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Guide for evaluation and improvement of long-term treatment compliance of Major Depressive Disorder

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INTRODUCTION

Major depression disorder (MDD) is a relevant public health problem. Its pertinent diagnosis and effective treatment are an important responsibility of the health care institutions. It has been calculated that the overall burden of the disease due to MDD currently occupies the third place in the world as the most important cause of disability adjusted life years (DALY). DALY are calculated by updating the years of future life exempt from disability that would be lost in a certain period due to premature deaths or disability conditions caused by the disease. The projections for the next 25 years suggest that MDD will become the first cause of disability adjusted life years, followed by ischemic cardiovascular disease.¹

Major depressive episode (MDE) is the most frequent mental disorder in Spain.² A total of 3.9% of those over 18 years of age have had MDE in the last 12 months (prevalence-year) and 10.5% have had MDE at some time in their life (prevalence-life). Prevalence of MDE in women is twice that of men and the adjusted Odds Ratio of presenting MDD in women compared to men is 2.8 (95% CI: 1.9-4.1). The cost in economic terms is high,^{3,4} but the cost in terms of suffering is incalculable. MDD interferes with the overall functioning of the patient and can affect both quality of life of the ill person as well as that of their family.

On the other hand, it appears that less than half of those diagnosed with any MDE will have a recurrence over their lifetime, which increases the importance of this disorder. In this sense, most of the clinicians and action guidelines maintain that the patient should take their medication for prolonged time periods (in some cases during their entire life) with the objective of preventing disease recurrences.⁵ Within this scenario, long-term treatment noncompliance of MDD is an important obstacle in the care of these patients.^{6,7} It has been calculated that between 10% and 60% of the patients do not comply with the MDD treatment.⁸ This prevalence has

not significantly changed in the last decades in spite of the introduction of new drugs. If the magnitude of the problem and its implications are considered in terms of morbidity and disability, treatment compliance of MDD has been studied little, especially when we compare it with the extensive number of investigations existing on the effectivity of antidepressant medication.⁹

In the scientific publications, we often find the Anglicism "compliance" to refer to treatment compliance, although it is also used to describe different behavioral phenomena: never initiating the medication after the therapeutic indication, premature abandonment of the treatment (abandonment versus complete one of the treatment in observational studies and clinical trials) adherence (percentage of days in which the drug dose was adequately taken) and intake of additional tablets or lost doses (at least two consecutive days of either one described).¹⁰

Different methods have been used to measure therapeutic compliance such as self-recording by the patient, tablet counting, electronic devices (e.g. medication event monitoring systems [MEMS]) or clinical evaluation. However, the validity and reliability of these methods are insufficient¹¹ and some more reliable methods such as the measurement of the levels of medication in blood cannot always be conducted in scenarios of primary care and even in the hospital setting.¹²

In this context, and giving preference to randomized studies and meta-analysis, a clinical practice guideline has been elaborated that contains recommendations based on the best scientific evidence available. When there is no scientific evidence for the recommendations, consensus of the clinical experts on the clinical -therapeutic attitude aimed at improving compliance in the long-term treatment of MDD was obtained.

This clinical guideline presents the current scientific evidence and makes recommendations derived from the consensus on the clinical -therapeutic management of these

patients in our country, both on the care level – which is the closest to reality – as in another that could be classified as ideal. The latter is understood as that which would be performed by the professional if all of the human, economic and organizational resources were available to conduct these activities.

The inevitable changes in the status of the scientific and technological information require periodic review and updating of the information available on health whenever this is necessary. This clinical guideline cannot be extended to all the patients and each one of the recommendations should be individualized. Appropriate use, modifications adopted or decisions of ignoring these and other recommendations, completely or partially, are total responsibility of the professionals who use the clinical guideline.

METHOD

This clinical guideline provides evidence-based recommendations or those based on expert professional consensus to improve long-term treatment compliance of MDD. Keeping this objective in mind, thorough questions were developed in an attempt to respond to the clinical guideline. These questions were made following the PICO (patient, intervention, comparison, outcome) questions methodology and were obtained from reading articles selected and classified according to their quality.

