



# Adherence to antidepressants: A review of the literature

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## ABSTRACT

We have revised literature related to antidepressant adherence published in the last 15 years in Spanish and English. Adherence of antidepressants is a major problem all over the world, which affects response, cost of the illness and risk of relapse. Persistence in the treatment is important to avoid relapses and to ensure remission, but in many cases the lack of accurate information causes an early interruption of treatment. Some other sociodemographic factors seem to be common to bad adherence, as low income, low socioeducational status, severity of depression, difficult access to physicians or to the medication. In some reports factors as gender and age are found as risk factors to adherence, but not in all of them. Cultural beliefs about illness and medication are important in adherence. There is not a unique technique to improve compliance and persistence, even though near follow-up and personalized information are critical. Though the fear to become dependent or to the adverse effects is a key factor, new antidepressants have not changed the rate of non-adherence.

## Keywords

Adherence; Antidepressant; Antidepressant indication, Compliance, Patients' perception, Treatment response, Use of treatment

## Significant outcomes

A good use of antidepressant treatment influences greatly in the response of depressive patients and the indication to antidepressant treatment is an important point in that use.

Factors that determine the use of treatment are unclear and sometimes unattended, though social factors and physical health seem to be important.

In clinical practice it is important to improve a good use and, so on, response to treatment.

## Introduction

In the field of mental health, good use of treatments is a major health care concern, since the effectiveness of psychopharmacologic drugs is reduced greatly when patients fail to comply with treatment [1]. Inadequate treatment adherence is believed to be an underlying cause

of many cases in which depression becomes chronic and that it is a major compound of good use of the antidepressant treatment, even though less than half of all depressed patients treated with the traditional antidepressant medication show full remission [2]. Patient adherence is a critical aspect of effective clinical management [3].

We have made a review of the literature relative to adherence through Medline and Ovid database, with the words "adherence", "compliance", and "antidepressant" limiting the review to articles written in English or in Spanish, in the last 15 years. Literature on the topic has grown exponentially in the last 5 years, and we have found also references on other fields of medicine, especially in chronic diseases. This aspect of adherence has not been treated previously as a risk factor of lack of response in other illnesses, as asthma or arterial hypertension, even though in psychiatry it has been observed long time ago.

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## Background

In the last years adherence has been described in two components: persistence (taking the medication throughout the intended course of treatment) and compliance (with medication directions) [4,5]. Actually, most of the papers don't take these two components into account in a different way.

### ■ Drug factors that influence in adherence

Adherence depends on patient factors (concerns about side effects, fear of addiction, beliefs about medication and illness, patient lower stage of change), clinical factors (lack of patient education, poor follow-up), social factors (isolation, poverty, lack of social support, low income, low educational level) or drug factors (cost, adverse effects) [3,6-9]. Non-adherent patients were more likely to experience an increasing risk of relapse and/or recurrence, emergency department visits, hospitalization rates, and increased severity of depression, as well as suicidal ideation [10]. Beliefs about medication seems to be a very important factor in antidepressant adherence: perception of necessity improves it, as being less worried about becoming dependent; belief about medicines causing harm, being overprescribed, experiment side-effects and severity of depression correlates negatively with adherence [11].

Factors that influence the treatment use include drug efficacy and possible adverse effects, hypochondrial and converse symptoms that are related to increased complaints about adverse effects [12], therapeutic regimen [1,13], and depression itself [14]. Psychiatric history, age, and sex do not seem to influence adherence, while a low socioeconomic status, over-prescribing on the part of the physician, and the stigma of mental disease and psychiatric treatment have all been related to treatment compliance [15]. One of the most common factors considered when prescribing antidepressants is the avoidance of specific side effects [16], what could improve patients' perception of the treatment. Other authors have found some sociodemographic factors as relevant for antidepressant compliance, being worse among the oldest and with a severe depression, and better among female and non-African American, in a sample of older people [17]; race/ethnicity has been found to be a robust predictor of early antidepressant adherence, with minority groups less likely to be adherent in American society [18]. Women seem to follow better treatment indications [19].

Gender factor could depend on different factors, such as economic factors: Jirón et al found that female had a worse compliance when this factor is combined with low income [20].

From the long-term point of view, inadequate adherence to treatment may be due to fear of becoming dependent on the drug rather than to its undesirable effects [21], as well as to denial of disease or a need for checking whether the problem persists [22].

The majority of antidepressant medication act through monoaminergic regulation, but depression is yet related to impairment of neuroplasticity and cellular resilience [2]. Some antidepressants, as agomelatine, may increase neurotrophin signalling promoting neuronal and synaptic remodelling as well as the formation of new hippocampal neurons both in the hippocampus and prefrontal cortex, and others, as tianeptine, can modulate glutamatergic transmission, with a different profile of side effects that could improve the data about adherence.

### ■ The problem of measure compliance

In the literature on this topic, figures for poor adherence to antidepressants, among patients with affective disorders, varies between 10-30% and 60% [23,24]. These figures do not appear to have changed after the introduction of newer drugs, with reduced undesirable effects.

