless, it is still likely that the heterogeneity of the intervention performed in the studies conducted in a pharmacy service was lower than that of the studies conducted in a community pharmacy and this could have introduced heterogeneity in the results obtained. However, this has a positive aspect since the evidence generated by the studies conducted in community pharmacy has higher external validity than that generated in a pharmacy service.

Finally, the overall sample size of the studies conducted in pharmacy services was higher than in the studies conducted in the community pharmacy. This, together with the greater heterogeneity present in the studies conducted in the community pharmacy, could have limited the power of the meta-analysis to detect statistically significant differences. In fact, when the results of the PRODEFAR study were added to the analysis (Chapter 2: Section 5), the community pharmacy subgroup pooled results showed a tendency towards a statistically significant result, supporting the hypothesis of a lack of power to detect differences in this group.

3.1.2.2 Differences in the intervention provided

Another factor that could have influenced the difference observed between the community pharmacists and those in a pharmacy service is the intensity of the intervention. Interventions made in the pharmacy services were more intensive and included more components than those carried out in the community pharmacy. Among interventions addressed to depressed patients, those which are more intensive and consist of a larger number of elements involved have shown better results (15;16).

In this regard, because of the characteristics of the service, pharmacists in a pharmacy service can have advantages over community pharmacists when administering this type of intervention.

In a clinic pharmacy service, the pharmacists can get access to the patient's clinical history at the center. The pharmacist can use it to review the patients' history and to approach them, facilitating the continuity in the service and making it easier to monitor them. As part of the interventions conducted in the pharmacy settings, pharmacists could facilitate patient access to the physician or to the mental health specialist and make or recommend changes in antidepressant medication.

In the community pharmacy setting, the patient has no clinical history and is not affiliated to the pharmacy in any way. This means that he/she can move from one pharmacy to another, hampering the continuity of care and the follow-up of the patient. Furthermore, since the pharmacist has no access to the patient's clinical and pharmacological history, there is limited clinical information about the patient which, in turn, restricts the options in terms of complexity of the intervention.

The relationship between the community pharmacist and the general practitioner is complicated and, consequently, it is unusual. A number of barriers that hinder collaboration between the general practitioner and the community pharmacist

have been reported. Some of them have to do with professionals' attitudes and beliefs and others are related to organizational and legal aspects. One of the organizational and legal aspects suggested as a barrier to collaboration between general practitioners and community pharmacists in Spain is specifically related to the fact that the number of pharmacies in one area is large and patients have no formal link to any particular one of them, thus impeding collaboration (17).

If a collaborative relationship does not exist between the general practitioner and the pharmacist, the latter cannot suggest changes in the pharmacotherapy to the general practitioner or facilitate access of the patient to it. Furthermore, community pharmacists are not allowed to introduce adjustments or changes in the therapy for depression. As a result, the community pharmacist has little room for manoeuvre, making it difficult to conduct a more intensive intervention.

Another negative consequence of this limited engagement of the patient with the pharmacist is that it prevents the establishment of a good patient-pharmacist relationship, which could make it difficult for the patient to follow pharmacists' advice when changing his/her behavior (18).

3.2 Is a pharmacist intervention conducted in Spain effective in the improvement of adherence to antidepressants and patient wellbeing?

3.2.1 Impact of the pharmacist intervention on adherence

The PRODEFAR intervention, developed by our research team (Annex I), proved not to be effective in the improvement of adherence to antidepressants (Paper3). However, patients in the intervention group tended to adhere more than those in the control group and the difference in adherence between groups, although not statistically significant, was clinically relevant (small number needed to treat in order to get a new adherent patient).

The naturalistic nature of the study design led to a high number of patients not receiving the intervention as intended (26% in the intervention group) because they decided not to refill the medication (7%) or they decided to refill it in a non-participating community pharmacy (19%). When the results of the study were analysed as a per protocol (PP) strategy, patients in the intervention group showed a higher probability of remaining adherent after 3 and 6 months after the initiation of treatment than patients in the control group and the difference was close to reaching statistical significance (p=0.055).

The results of our study are consistent with those reported by Brook and Rickles in The Netherlands and in the USA, respectively (4;5). Brook and Rickles did not find differences between groups in adherence in the intent to treat analysis but reported statistically significant differences between groups when they conducted a PP analysis. However, both studies used a per protocol definition that considered patients in the intervention group that received at least 3 intervention contacts with the community pharmacist. This definition of PP might have introduced bias since patients who received less than 3 intervention contacts (patients excluded

from the analysis in the intervention group) were less likely to adhere to antidepressants.

3.2.2 Impact of the pharmacist intervention on severity of symptoms

The pharmacist intervention had no impact on the severity of depressive symptoms measured using the PHQ-9. However, the main objective of the intervention was to improve adherence to antidepressants and, as explained in point 3.1.1 of the present chapter, the translation of the improvement in adherence into improvement in symptoms is not direct and can be affected by many factors.

3.2.3 Impact of the pharmacist intervention on health related quality of life

When the effects of the intervention on health related quality of life were evaluated, contrary to what was observed in a previous study (14), patients in the intervention group showed more improvement in self-perceived health related quality of life than patients in the usual care group. Health related quality of life is a measure of global patient status and can help us to take decisions most suitable to patient's needs.

Although statistically significant, the impact on health related quality of life was small. However, the intervention was mainly focused on medication and, consequently, we believe that its impact on health related quality of life is an aspect that deserves further exploration. We hypothesized that the conversations between pharmacists and patients could have improved patients' knowledge about the medication and the disease, improving their confidence in the medication and reinforcing the concept of depression as a disease, thus reducing sense of stigma. This could have been reflected in a more positive perception of their mental quality of life.

3.2.4 Shortcomings and barriers to a better pharmaceutical intervention

Although we found no statistically significant differences between groups in adherence, in the PP analysis the difference almost reached statistical significance. Furthermore, a considerable number of patients in the intervention group (26%) did not receive pharmacist care. Therefore, we think that the power of the study may be limited.

Moreover, previous reviews concluded that the interventions that show the best results in depressed patients are those that combine patient education, active monitoring and referral to the physician (15;16). The intervention evaluated was a low intensity intervention. The original design of the PRODEFAR intervention (Annex I) considered that the pharmacist would monitor the progress of the patient in subsequent visits to the pharmacy and, if necessary, refer the patient to the general practitioner.

However, during the development of the study, a number of barriers that complicated the pharmacist's work arose. Since there is no formal affiliation between the patient and the pharmacy, it was not possible for the pharmacists to

automatically identify the patients that needed pharmacist support for their antidepressant treatment. Furthermore, this also limited the follow-up of the patients if they decided to move from one pharmacy to another in subsequent visits.

With respect to facilitating patient access to the general practitioner, on several occasions the pharmacists identified a need for further information from the doctor or referral to them. In many cases, the pharmacists contacted the research team instead of using a referral form or a telephone call to the doctor. This makes us think that there were no well-established communication channels between the pharmacists and the general practitioners. To achieve a better understanding of this problem we developed a qualitative study to explore factors affecting pharmacist/physician collaboration (17). This study identified the professionals' perception of the usefulness of collaboration, the Primary Care Health Center manager's interest in collaboration, the professionals' attitude and geographic and legislative aspects as the key factors in initiating collaboration between the pharmacist and the physician. These factors were affected by economic and organizational aspects (i.e. PCHC resources) and by professionals' opinions and beliefs (i.e. opinions about the other professional group).

Patients with depression need integrated care. Consequently, if we want to implement interventions through the community pharmacy that greatly affect their outcomes, it will be necessary to first introduce a series of improvements in the conditions in which the pharmacists are currently working, increasing the currently available tools for pharmaceutical care and promoting the integration of the pharmacists into the primary care team.

3.3 Is a pharmacist intervention conducted in Spain cost-effective in the improvement of adherence to antidepressants and patient wellbeing?

The results presented in Paper 4 indicate that the PRODEFAR intervention was not cost-effective. The patients that received the pharmacist intervention were associated with increased costs but there were no statistically significant differences in adherence or clinical symptoms.

Since most of the difference in costs was due to productivity losses, better results were obtained when the health care system perspective was adopted in comparison to the societal perspective. When the health system perspective was considered, the cost-effectiveness acceptability curves showed a probability over 0.75 of the pharmacist intervention being cost-effective in terms of improvement of adherence and QALY. However, differences in costs and clinical effects were small, and the willingness to pay for an additional unit of effect would need to be high to reach an acceptable probability of the CPI being cost-effective in comparison with UC.

This result is concordant with the results obtained by Bosmans and colleagues in The Netherlands (19). They observed that an educative pharmacist intervention

plus a take-home educational videotape were not cost-effective, when compared with usual care, in either improvement of adherence or clinical symptoms.

Previous studies reported an association between improved adherence and reduction of relapse and costs in a long term period (20-22). We could not evaluate the cost-effectiveness of our pharmacist intervention in the long term since the information was limited to 6 months of follow-up.

To the best of our knowledge, only two randomized controlled trials on pharmacist interventions with depressed patients evaluated the cost-effectiveness of a pharmacist intervention; the one conducted in the Netherlands by Bosmans (19) and the one presented in Chapter 3. Both studies evaluated low intensity pharmacist interventions conducted by community pharmacists. Little is known about the cost-effectiveness of pharmacist interventions conducted in pharmacy services, which tend to be of higher intensity. Finley and colleagues are currently conducting a randomized controlled trial that will include an economic evaluation of a high intensity pharmacist intervention conducted by pharmacists in a pharmacy service (23).

In the two studies already published (19;Paper 4) the sample size calculation was based on the detection of differences in adherence, which was the main objective of the studies. Due to the high uncertainty surrounding costs, the cost-effectiveness analyses could have been underpowered. Inappropriateness of sample size has been pointed out as one of the main problems that researchers face when conducting economic evaluations alongside randomized controlled trials (24). In the future, studies should be designed specifically as a vehicle for economic evaluation of the impact of pharmacist care.

3.4 Future research

Future research needs to be developed in order to evaluate a more complex and intensive pharmacist intervention in community pharmacy. It will be necessary to take into account all the limitations identified here and to develop strategies that facilitate the attachment of the patient to the pharmacy and the establishment of a relationship between the pharmacist and the patient. Also needed, will be an improvement in the collaborative relationship between the pharmacist and the general practitioner, and the integration of the pharmacist into the primary care team. This should enable access to some parts of the patient's clinical history to help patients with depression.

For the economic evaluation of this intervention, a longer follow-up period is required (at least 12 months). Considering the uncertainty surrounding the costs in the sample size calculations is also necessary.

To sum up, further research is essential to study whether community pharmacist interventions in a fully collaborative environment are capable of producing more significant results in improving adherence to antidepressants and reducing both patient burden and costs.

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Chapter 4

Conclusions

Conclusions

1. A pharmacist intervention could be a good strategy to improve patients' adherence to antidepressants in primary care.

2. The evidence supporting the pharmacist intervention in depressed patients is still limited, especially in community pharmacy and outside the United States of America.

3. A low intensity community pharmacist intervention, such as the PRODEFAR intervention, proved to be ineffective in improving patients' clinical symptomatology or adherence to antidepressants.

4. A low intensity community pharmacist intervention, such as the PRODEFAR intervention, was shown to be effective in improving the patient's health-related quality of life.

5. A brief community pharmacist intervention, such as the PRODEFAR intervention, proved not to be cost-effective in comparison with usual care in the improvement of adherence, depressive symptoms and quality adjusted life years.

Annex I

Community pharmacist intervention in depressed primary care patients (PRODEFAR study): development and description of the intervention

This Annex presents the PRODEFAR intervention that was evaluated in Chapters 4 and 5 and the methods used to develop it.

I.i The PRODEFAR intervention

The research team's aim was to develop an intervention addressed to depressed patients treated in primary care that could be implemented by community pharmacists in Spain. The focus of the intervention was improvement of patients' behavior related to medication consumption, mainly adherence, with the ultimate objective of reducing the severity of depressive symptoms and improving the patient's quality of life.

I.ii Intervention design

A narrative review of the scientific literature was conducted to identify: 1) the main causes of non-adherence, 2) the strategies that had been demonstrated to improve adherence; and 3) the components of previous published pharmacist interventions that had been shown to improve patient adherence to antidepressants. The main results of this review are presented in Table I.i.

The PRODEFAR intervention was designed by a multidisciplinary team composed of pharmacists, general practitioners and psychiatrists with experience in research and community treatment of depressed patients. The information gathered in the review was presented to the group for discussion and identification of the best strategies, based on their own experience, which could be implemented in the community pharmacy to deal with patients initiating treatment with antidepressants.

I.iii The PRODEFAR intervention

The intervention had to be applied to the patient every time that he/she attended the community pharmacy to refill his/her antidepressant medication prescriptions or to ask for counseling in the course of the 6 months of the study.

The first prescription of antidepressants (which corresponded to the initiation of treatment) was considered to be the most important one. Consequently, the first contact with the pharmacist was the most intensive and the one that took the longest time to conclude. In the following sessions, the pharmacist had to monitor the patient's progress and reinforce the information delivered in the first contact session.

I.iii.a First contact with the patient in the PRODEFAR intervention

The first time that the patient attended the pharmacy, the pharmacists registered the patient's contact details. In a separate folder and using an anonymous study code to ensure patient's confidentiality, the pharmacists opened a patient's folder that was used to guide the intervention and register the interventions delivered to the patient in the community pharmacy.

Table I.i Results of the narrative review on adherence to antidepressants
Most relevant causes of non-adherence identified in the literature
Aversion to drug use, negative attitude to treatment and disbelief or lack of confidence in the efficacy of the drug (1-9).
Fear of the occurrence / occurrence of adverse effects in both the short and long term (2-7;9-11).
Delayed onset of action of antidepressant medication (2;5;9).
Disagreement of the patient with the diagnosis (1;3;7;8).
Feeling better and perceiving that the medication is no longer needed (7;9;10).
Reduction of self-care as a consequence of the depressive symptoms (5;9;10).
Refusal to accept the disease or the treatment associated with stigma (5;9;10).
Lack of family support or negative influence of social environment (5;9).
Patient's sociodemographic characteristics (being male, separated, divorced or widowed, being young or being older than 60 years, lower educational level, …) (4-9;11;12).
Strategies that improve patient adherence and medication-related behavior
To discuss the side effects of the treatment with the patient, as well as the benefit-risk balance of the treatment, before the initiation of the treatment and as it progresses (1;5;7;9;12).
To warn the patient about the risk of appearance of symptomatology if he/she forgets to take the medication (13).
To communicate explicitly to the patient the approximate duration of the treatment (5;9).
To introduce changes in the pharmacological treatment when necessary (5).
To facilitate communication and the access to the physician (1;5;14).
To actively monitor the patient (111;115)
Previous interventions conducted by pharmacists to improve adherence to antidepressants
To help patients understand and accept that depression is a disease and to improve their knowledge about the disease (10;15).
To make patients aware of the fact that depression can be treated and cured with antidepressants and to improve their knowledge about the treatment: mechanism of action, delay of the onset of action, non-addictive nature of the medication… (2;9;10;14-16).
To explain to patients how to properly use their antidepressant medication, reinforcing the need to take it daily and to continue the treatment even when they are feeling better (2;16)
To facilitate information about the benefits of taking the antidepressant medication, encouraging the patient to adhere to the appropriate medicine-taking habits (2;14;15).
To inform the patient about the potential side effects (2;9;15;16)explaining that these may not always appear and that, in most cases, the manifested side effects are not a cause for alarm (16) and disappear in few weeks (9).
To insist on the importance of not abandoning the medication without notifying the physician (15;16).
To invite the patient to consult without hesitation the pharmacist/physician (10;16).
To help the patient to adapt to their daily life routine the consumption of the medication (10).

Table I.ii shows the points included in the patient's folder that guided the first pharmacist intervention with the patient in the community pharmacy. The patient's folder included a semi-structured guide. When the pharmacists had discussed a

Table I.ii Topics to discuss with the patient in the first intervention contact

Patient knowledge and education about medication

□ Name of the medication
What is the name of your antidepressant medication?

□ Reasons for taking the medication and patient agreement
Do you know why you are supposed to take this medication? Do you agree?

□ Medication posology and dose
Do you know how much to take and how often?

□ Expected duration of treatment
Do you know for how long you should be taking your medicine?

□ Expected benefits
What benefits do you and your therapist expect to get from this treatment?

□ Missed doses
Do you know what to do in case you forget to take one pill?

□ Storage
Do you have any doubts about how to store your medication?

□ Interactions with medication/food
Are you worried about any medicine or food that you are taking and how it could interact with your new treatment?

Key points of support to the patient

□ Is it clear why you have to take antidepressant drugs?
You have a disease. If you were a diabetic, would you refuse to take insulin?

□ Inform on the benefits of taking medication correctly
Antidepressants are safe and effective. If you are consistent in your treatment and remember to take the medication every day you will notice that the symptoms improve more quickly.

□ Do you know when the medication starts to take effect?
Due to the characteristics of the drug and the disease, you will not start noticing an improvement until 2 to 4 weeks.

□ Do you know whether the treatment is supposed to conclude once you feel better?
Possibly, you will notice an improvement after few weeks of treatment. However, the antidepressant treatment must continue for several months, at least 6, in order to ensure total remission of symptoms and avoid relapse.

□Do you think that antidepressants are addictive?
Despite the popular believe about the addictive nature of antidepressants, the medicine you have been prescribed is safe, and cannot cause addiction.

□ Discuss the possible adverse effects as well as the risk-benefit balance
□ The adverse effects do not always appear and, in most cases, are not a cause for alarm

□Adverse effects lose intensity after a few weeks
Antidepressants affect every patient in a different way so not all patients experience side effects. If they appear, you must know that most of side effects occur at the beginning of the treatment and are of low intensity. Their intensity will decrease with time and they will probably disappear in few weeks. The most usual side effects of your medication are…

□Do you know what to do in case you experience any side effects?
Even if side effects occur it is important that you do not abandon the medication. The side effects will disappear after some time and you will feel an improvement in symptoms. If you experience a side effect that worries you, do not hesitate to contact us or your physician to try to find a solution to it that does not involve giving up on the healing process.