I. Search strategy

Searches were made in the data bases of Medline (Pubmed, 1966-present) and the Cochrane Library, with use of the MESH terms whenever possible. The following general search terms were considered: "Depressive Disorder," "Depression," "Patient Compliance," "Directly Observed Therapy," "Treatment Refusal," "Treatment Failure," "Treatment Outcome," "Antidepressant Agents" and other specific terms for each one of the variables described in the guideline. The searches were limited to the following terms: studies in humans, Clinical Trials, Meta-Analysis, Clinical Practice Guidelines, Randomized Controlled Trials, Clinical Trials Phase I, Clinical Trials Phase II, Clinical Trials Phase III, Clinical Trials Phase IV, Consensus Development Conference and NIH, Controlled Clinical Trials.

Once the bibliographic search was performed, a first screening was made of the non-relevant articles. This process was carried out by two reviewers. The lists of references selected for each area were analyzed by a scientific team in order to determine if there were any relevant articles that had not been included in the research results.

Once the absence of level 1 and 2 evidence was determined according to the Scottish Intercollegiate Guidelines

Network (SIGN), specific searches were made for cohort and case-control studies to respond to the questions generated by the clinicians.

II. Quality of the material obtained

Once the articles were selected, they were read completely to avoid making decisions on their relevance based on incomplete information contained in the title or summaries. The publications were evaluated using the following instruments for the evaluation of the quality of scientific works: CONSORT (evaluation of clinical trials), QUOROM (Systematic reviews/meta-analysis) and the AGREE (Appraisal of Guidelines Research & Evaluation).

III. Level of scientific evidence and Grade of recommendation

After identifying the sources with the level of quality desired, the Level of Evidence and Grade of recommendation were classified according to the revised SIGN system (classification that can be observed in table 1). Once the evaluation and classification of the articles were made by a team of clinical epidemiologists, the articles were distributed among the participating professional experts.

IV. Elaboration of the Consensus: Delphi Technique

By using the Delphi method, a consensus was obtained from the individual opinions of a group of experts. The technique entailed sending material for its scoring by the experts during several rounds to homogenize opinions and reach the consensus. As done in other revisions, the Delphi method required: clear statement of the problem, choice of experts, elaboration of the questionnaires sent to the experts (by the use of PICO questions not answered by the scientific evidence), practice development and extraction of the results. The data extraction was made using statistical software (SPSS version 17.0). The answers were classified into quartiles (25%, 50%, 75%, 100%). The mean, median, mode, standard deviation, maximum and minimum of the data obtained were also obtained. The answers with a concordance grade greater than 80% were selected for inclusion in this guide. A list of experts who participated in the elaboration of the consensus used in this guide is included at the end of this guide.

RESULTS

Observational studies have demonstrated the influence of different factors and treatment compliance of patients with MDD,⁹ being a woman, married, having high level of

studies and/or IQ are factors that increase compliance. The study of Pampallona et al. demonstrated better compliance when the prescription was made by a doctor within the usual medical office than in the emergency service. Regarding these social aspects and concomitant diseases, it was determined that a good social setting and absence of diagnoses of personality disorders and drug abuse were associated to better compliance. In relationship to the therapy, better compliance was associated to absence of adverse events related with the medication, absence of relapses and previous use of antidepressants (AD) or psychopharmaceuticals. The Pampallona study does not mention factors associated to better compliance in relationship to the organization of the health care system.⁹

Burra et al. (2007) developed a questionnaire that included elements from the AAGTC or Adult AIDS Clinical Trials Group Adherence Baseline Questionnaire, adapting it to the specific use of AD in patients with MDD. The objective of the questionnaire was to know the attitude of the patients regarding their medication, their perception on the efficacy of the treatment, and the most common reasons for lack of adherence. Other elements of the questionnaire examined the sociodemographic characteristics of those surveyed. Eighty patients filled out the questionnaire. Of these, 57/80 (71%), belonged to the hospital setting and 23/80 (29%) to the community psychiatric outpatient clinic. The most frequent reasons mentioned for non-treatment adherence were practical ones 1) forgetfulness, 2) changes in daily routine, 3) running out of medication and 4) being busy; among 17 others mentioned in the study. In order to improve long-term compliance in the follow-up of the patients, suggestions were given to introduce modifications in the behavior of the patients in their follow-up such as using weekly pill boxes, reminders to take the medication or advising them to take the medication every day at same time in order to add the medication taking into the daily routine in addition to assuring an adequate supply of the prescriptions between the visit.¹³ Furthermore, Bulloch et al. (2006), found that forgetfulness was the principal cause of treatment dropout in both genders and for all the ages, in patients with a single AD and with 2 or 3 simultaneous AD.¹⁴