A majority of physicians underestimate the problem of non-compliance. Despite the growing use of clinical guidelines, treatment algorithms, newer drugs with less adverse effects and other improvements in therapeutics, there continues to be a relevant difference between the efficacy of antidepressants seen in clinical trials and that seen in clinical practice. This difference may stem from a lack of information [25].

Adherence seems to be directly related to a patient's awareness of having been told about a drug's adverse effects by their physician: the less they remember about it, the worse their adherence is. In addition, it appears that there is a discrepancy between the instructions that physicians say they give to their patients and those that the patients actually recall being given [26].

On average, poor compliers have been found to stop taking their medication after only 43 days, even if the response to the medication is positive. However, poor compliance is seen after only 15

days if they develop an adverse effect, after 20 days if their condition worsens, and after 40 days if the response is less than they expected [27].

Psychiatrists tend to presume that non-adherence among patients with chronic depression is uncommon, and place it around 16% [17], lack of adherence is waited in psychotic illness, but usually we expect than people who are suffering depressive symptoms and come voluntarily to consultation would follow prescriptions. However, when asked if they made any mistake in the way they took their medication the day before, 1 out of every 3 patients admits to have made some mistake, and 8% acknowledge that mistakes occur 'very often'. Aspects that have been shown to influence a good use include the treatment's efficacy and the daily number of pills to be taken. Factors associated with a good adherence include the presence of family members, emotional stability, and positive relationship with the physician, and a perceived improvement with the drug. However, adherence decreases as the duration of therapy lengthens. Other studies have found adherence to be as low as 39.7%, with older patients, and those with higher scores on the scale of chronic disease, having better adherence [28]. Over 43% of patients do not comply with their long term treatments, and 75% fail to introduce the life habit changes recommended by their physicians [29].

One problem when speaking about adherence is the way to measure it in an objective way, Martín-Vázquez, et al. in 2011 made an investigation in 550 antidepressant treated patients, passing a questionnaire with two questions: patient's forgetting and perceived difficulty to complete the prescription and its accuracy. The compliance was good in 37.6% of all patients (they find treatment easy to follow and convenient and they declare that they never forget to take the medication). If good use is defined less strictly and patients who say they seldom forget are included, the percentage of subjects with good use grows to 52.4%. A bad use of treatment is less common among subjects with affective (30.1%) or anxiety (31.1%) disorders than among those with other diagnoses (48.6%). Response to treatment was worse in the group whose use of treatment is more frequently poor or doubtful. Of those patients who improved, but did not achieve complete remission of disease (66%), 33.3% took it bad, while only 20% of patients with complete remission of disease (12.2%) had referred a misuse. When social and demographic

factors are considered, differences were significant for education level and place of residence: worse with low educational level and people living in rural areas, far from Mental Health Centres. Use of treatment was also worse among subjects with a co-existent organic disease [8,9].

To measure compliance and adherence Párraga et al in 2014 made an investigation in a population of 185 adults that began treatment with antidepressants. They found that 46.9% of the sample showed an inadequate fulfilment when they use a method of counting pills, though with Morisky-Green's Questionnaire the results were 28.6% at six months. But early in the first two weeks the lack of adherence was 48.5% and 33.5%. Factors related with low adherence were younger age, low educational level, free treatment, no psychotherapeutic support, less visits to family doctor previously to treatment and few antidepressant treatments [30].

Other authors have used different methods to measure compliance, as Oller-Canet et al. who in 2011 compared the total number of prescriptions with the number of pharmacy dispensed prescriptions. They found a percentage of non-compliance of 33.96%, greater in people with other long-term treatments. Women used to follow treatment better than men. There were no differences if the prescription was made in Primary Care or in Mental Health Center [19].

The questionnaire "ESTA" was validated in Spanish to measure satisfaction with antidepressant treatment. It included variables related to compliance, severity of depression and adverse effects and non-surprisingly, the satisfaction was lower in the non-compliers group versus the compliers' one [31].

#### ■ Patient factors

Social and demographic factors that are associated with forgetfulness include low social and cultural levels, and living in rural areas, as has been found in several reports [7,8,9,20,30,32]. This suggests that the use of treatment is related both with the education level and with the accessibility to specialized care. It has been reported elsewhere that up to 50% of patients leave the physician's office without having fully understood the instructions provided for their treatment [32]. Low income and low educational level have been related to bad adherence in many papers [7,8,9,20,30]. This must be related with other factors as difficulty to have access to specialized resources, to acquire treatment, lack of social

support (that could aggravate per se the depressive symptomatology) and personal instability.

#### ■ Other difficulties in adherence

Use of treatment is also worse in patients with concomitant organic disease [12]. This is probably better understood as a consequence of the increased complexity of treatment, due to the association of psychopharmacological drugs with other therapies. Moreover, the coexistence of other diseases and drugs increases the probability of adverse drug effects and drug interactions, as well as the appearance of hypochondriac depressive symptoms, which could be related with non-compliance [12].