□ Invite the patient to visit the pharmacy if he/she has any queries or incidences.
Do not hesitate to contact us if you feel you need to. I am here to help you and to make sure that you get the most from your medication in the safest way. If you want to talk to me, my working hours are...

topic or issue in the guide he/she had to tick a box to register it. The order in which the topics were addressed could be modified to fit the natural progress of the interview. However, all issues had to be discussed to ensure consistency in the intervention.

The list of topics included examples of sentences that the pharmacists could use with the patient and to clarify what exactly needs to be stressed at each point.

Pharmacists, prior to participating in the study, received 8 hours of training about PRODEFAR. The training followed a manual created for the study and was accredited by the Catalonian council of continuous pharmaceutical training (*Consell Català de la formació farmacèutica contínua*) (Reference Number: 09F00676). Furthermore, all the pharmacists had a handbook with a summary of how to implement the intervention and what to discuss with the patient at each stage.

The two main points of the intervention were (see TableI.ii):

> **Patient knowledge and education about medication**: In the first part of the intervention the pharmacists had to make sure that the patient had all the necessary information about his/her medication.
>
> **Key points of support to the patient**: In the second part of the first intervention guide, a list of topics related to the medication that had been demonstrated to improve adherence when discussed with the patient, were listed. Pharmacists were asked to pay attention to possible patient's skeptical remarks in relation to depression and antidepressants. In patients with a skeptical attitude, pharmacists were instructed to focus more on the reinforcement of the concept of depression as a disease as well as highlighting the benefits of the treatment.

Furthermore, pharmacists had to answer any question that the patient spontaneously generated and register it.

I.iii.b Follow-up contact with the patient in the PRODEFAR intervention

Every time the patient attended the pharmacy after the first visit, the pharmacist was instructed to monitor the patient's progress and review some of the key patient support points. Table I.iii lists the topics that were included in the folder guide for discussion with patients during follow-up visits.

Most of the key patient support points had been discussed during the patient's first visit to the pharmacy. Therefore, the patients who had been educated the most about the treatment might find it tedious to discuss the topics of the first interview again. On the other hand, patients with more medication adherence difficulties could need a reminder of the intervention. For these reasons, pharmacists were asked to evaluate the patient's knowledge and only offer further clarification if they detected that patients had problems in relation to their medication.

In the case that a serious problem related to medication appears during the patient follow-up process, pharmacists could refer patients to the general practitioner by using the standard referral channels.

Table I.iii Topics to discuss with the patient in the follow-up intervention contacts

Key points of support to the patient

□ Is it clear why you have to take antidepressant drugs?

You have a disease. If you were a diabetic, would you refuse to take insulin?

□ Can you tell me what the consequences of taking the medication incorrectly are?

Antidepressants are safe medications, if you remember to take them regularly you will notice that your symptoms will improve faster.

□ (ONLY DURING THE FIRST MONTH) Do you know when the medication starts to take effect?

Due to the characteristics of the drug and the disease, you will not start noticing an improvement until 2 to 4 weeks.

□ How long do you think the treatment will last?

Possibly, you will notice an improvement after a few weeks of treatment. However, the antidepressant treatment must continue for several months, at least 6, in order to ensure total remission of symptoms and avoid relapse.

□ ¿Do you think that antidepressants are addictive?

Despite the popular believe about the addictive nature of antidepressants, the medication you have been prescribed is safe, and none of them can cause addiction.

□ Since the last visit, did any new adverse effect occur that worries you?

The effect of antidepressants is different for every patient, and not all patients experience side effects. If side effects appear, you must know that most of these effects take place at the beginning of the treatment, are of low intensity and their intensity will decrease in time, and will probably disappear in a few weeks.

□ Do you know what to do in case you experience any side effects?

Even when side effects occur it is important that you do not abandon the medication since these adverse effects will disappear after some time and you will feel an improvement in your symptoms. If you experience any side effects that worry you, do not hesitate to contact us or your doctor to try to find a solution to it that does not involve giving up on the healing process.

□ Invite the patient to visit the pharmacy if he/she has any queries or incidences.

Do not hesitate to contact us if you feel you need to. I am here to help you and to make sure that you get the most from your medication in the safest way. If you want to talk to me, my working hours are...

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Annex II

Publications not included in the thesis

1. Rubio-Valera M, Fernández A, Luciano JV, Hughes CM, Pinto-Meza A, Moreno-Küstner B, Palao DJ, Haro JM, Serrano-Blanco A. **Psychotropic prescribing in Catalonia: results from an epidemiological study.** Fam Pract. 2012 Apr;29(2):154-62. Epub 2011 Sep 15.

2. Rubio-Valera M, Jové AM, Hughes CM, Guillen-Solà M, Rovira M, Fernández A. **Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study.** BMC Health Serv Res. 2012 Jul 7;12(1):188. [Epub ahead of print]

3. Fernández A, Rubio-Valera M, Bellón JA, Pinto-Meza A, Luciano JV, Mendive JM, Haro JM, Palao DJ, Serrano-Blanco A; DASMAP investigators. **Recognition of anxiety disorders by the general practitioner: results from the DASMAP study.** Gen Hosp Psychiatry. 2012 May-Jun;34(3):227-33. Epub 2012 Feb 16.

4. Fernández A, Mendive JM, Salvador-Carulla L, Rubio-Valera M, Luciano JV, Pinto-Meza A, Haro JM, Palao DJ, Bellón JA, Serrano-Blanco A; DASMAP investigators. **Adjustment disorders in primary care: prevalence, recognition and use of services.** Br J Psychiatry. 2012 May 10. [Epub ahead of print]

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Psychotropic prescribing in Catalonia: results from an epidemiological study

Maria Rubio-Valera[a,b,*], Ana Fernández[a,b], Juan V Luciano[a,b], Carmel M Hughes[c], Alejandra Pinto-Meza[a,b], Berta Moreno-Küstner[b,d,e], Diego J Palao[f], Josep Maria Haro[a,g] and Antoni Serrano-Blanco[a,b]

[a]Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain, [b]Red de Investigación en Actividades Preventivas y Promoción de la Salud (RedIAPP), Spain, [c]Clinical and Practice Research Group, School of Pharmacy, Medical Biology Centre, Queen's University Belfast, Belfast, UK, [d]Unidad de Investigación, Distrito Sanitario Málaga, Fundación IMABIS, Málaga, Spain, [e]Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Universidad de Málaga, Málaga, Spain, [f]Servei de Salut Mental, Corporació Sanitaria i Universitaria Parc Taulí, Universidad Autónoma de Barcelona, Sabadell, Spain and [g]Centro de Investigación Biomédica en Red en Salud Mental (CIBERSAM), Spain.
*Correspondence to Maria Rubio-Valera, Fundació Sant Joan de Déu, Research and Development Unit, C/Picasso 12, 08830, Sant Boi de Llobregat, Barcelona, Spain; E-mail: mrubio@pssjd.org

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Background. Mental disorders (MDs) are mainly treated in primary care (PC), where psychotropic drug (PSD) prescribing is highly prevalent. Prescription of PSD is associated with clinical and non-clinical factors.

Purpose. To describe the patterns of PSD prescribing over a 12-month period and to determine the factors associated with this in a PC population.

Methods. Cross-sectional study. Data were collected on 3815 patients, via patient interview, on sociodemographics and MDs [*Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV criteria)]. Computerized records provided data on PSD prescribing. Multilevel logistic regressions assessed the factors that influence prescribing.

Results. Thirty-four per cent of PC patients were prescribed PSDs >12 months, with anxiolytics being the most commonly prescribed (22%). Fifty-three per cent of patients with any MD in this 12-month period were prescribed PSDs; however, 25% of patients without any of these disorders were also prescribed these medications. Higher rates of prescribing were associated with female gender, older age, presence of MD, being a househusband/housewife, consulting about psychological problems, increasing number of consultations and higher self-perceived disability. PSDs were less likely to be prescribed to patients born outside Spain and those consulting about physical conditions. PSD prescribing was higher in patients previously married and antipsychotic prescribing was higher in patients never married. No statistically significant associations were found between PSD prescription and education.

Conclusions. PSD prescribing rates are high in Catalonia and are associated with a number of clinical and non-clinical factors. A significant proportion of patients are receiving these drugs in the absence of MD. These findings need to be considered when prescribing in PC.

Keywords. Drug prescriptions, mental disorders, pharmacoepidemiology, psychotropic drugs, primary health care.

Introduction

Patients with mental health problems are frequently treated exclusively by a GP in Spain, which is similar to other countries.[1–6] Furthermore, access to specialized care for patients with more severe symptoms is usually achieved through a referral from a GP. Subsequently, after assessment and treatment in specialized care, patients with mental disorders (MDs) are usually referred back to primary care (PC) for follow-up. As reported previously, between 2% and 42% of PC patients are treated with psychotropic drugs (PSDs)[6–11] (antidepressants, anxyolitycs, antipsychotics and hypnotic–sedatives), with significant cross-national variations.[8] To date, Spanish

studies have found high rates of PSD prescription. For instance, Mateo *et al.*[6] described a prevalence of PSD prescribing of 21% in 1997. The prevalence was even higher (42%) in the study conducted by Secades *et al.*[11] in 2003.

These high rates of PSD prescribing, the most commonly given treatment for PC patients with recognized MDs,[1,7,8,12] highlight the importance of understanding PSD prescribing patterns in PC.

It has been widely reported that prescription and choice of psychotropic medication are associated with a large number of clinical and non-clinical factors in PC settings. The probability of PSD prescribing in PC is significantly related to many patient characteristics, with age and gender being the most frequently reported.[6–9,13,14] Ethnicity has been repeatedly identified as a factor related with PSD prescription in PC in the UK,[15–17] where lower rates of prescribing were associated with a higher proportion of ethnic minorities in the practice population. Similar results were reported in Australia, where patients born outside Australia were less likely to be prescribed PSDs.[14] This factor has not been previously explored outside these jurisdictions. Factors related to practice characteristics (such as list size, settlement and available alternative therapies), GP characteristics (such as gender, place of birth and previous mental health training) and other external factors (such as pharmaceutical companies' sales representatives) have also been shown to influence prescribing patterns.[14,16–19]

In view of this background, the purpose of the present study was 3-fold: to describe the patterns of PSD utilization in a representative sample of PC patients from Catalonia (Spain), to analyse the relationship with the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) diagnoses over 12 months and to determine the factors associated with PSD prescribing.

Methods

The source of data for this report is the Diagnostic and Assessment Study of mental disorders in PC (DAS-MAP), a cross-sectional epidemiological survey carried out in Catalonia (Spain) to estimate the lifetime and 12-month prevalence of MDs in a representative sample of adult PC patients. The methods and main results of the study have been described in detail elsewhere.[20] The study was approved by the Clinical Research Ethics Committee of the Foundation Sant Joan de Déu.

Participants and setting

A stratified multistage probability sampling design was used. The seven health regions of the Catalan Health Service comprised the sampling frame. Firstly, the PC centers were selected within each health region, with the PC centers selected proportional to the population of the region, with at least six PC centers per region. From the 350 PC centers in Catalonia in 2005, 80 were selected but 2 refused to participate (97.2% acceptance rate). Secondly, 913 GPs were invited to participate and 618 (67.7%) accepted. Thirdly, patients were randomly selected with a systematic sampling strategy from the daily list of patients of the participating family physicians. Altogether, 5402 subjects were selected from those who had requested an appointment with their GP; 654 (12.1%) did not attend their appointment. Replacement was prohibited to ensure that every individual had a known probability of selection. A total of 4748 were asked to participate. Among them, 764 (16.1%) refused to participate and 164 (3.5%) were excluded because they could not conduct an adequate interview. Finally, 3820 participants from 78 PC centers were included. One of the PC centers was excluded because of data loss. Therefore, the analysed sample comprised 3815 patients from 77 PC centers (80.3% of those initially invited).

Study measures

A total of 20 trained clinical psychologists evaluated the participants in the PC centers between October 2005 and March 2006 using a paper-and-pencil face-to-face interview.

A sociodemographic questionnaire collected information about gender, age, marital status, employment status, educational level and place of birth. Responders were also asked about the main reason for their appointment: physical, psychological (reporting mental or emotional problems), a combination, or other reasons such as the receipt of a prescription without a GP consultation. Presence of MDs was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I research version which included major depression episode, dysthymia and anxiety disorder modules, excluding obsessive–compulsive disorder)[21,22] and the Mini Neuropsychiatric Diagnostic Interview (MINI) (manic/hypomanic episodes, obsessive–compulsive disorder, substance and alcohol use disorders, anorexia nervosa and bulimia nervosa).[23,24]

The severity of disability was measured using the Sheehan Disability Scale (SDS),[25–27] which considers the severity of disability during the last month in three domains: work, family life/home responsibilities and social/leisure activities. A total score ranging from 0 (unimpaired) to 30 (highly impaired) can be obtained.

Assessment of PSD use

PSD use was assessed using the information from the computerized medical records. Evaluators extracted information about any psychotropic medication prescribed to the participants in the previous 12 months irrespective of the presence or absence of MDs. The analyses presented in this paper refer to any episode of use of such drugs in a 12-month period, not distinguishing between occasional use and long utilization.

In this study, PSDs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system including antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C) and antidepressants (N06A). Lithium is a mood stabilizer and differs from other drugs in its ATC subgroup (N05A) in a clinical perspective. However, it is still assigned to the antipsychotics subgroup of the ATC classification and it was categorized in this way for these analyses. Only 14 patients in the whole sample had been prescribed lithium.

Statistical analyses

The proportion of participants with prescribed PSDs in the 12 months previous to the interviews was stratified by gender and MDs. For the bivariate comparison of proportions, Pearson's chi-square was applied.

In order to establish factors associated with prescription of PSDs, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by multilevel logistic regression with GP and PC center as random factors.

Firstly, we tested whether multilevel logistic regression was more appropriate than usual logistic regression comparing the null models with those including PC center as a random factor. The likelihood ratio tests were highly significant for all models with the exception of the ones that included any antipsychotic and any hypnotic–sedative as dependent variables. Therefore, these models were tested with logistic regression. Then, we compared the models that included PC center and GP as random factors to those with only PC center. The likelihood ratio test was not significant for any of the models. Therefore, for the models with any PSD, any antidepressant or any anxiolytic as dependent variables we used PC center as random factor.

Secondly, univariate analyses were performed with all the variables that had shown to be associated with PSD prescription in the scientific literature.[6–9,13–17] The final multivariable models included those variables that had been significant ($P \leqslant 0.20$) in univariate analyses.[28] Age and gender were retained because of an *a priori* assumption. In the models including PC center as random factor, the variance at the PC center level was estimated.

Finally, the area under the receiver operating characteristic (ROC) curve was calculated to estimate the discriminative power of each model. We conducted the analyses using STATA 11.[29]

Results

Sociodemographic characteristics and PSD prescribing

The final sample was 3815 patients (Table 1). The mean age was 54.4 years (SE = 0.45; range: 18–97), mean disability as measured with the SDS was 6.8 (SE = 0.25; range: 1–30) and the mean number of visits to PC center in the last 12 months was 6.4 (SE = 0.14; range: 1–60). The main reason for consulting with the GP was physical (71.5%) and 31.2% of participants were diagnosed as having a MD in the previous 12 months according to DSM-IV criteria.

Overall, 33.6% of the PC patients had been prescribed PSDs in the previous 12 months (Table 2). A single PSD was prescribed to 19.1% of PC patients in the last 12 months, while 14.5% of participants were prescribed more than one drug. Anxiolytics were the drugs most commonly prescribed (22.3% of the total sample and 55.0% of participants with only one PSD),

TABLE 1 *Sociodemographic characteristics of the DASMAP study sample*

	N (%)
Gender[a]	
Male	1408 (37.1)
Female	2402 (62.9)
Age group (years)[b]	
18–24	184 (4.8)
25–34	467 (12.2)
35–49	850 (22.2)
50–64	1117 (29.7)
>65	1187 (31.2)
Marital status[c]	
Married or living with someone	2453 (64.4)
Never married	648 (16.9)
Previously married	710 (18.7)
Working status[d]	
Paid employment	1311 (33.9)
Paid employment but on sick leave	441 (12.1)
Househusband/housewife	511 (14.1)
Retired	1131 (29.0)
Others	409 (11.0)
Education[e]	
No studies	469 (12.5)
Primary	1865 (48.7)
Secondary	964 (25.7)
University	477 (13.1)
Place of birth[b]	
Catalonia	2153 (54.4)
Other Spanish regions	1352 (37.2)
Outside Spain	300 (8.1)
Main reason for consulting	
Only physical	2574 (68.5)
Only psychological	265 (7.3)
Physical and psychological	101 (3.0)
Others	875 (21.2)
12-month prevalence of MDs according to DSM-IV criteria	
Any of the assessed MDs[f]	1139 (31.2)
Only mood disorder	264 (7.2)
Only anxiety disorder	445 (12.2)
Comorbidity mood–anxiety	199 (5.7)

[a]Five missing values.
[b]10 missing values.
[c]Four missing values.
[d]12 missing values.
[e]40 missing values.
[f]Assessed MDs included major depression episode, dysthymia, anxiety disorder, manic/hypomanic episodes, obsessive–compulsive disorder, substance and alcohol use disorders, anorexia nervosa and bulimia nervosa.