In the study performed by Demyttenaere et al. (2001) that evaluated dropout and non-compliance of the antidepressant medication in primary care, it was found that the likelihood of not abandoning the treatment in patients with MDD was 88% at the end of 4 weeks, 77% at the end of 8 weeks, 68% at the end of 12 weeks, 58% at the end of 16 weeks, 52% at the end of 20 weeks and 53% at the end of six months. Within the reasons mentioned by the patients for discontinuing the treatment, the article listed the following: "feeling better" (55%), "adverse affects" (23%), "fear of dependence on the drug" (10%), "feeling uncomfortable taking medication" (10%) and "lack of efficacy" (10%). In this sense, the patients were allowed to give multiple rea-

sons for their noncompliance and abandonment of the antidepressant medication.^{15, 16}

FORMAT OF THIS GUIDE

In each one of the following chapters of this guide, the format has been applied according to the following legend:

1. Number of depressive episodes and treatment compliance

1. RECOMMENDATION

2. GRADE OF RECOMMENDATION

The clinicians should consider that the previous depressive episodes that were treated satisfactorily favor better compliance in the long-term treatment of MDD [GRADE OF RECOMMENDATION C]. The number of depressive episodes is related with compliance with the AD treatment. Patients with recurrent episodes frequently have better compliance than those with a first MDE.

3. GRADE OF SCIENTIFIC EVIDENCE PROVIDES THE REFERENCE THAT SUPPORTS EACH PARAGRAPH

2+

Non-compliance with the treatment varies from 10% to 60%. It is important to indicate that the systematic revisions and/or meta-analysis of the clinical trials may find mean compliance frequencies between 66% and 79%, greater than in observational and naturalistic studies.¹⁶⁻²⁰

2-

Chakraborty et al. (2008), in a 3-month follow-up for a first episode of depression found that 88% of the patients did not take their AD correctly and the discontinuation rate reached 38%. Akincigil et al. found a 50% compliance during the acute treatment phases.²¹

2-

Bockting et al., in a study in patients with recurrent depression, found that lack of treatment compliance with AD (continuation and maintenance) varied from 39.7% to

The grade of scientific evidence and of recommendation has been classified according to the revised SIGN system (Tables 1a and 1b):

Table 1a	Levels of scientific evidence
1++	High quality meta-analysis, systematic reviews of clinical trials or high quality clinical trials with very little risk of biases.

1+	Well performed meta-analyses, systematic reviews of clinical trials or clinical trials with high quality with very little risk of biases.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high quality with high risk of biases.
2++	Systemic reviews of high quality of cohort studies or cases and controls with very low risk of bias and high likelihood of establishing a causal relationship.
2+	Cohort studies or of case and controls that are well performed with low risk of bias and with a moderate likelihood of establishing a causal relationship.
2-	Cohort studies or of case and controls with high risk of bias and significant risk that the relationship will not be casual.
3	Non-analytic studies, such as case reports and case series.
4	Opinion of experts

The number of depressive episodes is related with AD treatment compliance. Patients with recurrent episodes frequently have better compliance than those with a first MDE.

2+ Noncompliance with the treatment varies from 10% to 60%. It is important to indicate that the systematic reviews and/or meta-analyses of clinical trials may find mean compliance frequencies between 66% and 79%, greater than in observational or naturalistic studies.¹⁷⁻²¹

2- Chakraborty et al. (2008), in a three month follow-up during a first episode of depression, found that 88% of the patients did not correctly take their AD and that the dropout rate reached 38%. Akincigil et al. found adherence of 50% during the acute phases of the treatment.²²

2- Bockting et al., in a study in patients with recurrent depression, found that lack of adherence to treatment with AD (continuation and maintenance) varied from 39.7% to 52.7%, with a mean of 47% at 2 years and 58% in other studies at 2 years.^{23, 24}

Considering the differences that can be found with these comparisons between studies in different populations, it was observed that AD compliance is poor in general both in the first episode as well as in recurrent episodes. In the studies reviewed, the rates of lack of compliance showed very wide ranges (that overlapped between themselves). Furthermore, factors were observed that seem to have greater weight in compliance to treatment than the variable "first episode versus recurrent episode of depression." However, an important consideration is that compliance of the patients with depressive episodes varies in time and initial compliance does not mean or guarantee compliance at other times of the natural history of the disease.