Another possibly involved factor is that presence of somatic suffering may lessen the relevance that the patient gives to his or her psychological problems, and the feeling that both go together and improvement in the somatic disease will improve all conditions. Whichever way, it must be remembered that depression is associated with a poor adherence to any medical treatment, as well as with a higher morbidity and mortality [14]. In fact, adherence to antidepressants is significantly associated with a decrease in the risk of mortality [33]. Non-compliance with therapy for somatic disorders may be due to an unrealistic lack of hope for improvement caused by depression, as well as to the tendency for social isolation and cognitive function deterioration that often accompanies depression [34]. Before use an augmentation strategy in depression, it's important to evaluate adherence, compliance and persistence, because 50% of all the patients that could be candidate to a second line therapy were non-adherent [35].

#### ■ Can psychiatrists enhance antidepressant adherence?

The fact that response to treatment was better among patients who used better the treatment too is an expected result, but it is important to keep this in mind while prescribing. Patients should be informed not only of the benefits expected from treatment, but of the time that may pass before those benefits become apparent to the patient. In addition, the possible adverse effects and drug interactions should be provided. Up to 72% of physician's declare having told their patients to keep taking the treatment for at least 6 months, yet only 34% of patients remember actually having been told so, with non-adherence being higher among those who have not spoken with their physicians about the duration and adverse

effects of treatment [26]. Poor compliance with antidepressant treatment is a relevant factor in a worse outcome of depressive disorders, more relapses and greater cost [19]. Lack of medical information or misunderstanding could be the origin of the poor compliance: usually patients discontinued treatment when they begin to feel better or feared to adverse effects [20].

Considering all of the above, we believe that the question of use of the drug treatment should be specifically addressed in all patients, and that insisting on this issue should be mandatory in all cases in which response is inadequate. We believe that for an issue as difficult to measure as "good use", the combination of variables such as forgetting to take medications and ease of the therapy, allows us to create a picture that is closer to the truth than either of them taken separately.

Differences in the treatment use observed between different diagnoses could be due to the variable severity of each disease or to the pertinence of the drug's indication, among other factors as insight, and the factors described above. For example, antidepressants are more effective in affective and anxiety disorders, so when they are used under these indications, patients may become more aware of getting better, therefore, improving their use of the antidepressant treatment. The association in the first month of benzodiazepines to the antidepressant treatment, which could minimize the initial adverse effects, seems to improve adherence, especially persistence, though the extended use is not recommended [4].

Given the scope of the problem of non-adherence, and its practical implications, it is necessary to adequately measure use of treatment, in order to gather information that may be used to plan programs that address this problem in the general population. Measuring the effect that any intervention may have on the therapeutic use of psychopharmaceuticals of patients with chronic disorders is difficult and furthermore, the size of the effect is likely to be moderate, whatever the complexity of the intervention [36]. There are no clear indications of which interventions may be effective [37]. However, these difficulties should not keep us from trying to address this issue, considering its relevance for the success of the treatment, and the risks that can surge when depression is not resolved, as suicidal increase, personal suffering, economic and social expenses. The most efficient strategy to improve adherence included patient

educational strategies, telephone follow-up to monitor patients' progress, providing medication and feedback to primary care providers [38], but educational interventions alone were ineffective, probably due to the lack of personalization in the presented material [5].

## Conclusion

Adherence to antidepressant treatment is a major problem all over the world. Emphasizing the importance of a good use of antidepressant drug treatment is especially relevant for those patients more likely to follow it poorly, which would be those whose major psychiatric diagnosis is neither an affective nor an anxiety disorder, with a lower sociocultural level, low income, taking other drugs for concomitant organic diseases and/or living in rural areas with more difficult access to specialized care. In these patients, it is particularly important to insist on the relation between good treatment use and therapeutic response, with personalized information, and the nearest possible follow-up. Psychiatrists and general practitioners should inquire whether their patients adequately understand and follow instructions, and offer them the chance to work together to solve difficulties that may arise during antidepressant treatment.

In the majority of the papers, the treatment is used in a proper way in less than 40% of the patients, among different countries and cultures. In the group of better adherence are included patients diagnosed of affective disorders, more than with depressive or anxiety symptoms not making up a major depressive disorder. When

people are taking more drugs to treat somatic illnesses are less prone to follow antidepressant treatment properly.

Treatment response is directly dependent of a correct psychopharmacological intake, so it's mandatory to reinforce it, to explain its action mechanisms in a proper way, according to patients' sociocultural level, and to check it frequently, particularly if the response is not good. Physicians have to take in account the two components of adherence: persistence and compliance and question about them in all the visits.

We will like to reinforce the importance to measure adherence and compliance, to prescribe antidepressant that have minimum side effects, to inform properly of these effects and the response latency, and to reinforce all the problems that can be found with psychoeducation.

## Limitations

We have only review papers in two languages, Spanish and English, because they are widely used all around the world and cover the majority of relevant investigation. The data bases used were selected for their high impact in journal classifications, though other data bases could have contribute with more information. Also, other factors that influence in adherence, as psychotherapeutic approach, have not been reviewed in this paper.

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