TABLE 2 *12-month PSD prescribing by therapeutic class and gender*

Drug	*N* (% of participants; 95% CI)		
	Total sample (*n* = 3815)	Men (*n* = 1408)	Women (*n* = 2402)
Any PSD***	1266 (33.6; 31.4–35.9)	328 (23.6; 21.3–26.1)	936 (39.5; 36.8–42.2)
One PSD***	731 (19.1; 17.6–20.6)	197 (14.1; 12.3–16.1)	533 (22.0; 20.1–24.1)
More than one PSD***	535 (14.5; 12.76–16.5)	131 (9.5; 7.7–11.8)	403 (17.5; 15.3–19.8)
Anxiolytics***	839 (22.3; 20.4–24.2)	211 (15.1; 13.0–17.4)	626 (26.4; 24.3–28.7)
Any antidepressant***	671 (18.2; 16.5–20.0)	165 (12.1; 10.2–14.2)	505 (21.8; 19.6–24.2)
Non-selective monoamine reuptake inhibitors***	84 (2.3; 1.8–2.9)	17 (1.3; 0.8–2.1)	67 (2.9; 2.3–3.7)
Selective serotonin reuptake inhibitors***	514 (14.0; 12.3–15.8)	137 (9.9; 8.2–12.0)	377 (16.4; 14.2–18.7)
Other antidepressants**	124 (3.3; 2.8–4.0)	31 (2.3; 1.7–3.3)	92 (3.93.1–4.8)
Antipsychotics	67 (1.7; 1.3–2.2)	25 (1.7; 1.1–2.5)	42 (1.7; 1.1–2.4)
Hypnotics and sedatives***	198 (5.3; 4.6–6.2)	45 (3.2; 2.4–4.1)	151 (6.5; 5.5–7.6)

**$P < 0.001$ 95% gender differences; ***$P < 0.01$ 95% gender differences.

generally from the benzodiazepine derivatives subgroup (22.2% of the sample). Antidepressants were the second most commonly prescribed PSD (18.2%), largely selective serotonin reuptake inhibitors (14.0% of patients). Hypnotics and sedatives and antipsychotics were much less commonly used (5.3% and 1.7%, respectively).

12-month DSM-IV diagnoses and PSD prescribing

Overall, 52.8% of participants diagnosed with any MD in the last 12 months were given a PSD at any point during the same period (Table 3). On the other hand, 24.9% of participants without any of the psychiatric disorders evaluated in the last 12 months were prescribed a PSD within the same 12-month period.

Of those who met the DSM-IV criteria for a mood disorder during the last year, 66.9% had been prescribed a PSD. A single PSD had been prescribed to 24.9% during this period, while 42.0% had been prescribed more than one drug. The drugs most commonly prescribed for mood disorders were antidepressants (48.5%) and anxiolytics (46.1%).

Among individuals with any anxiety disorder for 12 months according to DSM-IV criteria, 45.7% had been prescribed PSDs. About 22.4% had been prescribed exclusively one PSD and 23.3% had been prescribed more than one. The drugs most commonly prescribed for anxiety disorders were anxiolytics (34.5%) and antidepressants (26.2%).

Compared with mood and anxiety disorders only, the percentage of patients with comorbid mood and anxiety disorders who had been prescribed a PSD was higher (70.3%). A single drug was prescribed to 23.0% of those patients and more than one agent to 47.3%.

Factors associated with PSD prescribing

Gender and age had a highly significant association with the prescription of PSDs with exception of antipsychotics (Table 4). PSDs were more likely to be prescribed to women (OR = 1.75, 95% CI 1.45–2.10) and the probability of being prescribed these drugs during the last 12 months rose with increasing age (1-year increment OR = 1.03, 95% CI 1.02–1.03).

Marital status was also associated with PSD prescription. PSDs were more likely to be prescribed to patients previously married and antipsychotics alone were more likely to be prescribed to people never married (OR = 2.69, 95% CI 1.38–5.22). However, no statistically significant associations were found between PSD prescription and education.

PSDs were less likely to be prescribed to people born out of Spain (OR = 0.56, 95% CI 0.39–0.80) and more likely to be prescribed to homemakers (OR = 1.43, 95% CI 1.08–1.90).

Presence of mood and anxiety disorders had a highly significant association with antidepressant and anxiolytic prescription. Hypnotics and sedatives were more likely to be prescribed in presence of a mood disorder.

Apart from antipsychotics, there was a positive association between the number of visits to GPs and prescribing of PSDs (1-visit increment OR = 1.05, 95% CI 1.04–1.07). Moreover, the probability of being prescribed a PSD was higher when the main reason for an appointment was psychological (OR = 5.95, 95% CI 4.28–8.26) and lower when it was physical (OR = 0.72, 95% CI 0.60–0.87).

Self-perceived disability had a highly significant association with the prescription of every PSD (1-unit increment OR = 1.03, 95% CI 1.02–1.05).

In the multilevel logistic regressions, the variance at the PC center level ranged from 0.08 to 0.12 in the models with any PSD, any antidepressant and any anxiolytic as dependent variables.

Discussion

In this study, the prevalence of PSD prescribing in PC was 33.6%. These results agree with previous studies conducted in other Spanish regions that reported

TABLE 3 *12-month PSD prescribing by therapeutic class and MD*

Drug	*N* (% of participants; 95% CI)				
	Any MD[a]; *N* = 1139	No MD, *N* = 2676	Only mood disorder, *N* = 264	Only anxiety disorder, *N* = 445	Comorbidity mood–anxiety, *N* = 199
None	537 (47.2; 42.7–51.8)	2012 (75.1; 72.7–77.3)	89 (33.1; 27.6–39.2)	238 (54.3; 47.7–60.7)	58 (29.7; 22.5–38.1)
Any PSD	602 (52.8; 48.2–57.3)	664 (24.9; 22.7–27.3)	175 (66.9; 60.8–72.4)	207 (45.7; 39.3–52.2)	141 (70.3; 61.9–77.5)
One PSD	260 (22.5; 20.0–25.3)	471 (17.5; 15.7–19.5)	65 (24.9; 19.8–30.7)	105 (22.4; 18.3–27.2)	46 (23.0; 18.2–28.5)
More than one PSD	342 (30.2; 26.2–34.6)	193 (7.4; 6.2–8.8)	110 (42.0; 36.7–47.6)	102 (23.3; 18.5–28.9)	95 (47.3; 19.9–54.8)
Anxiolytics	423 (36.9; 33.0–41.2)	416 (15.6; 14.0–17.3)	119 (46.1; 40.1–52.2)	154 (34.5; 28.5–41.2)	95 (46.1; 39.4–52.9)
Any antidepressant	396 (35.2; 31.5–39.2)	275 (10.5; 9.1–12.1)	128 (48.5; 42.1–54.9)	116 (26.2; 21.5–31.6)	114 (57.4; 49.1–62.3)
Non-selective monoamine reuptake inhibitors	41 (3.6; 2.5–5.2)	43 (1.7; 1.3–2.4)	13 (5.0; 2.8–8.7)	15 (3.0; 1.7–5.0)	13 (6.9; 3.7–12.6)
Selective serotonin reuptake inhibitors	304 (27.2; 23.5–31.2)	210 (8.0; 6.8–9.4)	101 (38.4; 31.9–45.4)	80 (18.4; 14.0–23.8)	88 (44.4; 37.1–52.0)
Other antidepressants	85 (7.4; 6.0–9.0)	39 (1.5; 1.1–2.0)	26 (9.2; 5.7–14.4)	24 (5.5; 3.5–8.5)	31 (15.4; 11.5–20.3)
Antipsychotics	31 (2.7; 1.8–3.9)	36 (1.2; 0.8–1.8)	11 (4.3; 2.1–8.7)	9 (2.0; 1.0–3.8)	7 (3.1; 1.3–7.0)
Hypnotics and sedatives	89 (7.8; 6.1–9.9)	109 (4.1; 3.3–5.1)	31 (12.1; 8.5–16.9)	27 (5.7; 3.6–8.8)	22 (10.7; 6.7–16.7)

[a]Assessed MDs included: major depression episode, dysthymia, anxiety disorder, manic/hypomanic episodes, obsessive–compulsive disorder, substance and alcohol use disorders, anorexia nervosa and bulimia nervosa.

a 12-month prevalence of PSD prescription or consumption between 21% and 42%.[6,11] These rates are higher than the ones reported in studies carried out in other countries, which range between 2.1% and 31.7%.[7–10] However, most of these studies considered periods <12 months, which could partially explain the differences in rates. Prevalence of MDs cannot fully explain this difference since this has been reported to be lower in Spain than in other developed countries.[20,30] In Spain, population coverage by the National Healthcare Service (NHS) is almost universal (over 95%) and guarantees quite a comprehensive benefits package to all citizens.[31] GP is the gatekeeper to the system so that high use of PC services by the general population is generated. As in other European countries, the NHS is financed by the general taxes levied by the state. Medical visits and hospital admissions are fully covered by the NHS and prescribed medications are covered completely for retired persons and partially for those still employed.[31] Systems whereby medicines are free and access to GP is relatively easy may encourage more prescribing.[7,8] Cross-cultural differences in clinical practice, organizational factors and availability of alternative therapies could also influence the prescription patterns of GPs.

Altogether, 52.8% patients who met DSM-IV criteria for any of the psychiatric disorders evaluated, 66.9% patients with a mood disorder, 45.7% patients with anxiety disorder and 70.3% patients with comorbid anxiety and depressive disorder received PSDs. The use of different diagnostic methods (different validated instruments and GP recognition) allows only crude comparisons with other studies; however, these rates are similar to those reported previously in general practice.[7–9] As in many other earlier studies, anxiolytics were the PSD most often prescribed.[6,8–11] On the other hand, a considerable number (24.9%) of patients without any of the psychiatric disorders assessed according to DSM-IV criteria in the last 12 months were prescribed a PSD. These results also reflect those found in previous studies where 24% and 27% of patients without MD according to validated diagnostic instruments had been prescribed a PSD.[7,9] Some psychiatric disorders, such as psychosis, somatoform disorders or post-traumatic stress disorder, for which psychotropic medication is suitable, were not assessed in this study so this may account for this difference. Furthermore, these drugs could have been prescribed to treat diseases other than MDs, such as personality disorder or neurological disorders, or could correspond to chronic treatments of patients with recurrent depression. However, differences in rates of psychiatric diagnosis obtained using GP criteria and structured psychiatric interviews may also account for these patterns.[32] Moreover, the prevalence of subthreshold psychiatric symptoms is high in PC[33] and GPs could be prescribing PSD to treat patients presenting with these

TABLE 4 *Factors associated with PSD prescribing over 12 months by therapeutic class*

Factors assessed	OR and 95% CI				
	Any PSD	Any antidepressant	Any antipsychotic	Any anxiolytic	Any hypnotic-sedative
Gender					
Male	1	1	1	1	1
Female	1.75 (1.45–2.10)***	1.46 (1.15–1.84)**	0.75 (0.46–1.38)	1.63 (1.33–2.00)***	1.77 (1.22–2.58)**
Age (1-year increment)	1.03 (1.02–1.03)***	1.02 (1.01–1.03)***	1.01 (0.99–1.04)	1.02 (1.01–1.03)***	1.03 (1.01–1.04)**
Marital status					
Married or living with someone	1	1	1	1	1
Never married	1.12 (0.87–1.45)	1.16 (0.85–1.58)	2.69 (1.38–5.22)**	1.03 (0.78–1.36)	0.63 (0.34–1.16)
Previously married	1.29 (1.05–1.58)*	1.10 (0.85–1.41)	1.47 (0.79–2.75)	1.16 (0.93–1.44)	1.34 (0.95–1.89)
Education					
No studies	1	ni	ni	1	1
Primary	0.94 (0.73–1.22)	ni	ni	0.87 (0.66–1.14)	1.30 (0.83–2.05)
Secondary	1.08 (0.78–1.49)	ni	ni	0.96 (0.68–1.34)	1.37 (0.76–2.48)
University	1.12 (0.78–1.62)	ni	ni	1.01 (0.68–1.48)	1.83 (0.94–3.55)
Place of birth					
Catalonia	1	1	ni	1	1
Spain	0.97 (0.80–1.16)	1.14 (0.91–1.41)	ni	0.86 (0.70–1.04)	1.26 (0.91–1.74)
Outside Spain	0.56 (0.39–0.80)***	0.60 (0.38–0.95)*	ni	0.65 (0.44–0.95)*	0.42 (0.15–1.17)
Working status					
Paid employment	1	1	1	1	1
Paid employment but in sick leave	0.98 (0.73–1.32)	1.04 (0.74–1.45)	0.82 (0.34–1.98)	1.20 (0.89–1.62)	0.77 (0.43–1.38)
Househusband or housewife	1.43 (1.08–1.90)*	1.19 (0.85–1.67)	1.50 (0.56–4.03)	1.46 (1.07–1.96)*	0.99 (0.56–1.75)
Retired	0.98 (0.73–1.31)	0.77 (0.54–1.11)	1.52 (0.59–3.92)	1.02 (0.74–1.40)	1.32 (0.75–2.32)
Others	1.16 (0.86–1.56)	1.28 (0.91–1.80)	1.76 (0.79–3.90)	1.05 (0.76–1.44)	0.93 (0.51–1.69)
12 month mood disorder					
No	1	1	1	1	1
Yes	2.57 (1.98–3.30)***	2.91 (2.24–3.78)***	0.90 (0.46–1.75)	1.91 (1.48–2.44)***	1.51 (1.00–2.27)*
12-month anxiety disorder					
No	1	1	1	1	1
Yes	1.75 (1.40–2.17)***	1.75 (1.38–2.22)***	0.83 (0.44–1.55)	1.76 (1.42–2.19)***	1.09 (0.75–1.60)
Number of visits to general practitioner (1-visit increment)	1.06 (1.04–1.07)***	1.03 (1.01–1.04)***	1.01 (0.98–1.04)	1.04 (1.03–1.06)***	1.03 (1.01–1.05)***
Main reason for consulting					
Not physical	1	1	ni	1	1
Physical	0.77 (0.64–0.93)***	0.75 (0.60–0.93)**	ni	0.73 (0.60–0.89)***	0.76 (0.55–1.05)
Not psychological	1	1	1	1	1
Psychological	7.06 (5.12–9.74)***	5.60 (4.18–7.49)***	3.24 (1.74–6.06)***	2.80 (2.13–3.69)***	1.95 (1.25–3.04)**
Self-perceived disability (1-unit increment)	1.04 (1.03–1.05)***	1.04 (1.03–1.05)***	1.08 (1.05–1.11)***	1.02 (1.01–1.03)***	1.04 (1.02–1.06)***
Variance explained by the PC center	0.11 (0.06–0.23)	0.12 (0.05–0.29)	–	0.08 (0.04–0.21)	–
Area under the ROC curve	0.80 (0.79–0.82)	0.83 (0.81–0.84)	0.76 (0.74–0.77)	0.77 (0.75–0.78)	0.75 (0.74–0.77)

ni = not included [variables that had not been significant ($P \leq 0.20$) in univariate analyses].
Significance levels: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

subthreshold psychiatric symptoms or those presenting with normal sadness.

In common with other studies, some sociodemographic and clinical features were strongly associated with the prescription of PSDs. As in many previous studies, the likelihood of prescribing was related to female gender[6–9,11,13,14] and increased age.[6–9,13]

The Spanish legal framework entitles all residents in Spanish territory to full health coverage, regardless of their nationality and legal status.[31] Those immigrants in an illegal administrative situation are also fully entitled to health care, provided that they are registered as residents in the municipality. Spanish law allows the existence of some non-shared data among different

administrations to protect citizens' privacy; thus, non-legal residents in Spain can register (and do so in large numbers) in municipal registries and become entitled to health care and education.[31] Consequently, PC registers also include this group that usually is not entitled to formal health assistance in most national health systems even those under a universal coverage schema. However, patients born outside Spain were less likely to have been prescribed a PSD. This has also been reported in previous studies that identified lower rates of PSDs prescription in populations with high densities of minority ethnic groups.[14–17] This may be due to a lower prevalence of MDs or by cultural and language related factors, such as self-perception of need for treatment, access and utilization of health services, disease recognition by the practitioner and attitudes regarding use of pharmacological treatment.

Reflecting findings from previous studies, there was a positive association between presence of a mood or anxiety disorder identified and drug prescription.[6–9,16,34] Similarly, the likelihood of being prescribed a PSD was higher in those patients who attended to consult about psychological problems and in those with a higher self-perceived disability,[8] factors that could be related to an increased probability of recognition of disease[35] but also with the patient expectations and attitudes towards receiving medication.[34] Prescribing was also positively related with an increased number of visits to GP[6,7,11,36] what could increase recognition of disease. Higher number of visits to GP in patients with depression and anxiety can be also due to more frequent monitoring by the doctor.[37,38]

Contrary to the findings of other studies, marital status,[6,8,9,13] education level[8,13] and working status[6,8] showed to be very poorly or not at all associated with PSD prescription in PC.

The present work makes an important contribution to the actual knowledge of PSD prescribing patterns in PC. Previous studies considered smaller sample sizes[6,7,9,11] or extracted information for shorter periods of time.[8,10,14] The DASMAP study uses a one-phase design with a randomized recruitment of a multisite, geographically diverse and highly representative sample of PC patients, which improves the generalizability of our results. Furthermore, in our approach to data collection, we combined a 12-month period and face-to-face interviews with review of clinical records. This allowed us to administer structured psychiatric interviews with high accuracy and reliability to assess the presence of MDs while information about prescribed PSD was directly extracted from computerized records, thereby minimizing recall bias.

However, the results of the study should be interpreted with the following limitations in mind: firstly, the DASMAP is a cross-sectional study so causality cannot be established in relation to the factors associated to PSD prescription. Secondly, data about PSD prescribing were collected from clinical history and the information could be affected by the extent to which GPs completed it. Furthermore, information about the length of time for which medication was prescribed was not available what limits interpretation of the findings. Thirdly, it is important to highlight that 15% of patients to whom an antidepressant is prescribed never starts to take the medication.[39] To overcome this issue, it would be interesting to evaluate the data from pharmacy records that provide information about medication dispensed. However, this does not guarantee that medication is consumed. Fourthly, we grouped drugs according to the ATC system in which some drugs that may be used for two or more equally important indications are usually only given one code, on the basis of the available literature. That is the case of some benzodiazepines that are assigned to the anxiolytics group but may be used as hypnotics and/or sedatives so we cannot know the indication for which they were prescribed. However, we decided to use ATC system because it is suggested by the WHO Collaboration Centre for Drug Statistics Methodology as the gold standard for international drug utilization research and it is suitable for international comparisons.[40] Finally, we did not evaluate some relevant GP and organizational variables that have been previously associated with PSD prescribing such as previous mental health training or list size. The impact of pharmaceutical representative visits on prescribing was not either assessed in this study. However, in Catalonia, GPs are given financial incentives derived from the accomplishment of certain strategic goals such as rational prescription and use of generic drugs, what may be limiting the impact of pharmacy industry on prescribing patterns.