Table 1b	Grades of recommendation
A	At least one meta-analysis, systemic review or clinical trial classified as 1++ and directly applicable to the target population of the guide; or a volume of scientific evidence made up of studies classified as 1+ and with large consistency between them.
B	A volume of scientific evidence made up of studies classified as 2++, directly applicable to the target population of the guide and that show great consistency between themselves; or scientific evidence that can be extrapolated from studies classified as 1++ or 1+.
C	A volume of scientific evidence made up of studies classified as 2+ directly applicable to the target population of the guide and that show great consistency between themselves; or scientific evidence that can be extrapolated from studies classified as 2++
D	Scientific evidence of level 3 or 4; or scientific evidence that can be extrapolated from studies classified as 2+

I. Factors related with the disease

We found characteristics of the disease that positively or negatively affect AD treatment compliance. The grade of depression and presence of symptoms associated (as psychoses, anxiety, apathy, suicidal ideation, and cognitive symptoms) affects, among other factors, compliance of antidepressant treatment.

1. Number of depressive episodes and treatment compliance

RECOMMENDATION

Clinicians should keep in mind that previous satisfactorily treated depressive episodes favor better compliance in the long-term treatment of MDD (GRADE OF RECOMMENDATION C).

2. Phases of antidepressant treatment and compliance.

RECOMMENDATION

Antidepressant treatment is related with compliance in major depressive disorder. Clinicians should keep in mind that the maintenance phase is the most problematic in relationship to compliance with antidepressant treatment in patients with Major Depression. (GOOD CLINICAL PRACTICE).

2+ In this sense, it has been observed that during the acute phase of depression, AD treatment compliance reaches 50% and in the continuation and maintenance phases, approximately 47%. The relationship between time of diagnosis and compliance does not show greater variations within one population, but variations can be observed in the individual cases.^{8, 24}

- 3 These findings confirm other studies conducted in chronic diseases, in which treatment compliance has been found to be approximately 50% with variations of 31% to 71%.²⁵

3. Severity of the depression and compliance.

RECOMMENDATION

Clinicians should consider the severity of the depression in relation to treatment compliance. The severity of the depression significantly affects antidepressant treatment compliance. The patients with mild depression complied better than patients with moderate and severe depression (GRADE OF DEPRESSION B).

- 2++ In regards to the severity of depression and compliance, in the LIDO study, patients with the highest score on the Depression Scale of the Center for Epidemiological Studies (CES-D), classified as patients with moderate-severe depressions, have a higher percentage of improvement (24%), but also have the highest percentage of dropouts from the study, this being 19.8%. Equally, a logistic regression using the study withdrawal variable as dependent variable found that the most depressed patients were more likely to withdraw from the study ($\beta = 0.037$, $p < 0.05$).²⁶
- 3 Along this same line, other studies have suggested that patients with mild depressive symptoms comply more to the treatment, 27 while those patients with more severe symptoms show less treatment compliance. 28 Therefore, the study suggests that severity of the depression inversely affects treatment compliance, that is, the greater the severity, the less the compliance to the treatment and vice versa.

RECOMMENDATIONS (FROM POINT 4 TO POINT 7):

Clinicians should consider the presence of symptoms concomitant to depression in relationship with treatment compliance. Anxious, psychotic, apathy and cognitive symptoms are associated with compliance to antidepressant treatment. Patients with concomitant symptoms have worse treatment compliance regarding those with purely depressive symptoms. However, those with MDD and anxious symptoms have greater compliance regarding those patients who have, concomitantly, psychotic symptoms, apathy or cognitive symptoms. (GRADE OF RECOMMENDATION D).