Conclusions

This epidemiological study confirms that PSDs are highly prescribed in PC in Spain and play a very important role in the management of PC patients with MDs. Furthermore, the prescription rates of those drugs are higher than those reported in other countries even though prevalence of psychiatric disorders is lower. Importantly, these data revealed that almost a quarter of patients were receiving these drugs; yet; they had no MDs.

The findings from this study should help inform the development of an intervention which would seek to improve psychotropic prescribing in Spanish PC.

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Declaration

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Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study

Maria Rubio-Valera[1,2*], Anna Maria Jové[2,3], Carmel M Hughes[4], Mireia Guillen-Solà[2,5], Marta Rovira[2,5] and Ana Fernández[1,2]

Abstract

Background: Although general practitioners (GPs) and community pharmacists (CPs) are encouraged to collaborate, a true collaborative relationship does not exist between them. Our objective was to identify and analyze factors affecting GP-CP collaboration.

Methods: This was a descriptive-exploratory qualitative study carried out in two Spanish regions: Catalonia (Barcelona) and Balearic Islands (Mallorca). Face-to-face semi-structured interviews were conducted with GPs and CPs from Barcelona and Mallorca (January 2010-February 2011). Analysis was conducted using Colaizzi's method.

Results: Thirty-seven interviews were conducted. The factors affecting the relationship were different depending on timing: 1) Before collaboration had started (prior to collaboration) and 2) Once the collaboration had been initiated (during collaboration). Prior to collaboration, four key factors were found to affect it: the perception of usefulness; the Primary Care Health Center (PCHC) manager's interest; the professionals' attitude; and geography and legislation. These factors were affected by economic and organizational aspects (i.e. resources or PCHC management styles) and by professionals' opinions and beliefs (i.e. perception of the existence of a public-private conflict). During collaboration, the achievement of objectives and the changes in the PCHC management were the key factors influencing continued collaboration. The most relevant differences between regions were due to the existence of privately-managed PCHCs in Barcelona that facilitated the implementation of collaboration. In comparison with the group with experience in collaboration, some professionals without experience reported a skeptical attitude towards it, reporting that it might not be necessary.

Conclusions: Factors related to economic issues, management and practitioners' attitudes and perceptions might be crucial for triggering collaboration. Interventions and strategies derived from these identified factors could be applied to achieve multidisciplinary collaboration.

Keywords: Interprofessional Relations, Family Physicians, Pharmacists, Qualitative Research

Background

General practitioners (GPs) and community pharmacists (CPs) are encouraged to collaborate to improve patient care [1,2] Pharmacists' interventions within the healthcare team improve patient outcomes in physical [3-5] and mental conditions [6]. On the other hand, miscommunication between GPs and CPs is a cause of preventable hospital admissions [7]. However, during the implementation of a trial evaluating a complex intervention [8] we realized that GPs and CPs had difficulties communicating with each other. Despite working in the same geographical area and sharing patients, some doctors and pharmacists used the study researcher to transmit information to the other professional or to obtain additional information about the participants. Surveys have been conducted exploring this issue, pointing out that exchange characteristics (i.e. trustworthiness or role specification) are the factors most

* Correspondence: mrubio@pssjd.org
[1]Research and Development Unit, Fundació Sant Joan de Déu, Calle Picasso 13, Sant Boi de Llobregat, Barcelona 08830, Spain
[2]Red de Investigación en Actividades Preventivas y Promoción de la Salud (RedIAPP), Barcelona, Spain
Full list of author information is available at the end of the article

frequently associated with GP-CP collaboration [9,10] but quantitative work provides only a limited understanding of what promotes collaboration. Qualitative studies may untangle some of the deeper reasons preventing such collaboration [11]. Qualitative work has been conducted in the UK, Australia and USA to explore factors affecting GP-CP collaboration [12-15]. These qualitative works highlighted the fact that professionals from each discipline were not personally acquainted, territoriality, and the pharmacist's conflict of interest with regard to selling medications as the barriers that most affected mutual trust and respect between practitioners, thus impeding collaboration. Some of these studies explored the factors affecting collaboration in areas where multiple chain pharmacies and single independent pharmacies coexisted, reporting higher distrust and lack of interest among GPs towards collaboration with chain pharmacists. However, the impact on collaboration of publicly funded and privately managed PCHC in comparison with publicly funded and publicly managed PCHCs has not been previously assessed. Nor did these studies explore the perception of the Primary Care Health Centers (PCHC) managers or the impact on the GP-CP relationship of external agents that participate in the process such as the patient and the pharmacy assistant.

Differences between the health systems and the model of community pharmacy require a country-specific study in Spain. The Spanish national health system (NHS) is publicly funded. The organization and provision of health services depends on each of the 17 regional governments through which Spain is governed [16]. This generates differences in health policies between regions [17,18] which could affect the organization of primary care health centers and pharmacies as well as the way in which collaboration is manifested between GPs and CPs. Table 1 summarizes the main characteristics of Spanish primary care, comparing the organization of the PCHCs and the pharmacies.

The aims of this study were: 1) to identify and analyse barriers and facilitators in collaboration between GPs and CPs in Spain and 2) to explore whether differences exist between GPs and CPs based on the geographical region where they work and previous experience of collaboration.

Methods

A descriptive-exploratory qualitative study using face-to-face, semi-structured interviews (January 2010-February 2011) was undertaken using a phenomenological approach.

The study population comprised GPs and CPs from 2 Spanish regions: Catalonia (Barcelona) and the Balearic Islands (Mallorca). Commitment to primary care is higher in Catalonia than in Balearic Islands and there is a greater investment of resources in primary care with respect to total health expenditure [18] Consequently, in comparison with Balearic Islands, there is a higher density of PCHCs, a lower ratio of patients per GP, a greater number of services integrated within primary care (i.e. dentistry) and better access to diagnostic procedures by GPs in Catalonia. A further important difference between the regions is the coexistence of the private and public model in Catalonia, which is reflected in the presence of "Entidades de Base Asociativa" (EBAs) (see

Table 1 Summary of the main characteristics of the PCHC and community pharmacies in Spain

	Primary care health centers	Community pharmacies
Owner	Predominantly state-owned	Privately owned (the pharmacy owner must be a licensed pharmacist and each pharmacy may own only one pharmacy)
	Every PCHC contains several GP surgeries with few exceptions in rural areas of Spain	
Funding	Publicly funded	Offers both publicly funded services (i.e. drugs that are financed by the state) and privately funded services (i.e. over the counter drugs)
		A large part of the profit derives from selling financed drugs.
Management	Predominantly publicly run (the manager is one of the GPs from the PCHC team that combines clinical activities with management activities)	Privately run (usually by the owner)
	In some regions, privately managed PCHCs exist. This is the case with the "Entitades de Base Asociativa" (EBAs). EBAs are limited companies comprised of health professionals that establish a contractual relationship with the NHS to offer health services in exchange for capitation financing, a theoretical cost per person independent of the real costs incurred.	
Compensation	Most GPs are employed by the public sector and receive fixed salaries.	CPs are owners of the community pharmacy or employed in exchange of a fixed salary.
	Management by Objectives (MBO) has been introduced to improve quality of the service and reduce cost. For instance, GPs are paid a bonus if they prescribe a high percentage of generic drugs and/or those of proven efficacy.	

Table 1) that do not exist in the Balearic Islands. In both regions management by objectives (MBO) is used. The MBO system gives GP incentives (usually financial) if they fulfill the objectives set by the health system (i.e. prescription of drugs of proven efficacy). Electronic prescribing links the GP's prescriptions with the community pharmacists and acts as a communication channel between the two professionals. The implementation of electronic prescribing in the Balearic Islands began in 2006, long before its introduction in Catalonia. By the time we conducted the study interviews, electronic prescription had long been established in the Balearic Islands while in Catalonia only GPs and CPs from some areas were using it, primarily in rural areas and small cities. In Barcelona, it was in the implementation stage.

We also considered whether recruited practitioners had previous experience of collaboration (defined as having had regular face-to-face contact with the other group of professionals). We theorized that practitioners from different regions and those with previous experience compared with those with none would have different opinions towards collaboration thus maximizing the possibility of finding disconfirming cases (theoretical sampling [11]).

The PCHC manager in Spain is usually a GP from the team of physicians who combines clinical work with the management of the PCHC. While in charge, the manager officially represents the PCHC and he/she administers the human and financial resources allocated to the health center. Consequently, the PCHC manager is responsible for distribution of the resources necessary for collaboration with the CP. Some of the GPs interviewed had experience as managers of the PCHC.

We contacted key informants from the fields of primary care (PC) and community pharmacy in Barcelona and Mallorca [the College of CPs, the Research Network on Preventative Activities and Health Promotion (RedIAPP) in PC and the School of Pharmacy-University of Barcelona] to identify those professionals who matched our sampling criteria. It was explained to the key informants that we were seeking professionals with experience of collaboration so that we would be referred to professionals whom we knew in advance would take part. Thereafter, practitioners were contacted by telephone and invited to participate. At this time we established a time for the interview but did not explain the study objective in detail. We did, however, ask them some brief questions, including whether they collaborated with any other health professionals. Once interviewed, participants were asked if they knew other practitioners who matched our criteria (snowball sampling [19]). One general practitioner declined to participate.

Participants were recruited until each theorized category (professional group, previous experience and region) independently achieved saturation of thematic findings.

Interviews were conducted in a place of convenience for the participant by AMJ (GPs from Barcelona), MRV (CPs from Barcelona), MG (GPs from Mallorca) and MR (CPs from Mallorca). The interview guide was developed by a team of researchers and clinicians including AMJ, AF and MRV taking into account their experience in the field as well as the results of the only paper that had been published at the time the study was designed [13]. The interview guide was piloted with one GP and one CP. The interview guide is summarized in Table 2. Interviews were audiorecorded, fully transcribed and anonymized.

In parallel with interviews, analysis assisted by Atlas-ti software was conducted. The information obtained was triangulated by the participation of three investigators [a GP (AMJ), a pharmacist (MRV) and a psychologist with experience in using qualitative research (AF)] who independently analyzed the interviews [11]. In the Mallorca interviews, a fourth analyst participated [a nurse and sociologist (MG) from Mallorca].

Analysis was conducted using Colaizzi's method for analysis [20]. The following is a complete description of the procedure. The process of generation of categories was largely inductive. Researchers became familiar with the interviews by listening, reading and re-reading them. Themes were identified and coded independently by each of the researchers involved in the analyses. Researchers then came together to compare and discuss differences in the analyses. Themes were then re-coded and classified, identifying common patterns and convergences and divergences in data through a process of constant comparison. With the assistance of a fifth researcher, a pharmacist with experience in undertaking qualitative research and collaboration between pharmacists and GPs (CMH), findings from the analysis were integrated to formulate a theoretical model for the phenomenon under investigation. Finally, respondent validation was conducted, comparing our interpretation of the phenomenon with those who had participated. Participants were sent a summary of the findings and invited to a meeting where findings were presented and discussed. Fourteen out of thirty-seven professionals participated in this validation. Changes suggested by participants were incorporated into the final description of the phenomenon.

In order to guarantee the validity of this research [11,21] the study was externally audited from the beginning to its conclusion by a group of researchers from the "Qualitative Health Research Group" (led by Dr Vázquez ML) of the "Consorci de Salut i Social de Catalunya". Interviewers and main analysts kept a personal

Table 2 Topic guide for the interview

Topic guide	Suggested questions to help the interviewer
Relationship nowadays	*How is your relationship with the CP/GP?*
	- If there is no relationship: *Why do you think that there is no relationship?*
	- If the relationship is good/bad/regular: *What do you think that makes the relationship good/bad/regular?*
Utility of the collaboration	*Do you think that it would be useful to potentiate the teamwork between the GP and CP? Why?*
	What advantages do you see in working in collaboration with the CP/GP? And what disadvantages do you see in collaborating with the CP/GP?
Opinion about the other group of professionals	*What do you think about the CP/GP?*
	How do you think that CP/GPs see GP/CPs?
Barriers for communication	*If you tried to get in contact with the CP/GP at any time, what difficulties did you have?*
	You told me that when trying to get in contact with the CP/GP you had problems because... can you think of any others?
Barriers for collaboration	*What do you think makes collaborative work difficult?*
Facilitators for communication	*What steps do you think could be taken to improve communication with CPs/GPs?*
Facilitators for collaboration	*How do you think collaborative work could be promoted or strengthened?*
Impact from the National Health System	*Is there any aspect in the organization of the health system that you think is affecting the relationship between GPs and CPs? In what sense?*

GP = General practitioner; CP = Community pharmacist.

research diary in which any reactions to events occurring during the research were recorded. All participants gave informed consent and the study was approved by the Foundation Sant Joan de Déu Clinical Research Ethics Committee.

Results

A total of 37 interviews were conducted that lasted 5–99 minutes (mean: 23 minutes) (Table 3 shows the sample characteristics). Nine GPs and nine CPs had had previous experience in collaboration with the other group of professionals and 4 of the GPs belonged to an EBA.

In the group of participants with previous experience the collaborative experiences differed from one another. Some examples of activities were: interdisciplinary professional training, detection and resolution of medication related problems, carrying out tests or clinical analysis (e.g., glycemia) at the pharmacy for patients who require regular monitoring, rationalization of expenses, special care for people with mobility problems, personalized medication dosage system (weekly blister packs for patients taking a variety of medications) and public health education, and so on.

Factors affecting GP-CP collaboration

The factors affecting the relationship varied depending on the timing in relation to the collaboration: 1) Before collaboration started (prior to collaboration) and 2) Once the collaboration had been initiated (during collaboration).

Prior to collaboration, GPs and CPs worked on their own. This first phase was a process of team-building that allowed collaboration to begin. The factors identified assigned to this first stage in the process of generation of the theoretical model were central in facilitating or impeding the initiation of collaboration between the two professions.

During collaboration, a successful relationship between doctors and pharmacists has been established and the

Table 3 Characteristics of the participants

Characteristics of participants *(n = 37)*	**Barcelona**	**Mallorca**
General practitioners, *n*	9	9
Sex, *n*		
Male	6	4
Female	3	5
Mean age (range), years	48.7 (35–60)	47.6 (37–60)
Mean clinical work experience (range)*, years	21.8 (8–31)	19.6 (8–30)
Previous experience in GP-CP collaboration, *n*		
With previous experience	4	5
Without previous experience	5	4
Community pharmacists, *n*	10	9
Sex, *n*		
Male	4	4
Female	6	5
Mean age (range), years	50.4 (30–64)	47.7 (29–56)
Mean clinical work experience (range), years	23.7 (5–40)	17.2 (1–30)
Previous experience in GP-CP collaboration, *n*		
With previous experience	5	4
Without previous experience	5	5

* Three general practitioners from Barcelona and four from Mallorca also had experience as Primary Care Health Center managers.

factors affecting that relationship changed. The challenge from this point on is to maintain and consolidate collaboration to ensure continuity.

Practitioners from the group which had experience of collaboration provided data which was rich in the identification of collaboration facilitators. GPs and CPs without experience who had tried to collaborate without success provided information about barriers which prevented or limited collaboration. Finally, GPs and CPs without experience who had never engaged in collaboration reported barriers related to attitudes and preconceived perceptions.

Prior to collaboration

Prior to the process 4 key factors were identified which affected collaboration: A) perception of usefulness, B) PCHC manager's interest, C) attitude, and D) geography and legislation. Figure 1 shows the conceptual model of factors affecting the initiation of the collaborative relationship between GP and CP.

Perception of usefulness

A positive perception of usefulness was necessary in order to start the collaboration. Conversely, the perception of usefulness was negative when GPs and CPs believed that there were no advantages in collaborating or that collaboration would cause problems. Only professionals without previous experience from Barcelona thought that collaboration would be troublesome.

> *I think we shouldn't tamper with it* (the relationship with the doctor) *because I think that it's correct . . . if we look for something more we will have problems.* [CP2: Community pharmacist without experience in collaboration from Barcelona (CP WO BCN)].

However, participants stated that there were some factors that could influence a positive perception of usefulness. GPs and CPs with previous experience reported that evidence supporting positive outcomes of collaborative GP-CP relationships could make professionals change their mind about collaboration. Similarly, professionals stated that sometimes the NHS introduced strategies that affected both groups of professionals, e.g., the introduction of electronic prescribing, which could force a collaboration to start.

> *But thanks to electronic prescribing, given that just like any implementation of a system in which we are forced to work together . . . has forced this exchange, this feedback with the medical team . . . we have established a series of courses of action with the aim of having more fluid communication to solve this problem.* [CP10: Community pharmacist with experience in collaboration from Barcelona (CP W BCN)]

PCHC manager interest

To collaborate it was necessary that the PCHC manager was interested in promoting collaboration.

> *I think that a lot depends on the will of the manager of the PCHC; whether the manager of the PCHC is in*

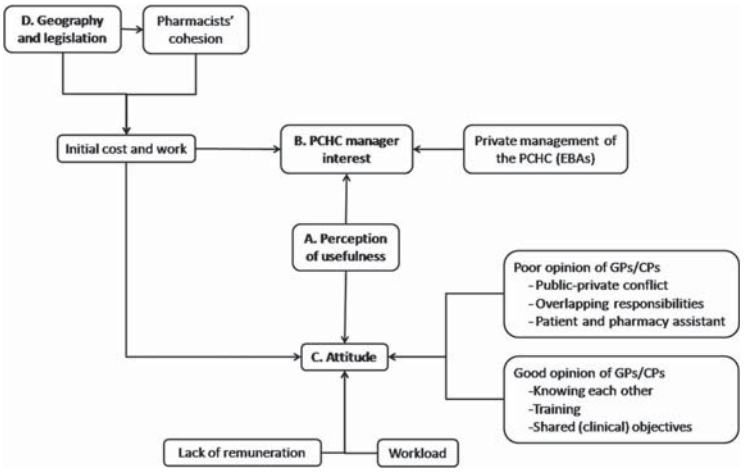

Figure 1 Factors affecting collaboration between general practitioners and community pharmacists prior to collaboration. PCHC: Primary Care Health Center; EBA: type of privately managed PCHC; GPs: General practitioners; CPs: Community pharmacists.

favor or not. So far I have had a PCHC manager against (cooperation). *Now they have changed this and she is already waiting for me.* [CP1: CP WO BCN]

The interest of the PCHC manager was influenced by his/her own perception of usefulness and by the initial cost in terms of infrastructure and human resources required to trigger the collaboration. EBA-type PCHCs in Barcelona were a good example of this (see Table 1). GPs and CPs suggested that collaboration was easier for two reasons: because the PCHC manager would be interested in collaboration as a strategy to reduce costs and improve outcomes for the center and because these PCHCs had smaller teams which were easier to coordinate.

The advantage of centers like this (EBA) *is that this health center is a small center. . . . There is more flexibility and greater speed when we want to get a project going.* [GP8: General Practitioner with experience in collaboration from Barcelona (GP W BCN)].

A barrier influencing the manager's interest was the perception that the NHS did not incentivize collaboration.

Attitude of the professionals

Attitude was strongly influenced by opinions held about the other professional. A good opinion would lead to respect and trust; key factors for collaboration. A negative opinion might be due to the perception that a "public-private" conflict existed. GPs and CPs believed that, through MBO (see Table 1) doctors were encouraged to prescribe cheaper drugs and less of them while the pharmacist, through selling medications, had a greater interest in non-rational use of medicines.

(Pharmacists must think) *that we are forced by the health policies that reward or punish some prescription styles . . . There are many doctors that* (say) *"I'm not giving* (prescribing) *this, do you know why? Because I'll get into trouble, because they'll penalize me". . . They* (CP) *must think, "Here, it's my money that's at stake, because I have a business and the doctor is a state employee and nothing's going to happen to him/her and he/she doesn't care.". . . And they must compare this difference of their feeling of responsibility, that they have a business and they must pay a salary to their assistants, that there are things to pay for. They have an element of the entrepreneur that we don't have.* [GP8: GP W BCN]

Overlapping responsibilities generated a negative opinion of the other professional. GPs and CPs believed that sometimes the other professional was performing tasks that should not be done by him/her. This concern was generated by the fact that the roles of professionals were not well defined.

We have the experience of seeing a productive cough, a dry cough, some mucosity. I think we can recommend a medication . . . a doctor will tell you: "but well, we are doctors and it is us who have to (prescribe)" *and, well, he/she is right, on the one hand they're right, but where is the line where we end and the doctor begins, you know?* [CP7: CP WO BCN]

GPs and CPs believed that patients generated conflict by relaying biased information or directly criticizing professionals.

(The patient) *is a tell-tale* (laughs). *Sometimes they also tell lies, you know? . . . They tell lies to both groups* (the doctors and the pharmacists). *This is also true, eh? They are blackmailers, they blackmail to get what they want.* [CP6: CP W BCN]

Pharmacy assistants created conflict by assuming roles of the pharmacist. This affected quality of patient care and the relationship with the doctor, who preferred to communicate with the pharmacist.

For some years, anybody could start off being the pharmacy guy (pharmacy assistant) *. . . He then started dispensing and ends up putting on a white coat and finally he acts as a pharmacist . . . the boss, the licensed pharmacist, he is almost always there but if he/she is not there, and I need to talk about something and I need his/her knowledge* [GP8: GP W BCN]

However, the view about the other profession changed when practitioners knew each other. Stigmatized views and conflicts were resolved.

The main advantage when collaboration is established is that it breaks a series of stereotypes that exist from the doctor towards the pharmacist, that there is intrusiveness, this or that. . . and the opposite, from the pharmacist towards the doctors, that they are arrogant, that they do this or that, all these things stop when two professionals with similar knowledge, or even a similar age, see each other, a lot of barriers are broken. [CP16: Community pharmacists with experience from Mallorca (CP W MLL)]

Another factor that may contribute to improving the physician's opinion of the pharmacist is the existence of shared goals to improve service, preferably if they are

clinical. Put bluntly, GPs and CPs felt that collaboration was only possible if the pharmacists involved in the team were highly trained and clinically competent.

Initiating collaboration involved extra work for these busy professionals who received no additional remuneration for it. GPs and CPs stated that their attitude would be even worse if the NHS forced them to collaborate without releasing them from other duties or offered economic incentives.

> *To attend to a patient, time is needed and this time is also money. And trained people are needed. For training, time and money are needed, you see? Everything until now has been paid by the pharmacist him/herself. . . . If fewer human resources are available, then somewhere we will have to make cuts.* [CP10: CP W BCN]

Geography and legislation

Legislative and geographical factors had the potential to increase the effort required to coordinate collaboration, which in turn also affected the professionals' attitudes. In poorly defined geographic areas with no clear neighborhood divisions, there were a large number of pharmacies and/or some of them were far from the PCHC. By law, patients can choose any pharmacy to fill their prescription and can switch from one to another in successive visits, making collaboration difficult. Therefore, professionals felt that working together was easier in small areas or when pharmacists in the area worked together and coordinated the delivery of services between them.

> *What happens is that I have the advantage that I am in a basic unit where I have a single reference pharmacy. So, of course, there is only one pharmacy with which I have regular contact . . . which is a very big advantage.* [GP17: General practitioner with experience from Mallorca (GP W MLL)]

According to GPs and CPs, another barrier is caused because pharmacies are privately owned and pharmacists are not seen as part of the health system structure.

> *I consider that the structure clearly leaves the pharmacist outside the national health system. That's why the pharmacists don't know which entity they are part of. We are private centers with an agreement with the administration. Yes, we are obliged to follow all the administration guidelines . . . because we are dispensing national health system prescriptions but then we are not considered as being part of the health system in any way. Not structurally, organizationally, legally, nowhere. If one is not considered* (as part of the system) *it is very difficult to be part of it.* [CP16: CP W MLL]

In the current system, pharmacy income is mainly centered on the payment for dispensing medications. Pharmaceutical care services which do not involve the sale of medications are, therefore, not remunerated so that doctors and pharmacists think that the system promotes an economic conflict of interest that makes it difficult for the pharmacist to collaborate on clinical tasks.

> *What we want is what is right for the patient. And, of course, earn our living with the medications . . . if only they paid me differently. That is a problem. I mean, I think that a problem that our relationship could have* (the doctor with the pharmacist) *is the idea that the doctor has that the pharmacist makes a profit from the medication. And I think that, well, we are earning a living, of course, and at the moment we earn a living with medications. It's a handicap we have.* [CP4: CP WO BCN]

Some doctors and pharmacists suggest that one possible solution is a change in the organization of the pharmacy, integrating it into the health center itself.

> *One possible solution which is not totally unviable is to create pharmacies inside the health center. So that there is a pharmacy service like there is in the hospitals. . . . De-privatize the pharmacies.* [GP17: GP W MLL]

During collaboration

Once collaboration had successfully started, the factors that influenced the relationship changed. Two key factors were identified at this stage: A) achievement of objectives and, B) change in the PCHC management. Figure 2 shows the relationship between the factors affecting GP-CP collaboration once collaboration had begun.

Achievement of objectives

For the relationship to be maintained over time, both professionals and the PCHC manager had to recognize the benefit of this collaboration. There were a number of factors that could help to fulfill the goals. According to GPs and CPs, it seemed essential to have a coordinator (s) or reference person(s), responsible for leading the collaboration and linking the two professional groups.

GPs and CPs felt that meetings needed to be held regularly so that professionals could discuss shared objectives. Meetings between GPs and CPs usually take place in the PCHC at lunch time, when the pharmacies are usually closed and the GPs change shifts so when food was provided it encouraged attendance. While this is not an ideal arrangement, the option of combining lunch with meetings is the most practical solution in a

Figure 2 Factors affecting collaboration between general practitioners and community pharmacists once the collaboration has been started. PCHC: Primary Care Health Center; CPs: Community pharmacists.

country where the midday meal is a social occasion and many business premises, including pharmacies, close between 2-5 pm. It was important to share a clinical chart so that both professionals could have access to complete patient information. Standardized working methods as well as standardized communication channels facilitated collaboration. For non-urgent consultations, a referral form assisted in information transmission.

> *One of the things that we had is that we phoned the health center to have direct access to the doctor's surgery. We had the switchboard number,... each doctor had a switchboard number and we dialled it. I mean we went in directly. This meant that any problem we had could be solved straight away.* [CP6: CP W BCN]

However, a positive attitude might change as a consequence of the increased burden or lack of financing that made collaboration impossible.

> *As we already have a lot of work, it couldn't work and it was cancelled. Because we all have enough work ... I don't think there was any other reason, there was no misunderstanding or anything else. It was just this, the pressure they were under and ours too.* [GP4: GP W BCN]

In addition to workload, wasting time with personal complaints in meetings could make GPs and CPs unwilling to collaborate. Pharmacists needed to work with each other and could be demotivated if they were unable to cooperate with their colleagues. Finally, if GPs and CPs were unable to agree on new objectives, collaboration would end.

> *Sometimes we* (GPs and CPs) *have meetings in the health center and the differences* (between GPs' and CPs' interests) *are so divergent that we don't have points in common. I mean, they* (CPs) *have their interests, that if their stock, that if I don't know what ... When we are having these meetings and you say: "but if we* (GPs) *really don't mind that the stock of generics is this brand or another"... Sometimes they speak about things that we don't understand* [GP13: General practitioner without experience from Mallorca (GP WO MLL)]

Change in PCHC management

If the new management team was not in favor of collaboration, practitioners would no longer have time or support to conduct meetings, collaborative work, etc.

> *The most important handicap appeared when they* (EBA's managers) *left... No other company was contracted; they* (the people of the NHS) *decided to manage the center by themselves. They designated a new manager and, at the beginning, we explained to her everything we had been doing and everything looked fine to her "very good, very good, very good" but we had neither meetings, nor health controls, nor... I mean, everything diminished.* [CP7: CP W BCN]

Discussion

Summary of main findings

This study highlights two stages associated with collaboration: prior to and during collaboration. Key factors prior to collaboration were perception of usefulness, PCHC manager interest, attitude, and geography and legislation. At this stage there was a process of team building that corresponded to the first stages of the model of development of Collaborative Working Relationship (CWR) [22] (Professional Awareness; Professional recognition; Exploration and Trial). During collaboration, which corresponded to the last stages (Professional expansion; Commitment to the CWR), achievement of common objectives and PCHC

management stability were the main factors to consider in perpetuating collaboration.

The most important difference between regions in terms of collaboration was due to the presence of EBAs, which only exist in Barcelona. Practitioners from this type of privately managed center were more motivated to initiate collaboration with the community pharmacies and, once initiated, the relationship seemed to be easily maintained over time.

Negative perception of usefulness was only reported by GPs and CPs without experience in collaboration from Barcelona. The fact that this particular view was only reported by professionals without previous experience in collaboration could be a consequence of previous bad experiences when having contact with the other professional. Although we consider that it could be the other way around and, in fact, it is the negative perception, or prejudice against collaboration, that prevents it. Regional differences cannot be explained with the information we have at present. It is possible that the search for negative cases (i.e. disconfirming cases) was more intensive in Barcelona than in Mallorca although it is also possible that the variance really is due to regional differences. This issue will require further exploration.

GP and CP speech were similar and they agreed on the majority of factors affecting collaboration. Although there are differences in the factors which affect each type of professional (i.e., the pharmacist's conflict of interest is related to an incentive to sell the greatest number of products while that of the doctor is connected with offering a service in which cutting costs results in salary bonuses) both professionals express them, being aware that this is the view others have of them which, in turn, affects collaboration.

Strengths and limitations

To the best of our knowledge, this is the first qualitative study conducted by a multidisciplinary team and the first conducted in Spain. Moreover, this is the first study that compares samples from two regions with different geographical characteristics and health policies. Taking into account distinct contexts improves the relevance of this study. A series of quality control measures were used to guarantee the trustworthiness of the conclusions.

Nevertheless, those who participated in the study were more likely to be interested in this topic. However, we recruited professionals without experience in collaboration and who held negative views regarding collaboration.

Interviews were conducted by a number of investigators, perhaps resulting in biased information, but an interview guide was used and recorded interviews were audited. However, CPs were interviewed by a pharmacist, and GPs were interviewed by a GP or a nurse, encouraging openness and honesty.

Comparison with existing literature

Results from this study are consistent with previous research [12-15]. The importance of mutual knowledge, role definition, CPs' conflict of interest and the territoriality of the GP concurs with previously reported results [12-15] although in our study a problem with territoriality was also reported by pharmacists who felt that GPs were assuming pharmacist roles. Since some GPs in Spain are incentivized through MBO, a stereotypical view of the GP being too worried about meeting targets and being rewarded by the health system was also demonstrated in our study.

Both professions had to perceive collaboration as economically profitable. However, as highlighted by our study, the PCHC manager also had to be motivated to promote this collaboration. In privately managed PCHCs, practitioners stated that collaborative care had led to a reduction in expenses, which could have been a motivation for managers to collaborate. This could be an important factor to consider when implementing collaborative relationship in areas or countries where PCHCs are privately managed.

Pharmacists in Spain only receive public funding for providing prescription medicines. Consequently, barriers related to lack of incentives from the NHS to initiate and maintain collaborative work were highlighted. Previous studies have reported pharmacists' concerns about potential increases in workload and adequacy of remuneration when new services are introduced [23] seemed to be a crucial factor in building multidisciplinary teams [12,14,15]. When professionals meet, preconceptions about the others can be overcome and shared aims, strategies and tools to enhance communication and lead to an improvement in services can be discussed. To maintain collaboration, it is preferable to share clinical objectives [14]. If only administrative issues are addressed, physicians are not interested and pharmacists feel frustrated. Working on clinical issues implies sharing patient clinical information [14]. Ethical and security considerations need to be taken into account when collaborating and the need for patient consent must be considered [22].

Conclusions

A better understanding of the GP-CP relationship enables us to develop strategies and interventions to promote collaboration. The most relevant strategies to implement are the encouragement of positive attitudes and the perception of usefulness on the part of the health administrators and professionals to take advantage of the new changes or strategies imposed by the health system as an opportunity to initiate collaboration (common objective); to promote face-to-face relationship development to overcome prejudices and enable

team work initiation and development; to designate coordinators responsible for coordinating teamwork; and to establish standardized agreed communication. Future research needs to be conducted to evaluate the effectiveness of these strategies.

Competing interests
The authors declare no competing interests.

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Author details
[1]Research and Development Unit, Fundació Sant Joan de Déu, Calle Picasso 13, Sant Boi de Llobregat, Barcelona 08830, Spain. [2]Red de Investigación en Actividades Preventivas y Promoción de la Salud (RedIAPP), Barcelona, Spain. [3]Primary Care Health Center Manso, Catalan Health Service (ICS), Carrer de Manso 19, Barcelona 08015, Spain. [4]Clinical and Practice Research Group, Queen's University Belfast, School of Pharmacy, Medical Biology Center, 97 Lisburn Road, Belfast BT9 7BL, UK. [5]Primary Health Care Center Mallorca, Research Unit, Health care Services of Balearic Isles (IB-Salut), Calle Reina Esclaramunda 9, Palma de Mallorca 07003, Spain.

Authors' contributions
MRV and AF developed the original idea for the research and, together with AMJ, designed the study protocol and coordinated the study. AMJ, MRV, MG and MR conducted the interviews. AMJ, MRV, MG, AF and CH participated in the analysis. MRV drafted the manuscript with the participation of AF and AMJ. All authors have corrected draft versions and approved the final version of the manuscript.

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Recognition of anxiety disorders by the general practitioner: results from the DASMAP Study

Anna Fernández, Ph.D.[a,b,c,*], María Rubio-Valera, M.Sc.[a,b], Juan A. Bellón, Ph.D., M.D.[b,d], Alejandra Pinto-Meza, Ph.D., M.D.[a], Juan Vicente Luciano, Ph.D.[a,b], Juan M. Mendive, M.D.[e], Josep Maria Haro, Ph.D., M.D.[a,f], Diego J. Palao, Ph.D., M.D.[g], Antoni Serrano-Blanco, Ph.D., M.D.[a,b]
DASMAP investigators

[a]*Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, Barcelona, Spain*
[b]*Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria (RedIAPP, Instituto de Salud Carlos III)*
[c]*Clinical and Health Psychology Department, Universitat Autònoma de Barcelona*
[d]*Centro de Salud El Palo Unidad de Investigación del Distrito de Atención Primaria de Málaga. Departamento de Medicina Preventiva y Salud Pública, Universidad de Málaga*
[e]*Centro de Salud La Mina. Institut Català de la Salut (ICS). Sant Adrià de Besos (Barcelona)*
[f]*CIBER Salud Mental (Instituto de Salud Carlos III)*
[g]*Centre de Salut Mental. Corporació Sanitaria Parc Taulí. Institut Universitari Fundació Parc Taulí-Universitat Autònoma de Barcelona (Sabadell, Spain)*

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Abstract

Objectives: The objectives were to determine the levels of general practitioner (GP) recognition of anxiety disorders and examine associated factors.
Methods: An epidemiological survey was carried out in 77 primary care centers representative of Catalonia. A total of 3815 patients were assessed.
Results: GPs identified 185 of the 666 individuals diagnosed as meeting the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) criteria for any anxiety disorder (sensitivity 0.28). Regarding specific anxiety disorders, panic disorder was registered in just three of the patients who, according to the SCID-I, did not meet the criteria for this condition .Generalized anxiety disorder was recorded by the GP in 46 cases, 4 of them being concordant with the SCID-I (sensitivity 0.03). The presence of comorbid hypertension was associated with an increased probability of recognition. Emotional problems as the patients' main complaint and additional appointments with a mental health specialist were associated with both adequate and erroneous recognition. Being female, having more frequent appointments with the GP and having higher levels of self-perceived stress were related to false positives. As disability increased, the probability of being erroneously detected decreased.
Conclusion: GPs recognized anxiety disorders in some sufferers but still failed with respect to differentiating between anxiety disorder subtypes and disability assessment.