4. Depression and anxious symptoms.

One of the symptoms that frequently appears with MDD is anxiety. There are two approaches to this symptom: a dimensional one in which the MDE has high levels of anxious

symptoms and another symptomatic approach, in which anxiety is a comorbidity. The study "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D) found a proportion of anxious depression of 44% to 46% when the Hamilton scale (Ham-D),²⁹ was used. This corroborates other studies with percentages of 40% to 50%.³⁰⁻³² Response to AD in patients with anxious depression is slower and even less when compared with that appearing in patients with depression without anxiety.³³

- 3 A retrospective study of 13,085 patients with anxiety disorders showed that treatment compliance in patients with dual diagnosis (depression and anxiety) was 46.8% vs. 40.2% ($p < 0.001$) in patients only with anxiety.³⁴ Thus, anxiety symptoms would seem to decrease compliance in MDD.
- 3 Furthermore, other studies show greater interruption of antidepressant treatment due to adverse effects in those patients with anxious depression regarding those who have depression without anxiety.^{35, 36}

5. Depression and psychotic symptoms.

Psychotic symptoms appear in 14% - 18.5% of the patients with MDD interviewed, 37 and up to 54% in hospitalized patients.³⁸

- 3 Symptoms associated to MDD significantly differ in those patients with MDE, therefore it has been suggested that they should be classified as a different subtype of MDD episode. Craig et al. (2007) studied 87 patients diagnosed of MD with psychotic symptoms, finding that only 30% of the patients between 6 and 24 months of treatment stated they had regularly used AD and only 25% stated they had regularly used antipsychotics.³⁸

Comparing these results with those of the previous section on compliance in depression and associated anxious symptoms, it is observed that in a population of patients with MDD and psychotic symptoms, treatment compliance is in a low range when it is compared with adherence in general depression, and it is also worse than in patients with depressive and anxious symptoms. No studies have been found that compare all the symptoms associated to depression and that can be compared with a single methodology and definition of compliance.

6. Depression and symptoms of apathy.

Apathy has characteristics in common with depression and can be diagnosed erroneously as only depression. The studies that have been performed up to now have also asso-

ciated apathy with dementia and Alzheimer's Disease.

- 3 A study performed by Feil et al. (2003) in 89 patients between 50 and 85 years of age, who were administered the 21-item Ham-D scales and the Apathy Evaluation Scale found that, independently of the grade of depression, the presence of apathy correlated with a decrease in some cognitive functions,^{39, 40} which leads to the consideration that the weight of this symptom in treatment compliance is important, above all, in elderly patients.

In spite of this, we have not found a specific study that relates this symptom and treatment compliance.

7. Depression and cognitive symptoms.

- 3 Cognitive symptoms are frequent in patients with MDD^{41, 42} and their relationship to treatment compliance has been evaluated in several studies. Bogner et al. (2006) did not find any relationship between compliance and cognitive status in a study with citalopram.⁴³
- 3 However, other studies relate cognitive symptoms during treatment with AD with a greater risk of relapse of MDE in patients who continue to experience cognitive problems.⁴⁴ In a study with 220 patients over 60 years, it was found that one of the best predictors of lack of treatment compliance was cognitive difficulties (OR 2.94, 95% CI 1.32-6.58).⁴⁵
- 3 Another study found, in a hierarchical logistic regression analysis, that disciplined personality and intelligence quotient (IQ) were the factors that could most firmly predict treatment compliance, even more than depression and anxiety.⁴⁶

Traditionally, cognitive deterioration has been associated empirically to lower treatment compliance. However, although these studies show that cognitive deterioration has less weight by itself in treatment compliance, randomized studies tend to exclude this type of patient, so that its relationship cannot be clearly established. More studies are needed to clarify the weight of cognitive deterioration in AD compliance.