Keywords: Anxiety disorders; Epidemiology; General practitioner

1. Introduction

Anxiety disorders, as a group, are the most common mental disorders, both in the general and in the primary health care (PHC) setting [1,2]. Among PHC attendees, 12-month prevalence of anxiety disorders ranges between 8% and 20% [3–7]. Those most often seen in the PHC are panic disorder (PD), with point prevalence ranging from

* Corresponding author. Parc Sanitari Sant Joan de Déu, Research and Development Unit-Fundació Sant Joan de Déu, Dr. Antoni Pujadas, 42. 08830 Sant Boi de Llobregat, Barcelona. Spain. Tel.: +34 93 640 63 50x12546; fax: +34 93 630 53 19.
E-mail address: afernandez@pssjd.org (A. Fernández).

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1.5% to 3.1%, and generalized anxiety disorder (GAD), with point prevalence from 3.7% to 8.5% [5,6,8,9].

In the last 20 years, considerable efforts have been made to increase recognition of both depression and anxiety by general practitioners (GPs). In spite of the substantial advance made with depression, anxiety disorders are still largely underdiagnosed by GPs [8]. Recent clinical guidelines for common disorders published by the National Institute for Health and Clinical Excellence (NICE) state that just 1 in 10 people with an anxiety disorder is identified in the primary care (PC) setting (compared with 1 in 3 for depressive disorder) [10]. Several factors are related to this low rate of recognition: patients' fear to express their anxious feelings due to the stigma, and lack of GP education in mental health issues. Recognition of anxiety disorders in the PHC could be complicated because patients also present comorbid chronic conditions and somatic complaints. GPs and patients are used to focusing on the physical symptoms, avoiding the possibility of a mental disorder [9]. Moreover, GPs work under extreme time pressure with increasing expectations of what should be done during a medical consultation. Many complain about the burden of their workloads, and they view psychiatric patients as adding to these demands and as 'blockers' who complicate and lengthen visits [11].

Recognition of anxiety disorders is important due to the serious impact that these conditions have from both a social and individual perspective. Anxiety disorders affect patients' quality of life, are highly debilitating and place extreme limitations on people's lives [12]. For instance, a study assessing the impact of anxiety disorders in the quality of life using the Short Form Health Survey showed that PD impacted the subscales of physical health and bodily pain, whereas the effects of GAD were observed in the subscales of emotional role [13]. The societal cost, both from a human and economic point of view, is also high. In a recent study, anxiety disorders ranked third in the burden of disease in PHC, being responsible for almost 805 quality-of-life years lost (per 100,000 PHC attendees) [14].

Moreover, anxiety disorders are associated to higher economical costs due to the use of health services and loss of productivity [15].

There is scarce scientific evidence on course of undetected and untreated anxiety disorders. A recent observational Dutch study concludes that there was no difference in the course of anxiety disorders between treated and untreated patients, with both groups showing a modest decrease in anxiety symptoms after 1 year. As the authors said, this result could be related to the kind of treatment that recognized cases receive (not necessary the treatment with the best evidence) [16]. On the other hand, other studies showed the opposite. A longer duration of untreated GAD was associated to a worse clinical course [17]. Similarly, if PD is left untreated, patients could develop other psychiatric conditions (such as agoraphobia or depression), which may complicate PD outcome [18,19].

As the majority of people suffering anxiety disorders are seen in the PHC, GPs are in a privileged position to detect these disorders in patients and either treat or refer them to the mental health specialist. Moreover, as some subtypes of anxiety disorders such as GAD and PD vary in severity, complexity, course and recommendations of treatment, it could be interesting to assess specific recognition of these anxiety subtypes. The aim of this study is to determine levels of anxiety disorder recognition by the GP and examine associated factors.

2. Methods

The study was a face-to-face, cross-sectional survey of a representative sample of adult patients (18 years or older) at PHC centers in Catalonia (Spain). Catalonia is one of the 17 autonomous regions that comprise Spain, with a population of 7,134,697 according to the 2006 census. In 1981, Spain began a process of decentralization of health service management, and this is now carried out by each autonomous region. Data were collected between October 2005 and March 2006 using a paper-and-pencil interview. Following an appointment with a GP, patients were invited to participate in the Diagnostic and Assessment Study of Mental Disorders in Primary Care (DASMAP study) [6] and were evaluated at the PC centers after written informed consent had been obtained.

2.1. Participants

A stratified multistage probability sample without replacement was drawn. Replacement was prohibited to ensure that every individual had a known probability of selection. The sampling frame was the seven health regions in Catalonia. Stage 1 involved the selection of the PC centers within each health region (there were 350 PC centers in Catalonia in 2005). The number of PC centers to be selected in each region was proportional to the population of the region. However, to ensure a minimum set of interviews from even the smallest regions, at least 6 PC centers were chosen per region. The probability of selection of each PC center was related to the population of the catchment area covered by the center. Eighty PC centers were selected for participation, and two refused (97.5% acceptance rate). In stage 2, all GPs (n=913) at the PC centers were invited to participate. A total of 618 GPs (67.7%) took part in the study. In stage 3, patients were selected with a systematic sampling strategy from the daily list of all patients with an appointment with each of the participating GPs. A total of 5402 patients were randomly selected. Of those, 654 (12.1%) did not keep their appointment with the GP and were not invited to join the DASMAP study. A total of 4748 were invited to take part. A further 764 (16.1%) declined to participate, and 164 (3.5%) were excluded because they showed cognitive impairment severe enough to preclude an adequate interview, leaving a study sample of 3820 participants from 78 PC centers. One of the PC centers was excluded from the statistical analyses because of data loss. The final analyzed sample consisted of 3815 patients

(80.3% of the patients initially invited) with a mean age of 54.3 years (S.D.=17.31; range: 18–97 years). Females made up 63% of the sample. More information about this study is available in Serrano-Blanco et al. [6].

2.2. Measures

All assessments were performed face-to-face by a group of 20 trained clinical psychologists. All received a 2-day training course provided by the study investigators (A.S.B., D.P., A.P.M.).

Anxiety disorders were assessed with the Spanish versions of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [20] with the exception of obsessive–compulsive disorder (OCD), which was assessed using the Mini Neuropsychiatric Diagnostic Interview (MINI) [21,22]. Both instruments allow diagnoses according to DSM-IV [23] criteria. One central DASMAP study objective was to assess the prevalence of mood and anxiety disorders in Catalonia PC since such disorders were expected to be the most prevalent. Therefore, we chose the SCID-I as it is one of the most frequently used and reliable instruments in the assessment of these disorders. As the complete SCID-I would have taken more than an hour to administer, for feasibility and due to the low prevalence of some mental disorders in PC, we decided to evaluate other mental disorders (OCD, manic/hypomanic episodes, substance and alcohol use disorders, anorexia nervosa and bulimia nervosa) with a shorter instrument, the MINI.

Self-perceived disability, self-perceived stress and self-perceived social support were assessed through the Sheehan Disability Inventory (SDI). Self-perceived disability was assessed using three questions of the SDI. The questions evaluated interference in three domains: work, social life and family life. Participants answered using a scale ranging from 0 to 10. The total score is the sum of the scores in the three items, ranging from 0 to 30, with higher figures indicating greater disability. Self-perceived social support was assessed by asking, "In the last week, how much support have you received from friends, relatives and co-workers, as a percentage of the amount you needed to cope?" Participants answered on a 0–100 visual scale. The question related with self-perceived stress was "Since your last visit, how much were you set back by stressful events or personal difficulties such as work, home, social, health, or financial problems?" Participants answered on a 0–10 visual scale [24,25].

Quality of life was assessed with the Spanish version 2.0 of the 12-item Short-Form Health Survey (SF-12) [26–28]. The SF-12 is a valid and reliable widely used instrument for the assessment of health-related quality of life. Two measures were derived from the SF-12: a physical component summary scale (PCS-12), indicating physical quality of life, and a mental component summary scale (MCS-12), indicating mental quality of life. Each scale uses all 12 items but with different weights. The PCS-12 and MCS-12 scales were scored using norm-based methods.

Chronic physical conditions were assessed using a checklist with questions about a wide range of conditions including asthma, bronchitis, ulcer, constipation, high blood pressure (BP), heart disease, heart attack, migraines, stroke, allergies, arthritis, back pain, cataracts, diabetes and neck pain. Participants were categorized through self-reports on the presence of each chronic physical condition.

All respondents were also asked about their main reason for consulting the GP: physical, emotional, administrative or a combination. In addition, they were asked whether they had seen a mental health professional (psychiatrist or psychologist) in the 12 months prior to the survey.

Previous 12-month diagnoses made by the GP (that is, same period assessed retrospectively by the epidemiological interview) were extracted by the interviewers from the electronic clinical chart and recoded into a dichotomous variable that included the presence or absence of an anxiety diagnosis. Interviewers were blind to the final interview diagnoses. GP diagnoses were based on the *International Classification of Diseases*, in its 9th or 10th version, or on The International Classification of Primary Care second version (ICPC-2) by the World Organisation of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians. Codes included are:

- From the ICPC-2: P01 (feeling anxious, nervous, tense); P02 (acute stress response); P74 (anxiety disorder/anxiety state); P79(phobia/compulsive disorder).
- From CIE-9: 300.0 and 300.00 (anxiety states); 300.01 (PD no agoraphobia); 300.02 (GAD); 300.09 (other anxiety disorder); 300.2 and 300.20 (phobic disorder); 300.21 (agoraphobia with PD); 300.22 (agoraphobia without mention of PD); 300.23 (social phobia); 300.29 (other isolated or specific phobia); 300.3 (OCD).
- CIE-10: F40 (phobic anxiety disorder); F40.0 (agoraphobia); F40.1 (social phobias); F40.2 (specific/isolated phobias); F40.8 (other phobic anxiety disorders); F40.9 (phobic anxiety disorder, unspecified); F41 (other anxiety disorders); F41.0 (PD); F41.1 (GAD); F41.2 (mixed anxiety–depression); F41.3 (other mixed anxiety disorder); F41.8 (other anxiety disorder); F41.9 (other anxiety disorder, unspecified); F42 (OCD).
- Any explicit mention to any anxiety disorder or anxiety symptomatology in the clinical chart not made trough the code was also codified as anxiety disorder.

2.3. Statistical analyses

The sensitivity, specificity, and positive and negative predictive value associated with physician identification of anxiety disorders were calculated by standard methods. Gold standard was the DSM-IV any anxiety disorders (pooled category including GAD, PD with/without agoraphobia, social phobia, specific phobia, OCD).

Table 1
Recognition of anxiety disorders by the GP

DSM-IV diagnosis	Codes included (GP diagnosis)	DSM prevalence[a]	GP prevalence[b]	Sensitivity	Sensitivity without missing data	Specificity	Positive predict value	Negative predict value
Any anxiety disorder	ICPC-2: P01, P02, P74, P79 ICD-9:300.0, 300.00, 300.01, 300.02, 300.09, 300.2, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3 ICD-10: F40, F40.0, F40.1, F40.2, F40.8, F40.9, F41, F41.0, F41.1, F41.2, F41.3, F41.8, F41.9, F42	18.49% (666/3815)	13.53% (489/3815)	0.28 (185/666)	0.32 (185/578)	0.90 (1845/3149)	0.38 (185/489)	0.86 (2845/3326)
PD (with or without agoraphobia)	ICD-9: 300.01, 300.21 ICD-10: F41.0	7% (253/3815)	0% (3/3815)	–	–	–	–	–
GAD	ICD-9: 300.02 ICD-10: F41.1	3.8% (132/3815)	1.26% (46/3815)	0.03 (4/122)	0.04 (4/111)	0.99 (3641/3683)	0.09 (4/46)	0.997 (3683/3815)
Any anxiety disorders among those with depression[c] (according to SCID-I)	All codes mentioned above plus codes of depressive disorders	41.67% (138/339)	31.02% (105/339)	0.44 (61/138)	0.47 (61/130)	0.78 (157/201)	0.58 (61/105)	0.67 (157/234)
Pure anxiety disorder (without depression)	All codes mentioned above without depression	16.02% (528/3476)	11.67% (384/3476)	0.24 (124/528)	0.28 (124/448)	0.91 (2688/2948)	0.32 (124/384)	0.87 (2688/3092)

[a] DSM prevalence used as the gold standard (any anxiety disorder includes PD with or without agoraphobia, GAD, obsessive–compulsive disorder, specific phobia and social phobia).
[b] Cases registered in the clinical chart by the GP.
[c] There are 339 patients with major depressive disorders. Prevalence=9.6% [6].

There were 695 of the 3815 participants (16.45%) who did not have GP diagnosis information (information missing from the clinical chart, that is, GPs did not report any kind of diagnoses: physical, mental or social). To minimize their effect, we excluded these cases when carrying out sensitivity data analysis. We present these data considering three distinct subpopulations: (1) overall cases, (2) cases with comorbid anxiety and depressive disorders and (3) cases with "pure" anxiety disorders.

As specific analyses, we also presented data about recognition of GAD and PD.

In order to ascertain factors associated with (1) concordant SCID-I/GP anxiety disorders and (2) false positives, we used multilevel logistic regression with GP and PC center as random factors. Firstly, we tested whether multilevel logistic regression was more appropriate than standard logistic regressions. When we compared the null models, including the PC center as a random factor, likelihood ratio tests were significant for all models. Secondly, we compared null models that included PC center and GP as random factors versus those with only PC center, and likelihood ratio tests were not significant. That is, the GP did not add additional information when considering factors associated with concordant SCID-I/GP anxiety disorders, so it was excluded as a random factor. However, it was added when considering factors associated with false positives, so in this case, GP remained in the model as random factor. Subsequently, we performed a univariate multilevel logistic regression. We included in the final models those variables that were significant ($P \leq .20$) [29] in univariate multilevel logistic regression analyses.

The statistical analyses were conducted using STATA 11. All significance tests were done using two-sided tests evaluated at .05 significance level.

3. Results

3.1. Recognition of anxiety disorders by the GP

Twelve-month prevalence of any anxiety disorder according to the SCID-I was 18.49% [95% confidence interval (CI) 15.77%–21.55%; n=666]. GPs identified 185 of the 666 individuals diagnosed with the SCID-I (sensitivity 0.28, or 0.32 when excluding diagnoses missing from the clinical chart). As expected, due to the relatively low prevalence of anxiety disorders, the specificity was high (0.90), whereas the positive predictive value was 0.38. The Kappa value was 0.20 (Table 1).

The sensitivity rate increased to 0.44 (0.47 when excluding diagnoses missing from the clinical chart) in cases with comorbid depressive disorders. On the other hand, among those with "pure" anxiety disorders according to the SCID-I, GP recognition decreased to 0.23 (0.28 when considering diagnoses missing from the clinical chart).

Regarding specific anxiety disorders, PD was registered in just three of the patients who, according to the SCID-I, did not meet the criteria for this condition. GAD was recorded by

Table 2
Factors associated with concordant SCID-I/GP recognition of anxiety disorders (adjusted results)

	OR	*P>z*	95% CI	
Women vs. men	1.56	.08	.95	2.56
Age	.99	.17	.97	1.00
SF12 quality of life (mental component)	.98	.07	.97	1.00
Paid employment but on sick leave vs. paid employment	.98	.94	.53	1.81
Others vs. paid employment	.85	.55	.51	1.43
Disability (Sheehan)	.99	.65	.97	1.02
Self-perceived stress (Sheehan)	.97	.46	.91	1.04
Self-perceived social support (Sheehan)	1.00	.94	.99	1.01
Presence of high BP	2.42	.001	1.47	3.98
Presence of diabetes	.70	.42	.29	1.68
Main complaint: mental or emotional problems	3.42	.000	2.11	5.53
Number of PC visits	1.02	.07	.99	1.05
Consulting with a mental health specialist (yes vs. no)	1.60	.04	1.02	2.52
Presence of DSM-IV major depressive disorders	1.45	.18	.85	2.46
Variance explained by PC center	.36	–	.11	1.16

the GP in 46 cases, 4 of them concordant with the SCID-I (sensitivity 0.03).

3.2. Who did the GP adequately identify as suffering from anxiety, according to the SCID-I?

Among those with anxiety disorders, emotional problems as main reason for consultation [odds ratio (OR)=3.42, 95% CI 2.11–5.53], having high BP (OR=2.42, 95% CI 1.47–3.98) and having seen a mental health specialist (OR=1.60, 95% CI 1.02–2.52) were associated with an increased probability of accurate recognition. Although comorbid depressive disorder showed a significant statistical association in the bivariate analyses, this association disappeared when adjusting for all the other variables (Table 2).

3.3. What are the factors associated with erroneous diagnoses according to the SCID-I?

Factors associated with false positives, that is, patients diagnosed with an anxiety disorder who did not meet SCID-I criteria, were being female (OR=1.54, 95% CI 1.12–2.12), having self-perceived stress (OR=1.09, 95% CI 1.03–1.14), the emotional problems as main reason for consultation (OR=3.68, 95% CI 2.39–5.68), number of appointments with the GP (OR=1.02, 95% CI 1.00–1.04) and having seen a mental health specialist (OR=2.19, 95% CI 1.49–3.22). Nevertheless, as the mental quality-of-life score increased, the probability of being erroneously identified as having an anxiety disorder decreased (OR=0.97, 95% CI 0.96–0.98), while as disability increased, the probability of being erroneously detected decreased (Table 3).

4. Discussion

This study has several strengths. To our knowledge, this is the first study focusing on recognition of anxiety disorders by the GPs conducted in a Mediterranean country. Previous studies were from USA, UK or China, countries with different cultural values and health systems. Moreover, it has been conducted in a large representative sample of PC attendees. This allows us to improve its external validity. In addition, the gold standard for anxiety diagnosis was applied through the administration of the SCID-I by trained psychologists. GPs' diagnoses were extracted from the electronic clinical chart, so it could be seen as a proxy for their real practice. Before discussing our study findings, some limitations should be noted. Firstly, since the DASMAP project is a cross-sectional study, we cannot conclude that factors associated with adequate diagnoses of patients with anxiety disorders are causally related. Secondly, due to the study design, we were not able to test whether adequate recognition was associated with better outcomes. Thirdly, we did not evaluate some relevant GP variables such as attitudes toward mental disorders or education in mental health, or organizational variables such as mean time per visit or the availability of multidisciplinary teams with mental health professionals, which could be associated with adequate recognition of anxiety disorders. Finally, it is important to emphasize that some of the disorders detected through the epidemiological interview may not have been debilitating enough for the patient to seek help. For instance, in our category of any anxiety disorder, we included specific phobias (12-month prevalence of 6%). A patient could have a SCID-I positive diagnosis of anxiety disorder because he or she is afraid of spiders, but this might not be considered serious enough to consult the GP. In spite of this, if we deleted specific phobias from the any anxiety disorder category, sensitivity only increased 3.6 points — from 28%

Table 3
Factors associated with false-positive diagnosis of anxiety disorders according to SCID-I (adjusted results)

	OR	*P>z*	95% CI	
Women vs. men	1.54	.007	1.12	2.12
Age	1.01	.14	0.99	1.02
SF12 quality of life (mental component)	0.96	.000	0.96	0.98
Paid employment but on sick leave vs. paid employment	1.20	.43	0.76	1.91
Others vs. paid employment	0.62	.01	0.43	0.90
Disability (Sheehan)	0.98	.03	0.95	0.99
Self-perceived stress (Sheehan)	1.09	.003	1.03	1.14
Self-perceived social support (Sheehan)	1.00	.69	0.99	1.00
Presence of cardiovascular disease	1.01	.96	0.65	1.58
Presence of respiratory disease	0.73	.18	0.46	1.16
Presence of pain-related health conditions	1.31	.11	0.94	1.81
Presence of high BP	0.94	.69	0.66	1.31
Presence of diabetes	0.83	.47	0.49	1.38
Main complaint: mental or emotional problems	3.68	.000	2.38	5.68
Number of PC visits	1.02	.03	1.00	1.04
Consulting with a mental health specialist (yes vs. no)	2.19	.000	1.49	3.23
Presence of DSM-IV major depressive disorders	0.70	.17	0.42	1.16
Variance explained by PC center	0.51	–	0.25	1.07
Variance explained by GP	0.54		0.23	1.29

to 31.65% — suggesting that the inclusion of specific phobia in our analyses did not affect sensitivity. We also had to bear in mind that some of our detected cases could be epidemiological false positives because, in epidemiological research studies, diagnostic criteria tend to be applied algorithmically and omit contextual aspects [30–32]. Finally, we are using a psychiatric diagnosis as a gold standard to assess GPs, and this may be inappropriate, as others have pointed out [33,34].

Despite these limitations, our study suggests that recognition of anxiety disorders by GPs in Catalonia is higher than expected. Whereas NICE states that just 1 in 10 is recognized, our results indicate that more than 1 in 3 is identified. Although our results are better than other studies, there are still a lot of patients suffering anxiety that remains undiagnosed and undertreated. Moreover, and in line with some recent papers [3,4,8], GPs fail to differentiate between anxiety disorder types. This is important because course of disease and recommended treatment will vary for GAD, PD or other anxiety disorders. Educational efforts should be made in order to teach GPs how to (1) detect anxiety symptomatology and (2) differentiate among anxiety disorders. To make detection easy, GPs could use brief screening questionnaires, such as GAD-7, which contains six GAD items and one PD item and also measures severity [5,35,36]. GPs could also add questions about patients' expectations, needs for treatment and disability.

Regarding factors associated with accurate recognition, it is well known that patients' explicit demand for care with respect to mental/emotional problems is associated with higher recognition by GP [37,38] and that additional contact with mental health specialists increases recognition. Nevertheless, these two factors are also associated with false-positive diagnosis of anxiety. If a patient presents as a main reason for consultation an emotional problem, GPs could possibly label a normal stress response as an anxiety disorder. In fact, our data show that erroneous diagnosis is also associated with high levels of self-perceived stress and with low levels of mental quality of life. This supports the idea that GPs may be medicalizing normal responses or emotional problems that are not mental disorders. Our data also show that GPs made erroneous diagnoses in cases that are not "debilitating enough" (as the probability of being erroneously diagnosed decreases as disability increases). Consequently, efforts are needed to educate the general population and GPs to distinguish between emotional problems and mental disorders. As we said before, the assessment of disability by the GP could be a useful cue in helping the GP to differentiate between them [39]. On the other hand, the relationship between additional mental health contact and both concordant and erroneous diagnosis is striking. This double association could be explained by the fact that GPs are used to referring patients that they believe have anxiety disorders to a mental health specialist. So, independently the anxiety diagnosis GP made is concordant with SCID-I or not, we find an association. Unfortunately, the cross-sectional study design and our limited data prevent us from drawing conclusions.

Regarding the association between high BP and accurate anxiety recognition by the GP, several hypotheses could be proposed due to conflicting evidence on the link between hypertension and anxiety. On the one hand, scientific evidence shows an association between anxiety symptoms and high BP. In fact, anxiety disorders have been reported as a risk factor of incident hypertension [40]. On the other hand, a recent paper [41] suggested that the act of diagnosing patients as hypertensive rather than having elevated BP per se might partly explain the higher levels of psychological distress in patients treated for hypertension. For instance, patients may express their emotional concerns or health anxiety for having hypertension. They could express anxious feelings, making detection easier. Similarly, it is possible that GPs know that anxiety is associated with hypertension and are consequently more aware when carrying out anxiety symptomatology assessment.

Being female and having an increase in the number of GP appointments are related to false-positive diagnosis. In one sense, this is logical as mental disorders (including anxiety disorders) have a higher prevalence in women and among frequent PC attendees [6,42,43]. GPs, being aware of this, could possibly make an erroneous anxiety diagnosis.

In conclusion, our data suggest that although GPs recognized some anxiety disorders, they failed in the key elements of differentiating between kinds of anxiety disorders and disability assessment. The latter aspect is of special importance in distinguishing between normal and abnormal emotional responses. Some brief questionnaires could help GPs to detect the different anxiety disorders. But only diagnosing is not enough. In order to improve the quality of life of these patients, evidence suggests that the best way to manage anxiety disorders in the PHC setting is with multimodal intervention programs, such as stepped collaborative care [10,35,36]. Future research will focus on how to implement these interventions.

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Adjustment disorders in primary care: prevalence, recognition and use of services

Anna Fernández, Juan M. Mendive, Luis Salvador-Carulla, María Rubio-Valera, Juan Vicente Luciano, Alejandra Pinto-Meza, Josep Maria Haro, Diego J. Palao, Juan A. Bellón, Antoni Serrano-Blanco and the DASMAP investigators

Background
Within the ICD and DSM review processes there is growing debate on the future classification and status of adjustment disorders, even though evidence on this clinical entity is scant, particularly outside specialised care.

Aims
To estimate the prevalence of adjustment disorders in primary care; to explore whether there are differences between primary care patients with adjustment disorders and those with other mental disorders; and to describe the recognition and treatment of adjustment disorders by general practitioners (GPs).

Method
Participants were drawn from a cross-sectional survey of a representative sample of 3815 patients from 77 primary healthcare centres in Catalonia. The prevalence of current adjustment disorders and subtypes were assessed face to face using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Multilevel logistic regressions were conducted to assess differences between adjustment disorders and other mental disorders. Recognition and treatment of adjustment disorders by GPs were assessed through a review of patients' computerised clinical histories.

Results
The prevalence of adjustment disorders was 2.94%. Patients with adjustment disorders had higher mental quality-of-life scores than patients with major depressive disorder but lower than patients without mental disorder. Self-perceived stress was also higher in adjustment disorders compared with those with anxiety disorders and those without mental disorder. Recognition of adjustment disorders by GPs was low: only 2 of the 110 cases identified using the SCID-I were detected by the GP. Among those with adjustment disorders, 37% had at least one psychotropic prescription.

Conclusions
Adjustment disorder shows a distinct profile as an intermediate category between no mental disorder and affective disorders (depression and anxiety disorders).

Declaration of interest
None.

With the reviews of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Statistical Classification of Diseases and Related Health Problems* (ICD) criteria for their 5th and 11th versions respectively, concerns about the relevance and usefulness of adjustment disorder diagnoses re-entered the mental health arena.[1–5] There are those who strongly support the value of the concept of adjustment disorder as a category, but are critical of the current criteria because of their vagueness and because they fail to sufficiently distinguish adjustment disorders from normal reactions to stressors.[2–4,6,7] Despite frequent statements on the high prevalence of adjustment disorders, few studies have addressed this issue. In fact, adjustment disorders have not been included in any of the main epidemiological studies carried out in recent years such as the World Health Organization (WHO) Mental Health Epidemiological Survey, the Epidemiologic Catchment Area study and the National Comorbidity Survey Replication. To the best of our knowledge, only the European Outcome of Depression International Network (ODIN) study reported prevalence of adjustment disorders in the general population, but solely for the subtype with depressive features, reporting a prevalence of 1%.[8] Another study of the general population of Zurich over 65 years old reported a prevalence of 2.3%.[9] In primary care, prevalence has been estimated to range from 1% in France for the anxiety features subtype,[10] to 18% for adjustment disorders overall in studies performed during the 1980s.[5] Strain *et al* reported a prevalence of 12% in hospital settings.[11] A recent meta-analysis estimated that the prevalence of adjustment disorders was 19.4% in oncological and haematological settings and 15.4% in palliative care.[12]

Conceptually, adjustment disorders are an intermediate health condition between normal responses to stress and more severe emotional disorders such as anxiety and depression.[2] A number of studies have found that adjustment disorders differ from mood disorders in some parameters. For instance, adjustment disorders were associated with more stressors, were more frequent in younger patients and less likely to occur in those living alone and in women.[11,13] Runeson *et al* reported a shorter interval (1 month) between adjustment disorders and the emergence of suicidal behaviour than that found for depression (3 months) in young people.[14] In contrast, other studies have failed to find differences between adjustment disorders and other psychiatric diagnoses.[4,8] Moreover, there is scarce information on how general practitioners (GPs) manage this disorder, and the controversy deepens when we consider that the second edition of the *International Classification of Primary Care* (ICPC-2) makes no reference to adjustment disorders.[15]

Our study aims were to estimate the prevalence of adjustment disorders in primary care; to explore whether there are differences between primary care patients with adjustment disorders, those with mood or anxiety disorders and those with no mental disorder; and to describe recognition of adjustment disorders by GPs and the treatment given to patients with a standardised diagnosis of adjustment disorder.

Method

The Diagnostic and Assessment Study of Mental Disorders in Primary Care (DASMAP) was a face-to-face, cross-sectional survey of a representative sample of adults (18 years or older) attending primary care health centres in Catalonia, one of the 17 regions or autonomous communities of Spain.[16] Since 1981 these autonomous communities have been fully responsible for health and social care which is publicly financed, and near-universal coverage is provided.[17] General practitioners have a key role in the recognition, diagnosis, treatment and referral of patients with mental disorders.

A stratified multistage probability sample without replacement was drawn. Replacement was prohibited to ensure that every individual had a known probability of selection. The sampling frame was the seven Catalonia health regions. The first stage consisted of the selection of primary care centres within each health region. A list of all centres and relevant data were obtained to enable the random selection. A previous filter of centres with fewer than 4000 attenders was done to exclude non-representative centres. The probability of selection of each centre was related to the population of the catchment area that it covered, so that centres with larger catchment areas were more likely to be selected. The number of centres selected in each region was proportional to the region's population. However, to ensure a minimum set of interviews even in the smaller regions, at least six centres were chosen per region. Of 352 centres, 77 participated in the DASMAP study. In the second stage, all GPs from the selected health centres were invited to participate. A total of 618 GPs agreed to take part. This represented nearly 69% of all GPs working at the 77 health centres. The third stage consisted of random selection of patients. A systematic sampling strategy was used, inviting every fifth patient from the daily appointment schedule of each participating GP. Of the 5402 patients pre-selected from the GP list, 654 did not keep their appointment, and 764 of the 4748 remaining patients declined to participate. A total of 169 patients were excluded because they showed cognitive impairment severe enough to preclude an adequate interview or they did not speak Spanish. The final sample comprised 3815 patients (80.5% of those contacted). Further DASMAP study information is available elsewhere.[16]

Measures

Mental disorders were assessed with the Spanish versions of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (major depressive episode, dysthymic disorder, anxiety disorder modules and adjustment disorders excluding obsessive–compulsive disorder) and the Mini International Neuropsychiatric Interview (MINI; manic/hypomanic episodes, obsessive–compulsive disorder, substance and alcohol use disorders, anorexia nervosa and bulimia nervosa).[18–20] Both instruments allow diagnoses according to DSM-IV criteria. One important DASMAP study objective was to assess the prevalence of mood and anxiety disorders in primary care in Catalonia,[16] since such disorders were expected to be the most prevalent. Therefore, we chose the SCID-I because it is one of the most frequently used and reliable instruments for the assessment of these disorders. Since the complete SCID-I would have taken over an hour to administer, we decided to evaluate other mental disorders with a shorter instrument (the MINI).

Chronic medical conditions, defined by the WHO as 'health problems that require ongoing management over a period of years or decades',[21] were assessed using a checklist including questions about a wide range of chronic physical conditions including asthma, bronchitis, ulcer, constipation, high blood pressure, heart disease, heart attack, stroke, epilepsy, migraine, allergies, arthritis, back pain, cancer, cataracts, diabetes, hearing impairment, neck pain, prostate-related conditions and vision impairment. Respondents were asked whether they had ever experienced any of the symptom-based checklist conditions. For conditions typically identified by medical diagnosis, respondents were asked whether a doctor or other health professional had ever told them they had the condition. Although checklist measures are imperfect, they provide useful information on both treated and currently untreated chronic conditions,[22] and could predict healthcare use.[23] Moreover, self-report of chronic physical conditions shows moderate to high agreement with medical records.[24]

Quality of life was assessed with the Spanish version 2.0 of the 12-item Short Form Health Survey (SF-12).[25,26] The SF-12 is a valid, reliable instrument for health-related quality of life assessment. Two measures were derived from the SF-12: a physical component summary scale (PCS-12) indicating physical quality of life, and a mental health summary scale (MCS-12) covering mental quality of life. Each scale uses all 12 items but with different weights. The PCS-12 and MCS-12 scales were scored using norm-based methods, with a mean of 50 and standard deviation of 10. Self-perceived disability (score 0–30), social support (0–100) and self-perceived stress (0–10) were assessed through the Sheehan Disability Scales.[27–29]

Respondents were also asked about their main complaint: physical, emotional, administrative or a combination. In addition, they were asked about the number of visits to their GP in the previous 12 months. Psychotropic drug use was assessed using the information from the computerised clinical history. Regardless of the patients' diagnostic status, evaluators extracted information about any psychotropic medication prescribed to the participant in the previous 12 months, without distinguishing between occasional and long-term use. Psychotropic drugs were categorised according to the Anatomical Therapeutic Chemical (ATC) classifications, including anxiolytics (N05B), hypnotics and sedatives (N05C) and antidepressants (N06A). Diagnoses made by the GP were extracted from the clinical chart and recoded into a variable that included the presence or absence of adjustment disorders, other mental disorders or social problems. The GP diagnoses were based on ICD-9 or ICD-10,[30,31] or on the ICPC-2.[15]

Procedure

A group of 20 trained psychologists evaluated the participants (training was provided by a panel of three experts and consisted of a 2-day course). Data were collected between October 2005 and March 2006 using a paper-and-pencil personal interview. After visiting their GP, individuals were invited to participate in the study. They were evaluated at the primary care centre after acceptance (signing an informed consent form). The instruments were administered during a clinical interview of approximately 45 min. Following data collection, responses were processed using response automatic capture software TeleForm (Autonomy Cardiff, Vista, California, USA). Ethical approval was obtained from the Sant Joan de Déu Foundation ethics board.

Statistical analysis

Prevalence estimates of adjustment disorders and subtypes were expressed in both absolute numbers and weighted percentages with 95% confidence intervals. The results of the analysis were weighted to account for the varying probability of selection, given the stratified sampling. Three different logistic models were fitted

to assess whether there were differences between adjustment disorders and major depression; between adjustment disorders and anxiety disorder; and between adjustment disorders and no mental disorder. In an additional analysis set we compared adjustment disorder plus depressive symptoms *v.* major depression, and adjustment disorder plus anxiety symptoms *v.* generalised anxiety disorder. Multilevel analyses were conducted considering primary care centre and GP as possible sources of random effects. The null models were statistically significant in all five comparisons for primary care centre, but in only one of the five comparisons for GP (adjustment disorder with depressive symptoms *v.* major depression). Thus, GP as a source of variability was ruled out in the analyses of the remaining four comparisons. Subsequently, we performed univariate multilevel logistic regression, including variables with significance $P \leqslant 0.2$ in univariate analysis in the final models.

Among those with adjustment disorders we estimated the percentage of cases recognised by the GP. The mean number of visits and the percentage of patients with a prescription of a psychotropic drug are described. We also tested multilevel analysis. Null models were not statistically significant, so we performed standard logistic regressions to ascertain which factors were associated with prescription among those with adjustment disorders. First, we tested bivariate models with psychotropic medication (yes/no) as the dependent variable and gender, age, type of adjustment disorder, disability, stress, social support, mental and physical quality of life, main reason for consultation, emotional problems and number of visits as the independent variables. In the final models we included variables with significance $P \leqslant 0.2$ in univariate analyses. The statistical analyses were conducted with Stata version 11 on Windows 7. All significance tests were made using two-sided tests evaluated at the $P < 0.05$ level of significance.

Results

Prevalence of adjustment disorder

Of the 3815 study participants, 2.94% (95% CI 2.21–3.91, $n = 110$) met SCID-I criteria for a diagnosis of current adjustment disorder. Taking adjustment disorder subtypes into account, 29 of the 3815 participants presented with depressed mood (0.77%, 95% CI 0.49–1.21) and 50 had anxiety symptoms (1.34%, 95% CI 0.88–2.02). The other people with adjustment disorder ($n = 31$; 0.83%, 95% CI 0.54–1.28) presented with another subtype (disturbance of conduct, unspecified or mixed symptoms). Table 1 shows the sociodemographic and clinical characteristics of the sample categorised by adjustment disorder subtypes and other disorders.

Comparisons with depression and anxiety disorders and no mental disorder

Table 2 shows the three final multivariate logistic models used to assess differences between adjustment disorder *v.* major depression; adjustment disorder *v.* anxiety disorder; adjustment disorder *v.* primary care patients with no mental disorder; adjustment disorder with depressive symptoms *v.* major depression; and adjustment disorder with anxiety symptoms *v.* generalised anxiety disorder.

Adjustment disorders and major depression

Adjustment disorders were less prevalent in women than major depressive disorder (odds ratio (OR) 0.36, 95% CI 0.17–0.77). Compared with those with major depression, those with adjustment disorders were less likely to report emotional problems as a main reason for consultation (OR = 0.24, 95% CI 0.09–0.67). Those with adjustment disorders reported a better quality of life (both physical and emotional) than patients with major depression and had a better perception of social support. In addition, those with adjustment disorders were less likely to have been prescribed an antidepressant than those with major depression (OR = 0.43, 95% CI 0.19–0.98). When considering only the depressive subtype of adjustment disorder, we found that participants with this subtype scored more highly on mental quality of life (OR = 1.11, 95% CI 1.00–1.24).

Adjustment disorder and anxiety disorders

In women, adjustment disorders were less prevalent than anxiety disorders (OR = 0.42, 95% CI 0.25–0.69). Patients with adjustment disorders also had higher mental quality of life scores (OR = 1.02, 95% CI 1.00–1.04). Chronic medical illnesses were less likely in participants with adjustment disorders than in those with anxiety disorders (OR = 0.45, 95% CI 0.23–0.89), whereas participants with adjustment disorders had higher scores on self-perception of stress than those with anxiety disorders. Comparing the subtype of adjustment disorder plus anxiety with the generalised anxiety disorder group, we found that adjustment disorder with anxiety was less prevalent in women and showed higher scores for mental quality of life (OR = 1.07, 95% CI 1.00–1.13). Prescription of antidepressants was also less likely in this subtype.

Adjustment disorders and no mental disorder

When comparing patients with adjustment disorders with primary care patients without mental disorders, we found that the former group had lower scores on mental quality of life than those with no mental disorder and also had higher levels of self-perceived stress. No other difference was found.

Recognition and treatment of adjustment disorders in primary care

Recognition

In only 2 of the 110 cases with a SCID-I diagnosis was 'adjustment disorder' written on the e-clinical chart (2%, 95% CI 0–4). In 17 of the 110 cases (15%, 95% CI 9–22) the GP detected some kind of emotional problem or mental disorder. In 3 of the 110 cases the GP coded a social problem. In 72 of the 110 cases the GP recorded only physical problems on the chart (65%, 95% CI 56–74). The remaining 16 cases (14%, 95% CI 8–21) had incomplete charts. Citing emotional problems as the main reason for consulting was found for 14 of the 110 patients with adjustment disorders (13%, 95% CI 8–21).

Use of services and treatment

The mean number of visits in the previous 12 months was 5.6 (95% CI 4.6–6.7). Regarding medication, 43 patients (37%, 95% CI 27–48; $n = 43$) had at least one psychotropic prescription. Of these patients, 71% (95% CI 56–83; $n = 32$) had at least one anxiolytic, 10% (95% CI 4–24; $n = 4$) at least one hypnotic–sedative and 45% (95% CI 31–60; $n = 18$) at least one antidepressant. After adjusting for $P<0.2$ variables in the bivariate models, factors associated with psychotropic prescription among those with adjustment disorders were:

(a) mental quality of life (SF-12): decreasing probability of prescription as quality of life improves (OR = 0.95, 95% CI 0.91–0.99);

(b) emotional problems as the main reason for consultation (OR = 6.19, 95% CI 1.46–26.18);

Table 1 Description of the samples[a]

	Overall AD $n=110$	AD with depression $n=29$	AD with anxiety $n=50$	Major depressive episode $n=339$	Anxiety disorder $n=666$	Generalised anxiety disorder $n=132$	No mental disorder $n=2676$
Female, %	60.3 (49.2–70.5)	65.3 (46.0–80.6)	52.3 (35.5–64.9)	79.1 (74.2–83.2)	75.9 (71.5–79.8)	79.4 (71.4–85.5)	59.2 (56.9–61.4)
Age, years: mean (range)	52.0 (47.9–56.1)	57.6 (50.4–64.8)	50.6 (44.2–57.1)	45.2 (38.5–52.0)	50.6 (48.9–52.2)	50.6 (48.0–53.1)	56.1 (55.1–57.1)
Job status, %							
Paid employment	39.8 (30.7–49.6)	32.3 (16.5–53.5)	41.2 (29.4–54.2)	26.9 (22.5–31.8)	34.1 (30.1–38.3)	41.1 (32.4–50.4)	33.6 (31.3–36.0)
Paid employment but on sick leave	14.6 (8.8–23.1)	18.3 (8.4–35.4)	9.4 (3.4–23.2)	26.7 (21.5–32.6)	16.6 (13.6–20.2)	12.6 (8.2–19.1)	9.8 (8.5–11.3)
Other	45.7 (35.3–56.4)	49.9 (31.2–67.8)	49.4 (36.1–62.8)	46.4 (40.7–52.2)	49.3 (45.3–53.3)	46.2 (37.5–55.2)	56.6 (54.1–59.0)
Chronic physical conditions, %	80.7 (72.3–87.1)	80.4 (62.0–91.2)	82.1 (71.0–89.6)	92.7 (89.2–95.1)	89.6 (87.5–91.4)	93.3 (86.6–96.8)	83.7 (82.0–85.2)
Assessment scale scores, mean (range)							
Mental quality of life (SF-12)	44.8 (41.7–47.8)	40.8(36.9–44.7)	49.8 (46.9–52.7)	27.4 (26.3–28.5)	39.6 (37.9–41.3)	42.3 (39.9–44.8)	51.2 (50.5–51.8)
Physical quality of life (SF-12)	46.2 (43.3–49.0)	42.7 (37.4–48.0)	45.1 (41.8–48.4)	40.5 (38.9–42.0)	44.5 (43.5–45.6)	45.9 (43.9–47.9)	46.2 (45.6–46.7)
Self-perceived disability	8.0 (5.7–10.3)	9.1 (5.1–13.0)	6.4 (3.5–9.2)	16.5 (15.4–17.7)	10.4 (9.3–11.4)	7.5 (6.0–9.1)	4.9 (4.5–5.4)
Self-perceived stress	5.4 (4.4–6.3)	5.4 (4.0–6.8)	5.3 (4.0–6.6)	6.7 (6.2–7.3)	4.8 (4.4–5.2)	4.7 (4.1–5.3)	2.4 (2.1–2.6)
Self-perceived social support	81.2 (76.3–86.0)	81.6 (70.8–92.3)	83.2 (75.2–91.1)	63.8 (59.2–68.3)	73.3 (70.2–76.4)	72.3 (66.7–77.9)	80.6 (78.7–82.5)
Mental/emotional problems main reason for consultation, %	12.7 (7.6–20.6)	14.3 (5.3–33.2)	11.3 (4.47–25.6)	35.2 (29.7–41.1)	23.7 (20.0–27.7)	21.3 (14.8–29.6)	4.7 (3.7–5.9)
Number of visits, mean (range)	5.6 (4.6–6.7)	5.9 (4.4–7.4)	5.6 (3.9–7.5)	9.9 (8.6–11.3)	7.6 (6.9–8.3)	6.5 (5.4–7.6)	5.9 (5.6–6.3)
Prescribed medication, %							
Anxiolytic	26.4 (12.5–36.2)	24.0 (12.4–41.2)	25.9 (14.4–42.2)	47.9 (43.0–53.0)	37.5 (32.4–42.9)	48.9 (39.0–58.9)	15.6 (14.0–17.3)
Hypnotic sedative	3.6 (1.3–9.4)	11.3 (4.0–28.2)	0	12.2 (9.0–16.3)	7.2 (5.3–9.7)	4.7 (2.2–9.9)	4.1 (3.3–5.1)
Antidepressant	16.7 (10.2–26.1)	16.8 (6.7–36.2)	10.5 (4.4–22.9)	52.5 (46.7–58.2)	35.4 (30.6–40.6)	33.8 (25.7–43.0)	10.5 (9.1–12.1)

AD, adjustment disorder; SF-12, 12-item Short Form Health Survey.
a. Data are weighted. Values in parentheses are 95% confidence intervals unless stated otherwise.

(c) age: increasing probability of prescription with ageing (OR = 1.04, 95% CI 1.00–1.07);

(d) being employed but on sick leave (OR = 4.47, 95% CI 1.02–19.52).

Discussion

We found the prevalence of adjustment disorders in Catalan primary care to be 2.94%, which is lower than expected and lower than in studies conducted over 20 years ago. When we compared our data with the most recent study by Semaan *et al*, focused on adjustment disorders with anxiety symptoms in primary care, rates were more similar – around 1%.[10] Our data are similar to those reported in the general population such as the ODIN and Zurich studies.[8,9] As others have shown,[1–5,8] this low frequency could be because adjustment disorder, being an exclusion criterion, is a subordinate diagnosis. In fact, the SCID-I only asks about adjustment disorders once all others have been checked.[18]

Table 2 Comparisons between adjustment disorders and other mental disorders

	Odds ratios (95% CI)[a]				
	AD (1) *v.* MDD (0)	AD with depression (1) *v.* MDD (0)	AD (1) *v.* anxiety (0)	AD with anxiety (1) *v.* GAD (0)	AD (1) *v.* no mental disorder(0)
Women (reference men)	0.36 (0.17–0.77)**	0.38 (0.06–2.13)	0.42 (0.25–0.69)***	0.27 (0.09–0.78)*	0.68 (0.43–1.06)
Age	1.02 (0.99–1.05)	1.02 (0.97–1.07)	1.01 (0.99–1.03)	1.01 (0.98–1.04)	1.00 (0.99–1.01)
Paid employment but on sick leave (reference paid employment)	1.43 (0.51–4.06)				
Other (reference paid employment)	0.97 (0.39–2.37)				
Mental quality of life (SF-12)	1.13 (1.09–1.17)***	1.11 (1.00–1.24)*	1.02 (1.00–1.04)*	1.07 (1.00–1.13)*	0.97 (0.95–0.99)**
Physical quality of life (SF-12)	1.07 (1.04–1.12)***				
Self-perceived disability	0.97 (0.92–1.02)	0.88 (0.76–1.00)	0.98 (0.95–1.01)		0.99 (0.96–1.02)
Self-perceived stress	1.07 (0.96–1.20)	1.10 (0.83–1.45)	1.17 (1.08–1.27)***		1.37 (1.28–1.49)***
Self-perceived social support	1.01 (1.00–1.02)*	1.02 (0.99–1.04)	1.00 (0.99–1.01)	1.00 (0.99–1.02)	
Presence of chronic physical illness	0.47 (0.16–1.38)		0.45 (0.23–0.89)*		
Emotional problems as a main reason	0.24 (0.09–0.67)**	0.43 (0.05–3.76)	0.60 (0.29–1.25)	1.69 (0.34–8.30)	1.79 (0.80–4.00)
Number of visits	0.95 (0.89–1.02)		0.97 (0.93–1.01)		
Any anxiolytic or hypnotic sedative (N05)	0.79 (0.37–1.68)	0.68 (0.15–3.20)	0.92 (0.52–1.62)	0.47 (0.13–1.59)	1.32 (0.77–2.26)
Any antidepressant (N06A)	0.43 (0.19–0.98)*	0.18 (0.01–2.35)	0.52 (0.27–1.01)	0.20 (0.04–0.94)*	0.93 (0.46–1.91)
PC centre variance	1.06 (0.27–4.08)	0.32 (0–224434.1)	0.86 (0.34–2.20)	3.53 (0.87–14.22)	2.16 (1.13–4.12)
GP variance		5.18 (0.31–121.42)			

AD, adjustment disorder; GAD, generalised anxiety disorder; GP, general practitioner; MDD, major depressive disorder; PC, primary care; SF-12, 12-item Short Form Health Survey.
a. Empty cells are variables that did not reach $P<0.2$ in the bivariate models.
*$P<0.05$, **$P<0.01$, ***$P<0.001$.

Considering adjustment disorders as a 'residual' category could be an added complication and a gap between theory and practice: the clinician knows that the symptoms will resolve quickly, but as the five-symptom threshold has been reached an adjustment disorder diagnosis cannot be made. From a clinical point of view, giving different diagnoses to two patients coping with a stressful situation because one had four symptoms (feeling sad most of the day, decrease in appetite, insomnia and fatigue) and the other five (same symptoms plus agitation) is not helpful.[6] Solutions to this could include eliminating adjustment disorders from DSM-5 or returning to the old classification regarding reactive/endogenous depression, or even creating a new stress response category.[7]

Comparison with other mental disorders

Our study showed adjustment disorder to be an intermediate category between absence of mental disorder and the meta-category of major depression/anxiety disorders. The condition has a distinctive profile: better than patients with either depression or anxiety, but worse than patients with no mental disorder. The same pattern is observed in comparison of specific subgroups: the main difference between adjustment disorders with depressive features and major depressive disorder is quality of life (better mental quality of life for those with adjustment disorders plus depressive symptoms), and the same is true for adjustment disorders with anxiety and generalised anxiety disorder. Nevertheless, the small sample size could explain why other differences were not found. Compared with those with major depression or anxiety disorder, adjustment disorders were less likely in women. This is consistent with other papers,[11,13] and could suggest they are different conditions. Another interesting finding is that patients with adjustment disorders reported high levels of self-perceived stress, even higher than those with an anxiety disorder. Although we did not assess specific stressors, the fact that patients with adjustment disorders perceive themselves as more stressed could support the Strain & Friedman idea of considering adjustment disorders as a stress response syndrome.[7]

Recognition and treatment

Specific recognition of adjustment disorders as a diagnostic entity by the GP is also low, although it seems that some kind of psychological or emotional distress is recognised. Among reasons for this, we should bear in mind that an adjustment disorder category is not present in the ICPC-2 and that only slightly less than 13% of people with adjustment disorders cited emotional problems as the main reason for consultation, which is known to be the main factor associated with mental disorder recognition by GPs.[32] In fact, one adjustment disorder criterion is related to marked distress that is greater than expected, which may be difficult to evaluate. General practitioners, aware that the distress is associated with a specific and temporary stressor, would prefer to monitor rather than label the patient. Moreover, we are considering the psychiatric point of view as a gold standard for GP activity and this may be inappropriate.

Regarding treatment, 37% of patients with adjustment disorders had a psychotropic drug prescribed; this is lower than previously reported.[10] Little evidence about treatment of adjustment disorders is available, but studies suggest that psychological interventions are more effective than drug therapy, which is not recommended.[1–5] However, the fact that anxiolytics were the most prescribed drug leads us to consider whether GPs are prescribing them to treat insomnia or as a point treatment for occasional high levels of anxiety. Unfortunately, this information was not available so we cannot determine prescription reasons. It is interesting that those with adjustment disorders also had a lower probability of antidepressant prescription (when compared with those with major depression), which could be seen as a proxy for severity. Nevertheless, our data suggest that there is a misuse of antidepressants in patients who could benefit from psychological treatment or just watchful waiting.

Strengths and limitations

A strength of this study is that it was conducted among a large, representative sample of people attending primary care. Moreover, few studies have been performed with such a large quantity of epidemiological data in primary care that also studied adjustment disorders using SCID-I. Given the revisions of DSM-IV and ICD-10, this is a critical moment for the presentation of data concerning adjustment disorders. However, some limitations should be mentioned. First, we did not specifically assess stressful life events but rather assessed adjustment disorders if participants spontaneously reported a stressful event in the previous months. This may have underestimated prevalence. Nevertheless, those who spontaneously reported a stressful event would be considered as more disabled, assuming we are not medicalising normal stress reactions.[2] Finally, self-reporting of chronic illness may have complicated the assessment.

Implications

In conclusion, our data suggest that adjustment disorders, as currently defined by the DSM, have a distinct profile that could be useful in classifying patients. Patients with adjustment disorders are less disabled but more stressed than those with mood/anxiety disorders. However, more debate and research is needed to determine whether the current definition is the most clinically useful conceptualisation.

Anna Fernández, PhD, Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, Red de Investigación en Actividades Preventivas y Promoción de la Salud en Atención Primaria (RedIAPP), Instituto de Salud Carlos III, and Clinical and Health Psychology Department, Universitat Autònoma de Barcelona, Barcelona; **Juan M. Mendive**, MD, Centro de Salud La Mina, Institut Català de la Salut, Sant Adrià de Besos, Barcelona; **Luis Salvador-Carulla**, MD, Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, and RedIAPP, Instituto de Salud Carlos III, Barcelona; **María Rubio-Valera**, MSc, RedIAPP, Instituto de Salud Carlos III, Barcelona; **Juan Vicente Luciano**, PhD, **Alejandra Pinto-Meza**, PhD, Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, and RedIAPP, Instituto de Salud Carlos III, Barcelona; **Josep Maria Haro**, MD, Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Barcelona; **Diego J. Palao**, MD, Centre de Salut Mental, Corporació Sanitaria Parc Taulí, Institut Universitari Fundació Parc Taulí–Universitat Autònoma de Barcelona, Sabadell; **Juan A. Bellón**, MD, RedIAPP, Instituto de Salud Carlos III, Barcelona, and Centro de Salud El Palo Unidad de Investigación del Distrito de Atención Primaria de Málaga, Departamento de Medicina Preventiva y Salud Pública, Universidad de Málaga; **Antoni Serrano-Blanco**, MD, Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, and RedIAPP, Instituto de Salud Carlos III, Barcelona, Spain; the DASMAP investigators

Correspondence: Dr Anna Fernández, Parc Sanitari Sant Joan de Déu, Research and Development Unit, Fundació Sant Joan de Déu, Dr Antoni Pujadas 42, 08830 Sant Boi de Llobregat, Barcelona, Spain. Email: afernandez@pssjd.org

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