8. Depression and suicidal behavior.

follow-up in patients with ideations and autodestructive behaviors in the clinical practice. (GOOD CLINICAL PRACTICE)

- 3 Suicidal behaviors form a part of the MDD. Suicidal ideation has been observed in 58% of the patients with MDD. The risk of nonfatal suicide attempts has been calculated to be about 40% after a first episode of MD and consumed suicides occur in 4% to 10% of patients with MDE.^{17, 47, 48}
- 2++Sokero et al. (2008) performed a study in 259 patients diagnosed of MDE. Suicidal ideation was detected in 38% of the patients during the initial interview, 16% of the patients had attempted suicide during the study and 3 patients had committed suicide during the 6 months of follow-up. Good AD treatment compliance was found among the patients; without suicidal ideation (69%), with suicidal ideation (71%) and with suicide attempts (70%). Equally, adherence to psychotherapy was good in the three groups (between 67% and 74%). Therefore, it was concluded that treatment compliance does not substantially vary between suicidal and non-suicidal patients.⁴⁹
- 1- There is preliminary evidence on the increase of suicidal ideation during the period of discontinuation of the SSRI/Venlafaxine. A total of 28 patients with MDD, for whom the physicians decided to switch the antidepressant medication, were randomly included in two groups: one that would have a short period of treatment interruption (3 days) and another with a long one (14 days). In both groups, symptoms derived from the interruption (measured by the DESS scale), worsening of the depression (measured with the MADRS scale) were recorded in a period of 5 to 7 days from the onset of the interruption. In the analyses by subgroups, a significant increase of suicidal ideation [$F(1.20) = 4.59, P = 0.045$] with SSRI of short half-life vs long-life AD, at 7 days of having interrupted the medication, was observed.⁵⁰

- Extrapolating these results to the usual situations of the clinical practice, in which the patients have low compliance or interrupt the treatment suddenly, we can say that the clinician should be alert to the appearance of ideations and autodestructive behaviors, for which it would be necessary to perform a close follow-up of the patients, especially in change of recent medication scenarios.

9. Remission of symptoms, relapses, recurrences, and their relationship with compliance.

RECOMMENDATION

Suicidal behaviors are not related with medication compliance in patients with Major Depressive Disorder (GRADE OF RECOMMENDATION C). The clinicians should maintain a close

RECOMMENDATION

Clinicians should consider that noncompliance with antidepressant treatment is related with a greater rate of relapses, although it has not been unequivocally determined if

noncompliance has the same effect on the recurrence rate. In patients with Major Depressive Disorder, noncompliance with the medication is still a complex problem under continuing investigation. (GRADE OF RECOMMENDATION C)

- 1+ Geddes et al. (2003), when they performed a systematic review of 31 randomized clinical trials in 4410 patients, found that the patients who continued with AD treatment had a 70% decrease in relapses OR (CI 95% 62–78; 2p<0.00001) versus those patients who interrupted the treatment.⁵¹ The study does not make any recommendations on the treatment duration, but stresses the need to identify those patients who have a greater risk of relapses.
- 3 Fawcett et al. (1995) found that treatment noncompliance in those diseases with a delay in the appearance of the therapeutic action (as occurs in the MDD) is a complex and little defined problem,⁵² on the contrary to what occurs in diseases in which there is a clear (and often immediate) relationship between noncompliance and symptom recurrence, as, for example, insulin-dependent diabetes.
- 2+ Finally, Bockting et al. (2008) concluded that most of the patients who had recurrence in the MDD had noncompliance of the therapy during the maintenance phase in a primary care scenario. However, the AD medication seemed to offer little protection against relapses in this group of patients. On the other hand, patients with limited treatment compliance in MDD suffered fewer relapses if they received cognitive therapy as a prevention of relapses.²³

II. Factors related with the patient.

In a recent study (2008) performed in Europe in 13,699 patients of both genders in general medicine medical offices, it was observed that the socioeconomical conditions of the patients increase the risk of having positive diagnoses for MDD and generalized anxiety disorder (GAT). In the specific case of the MDD, the socioeconomical factors that were significantly related with a greater prevalence of the condition were: female gender (relative risk [RR]= 1.5 for MDD alone; RR= 1.8 for MDD + GAT; p<0.0001); patients who lived alone, compared with those who lived with family or in community (OR= 0.61; p<0.0001); unemployed patients (OR= 1.42; p=0.002) and self-employed workers (OR= 0.70; p=0.02) in regards to 5 other work categories mentioned. This study, even though it stresses the importance of the socioeconomical factors in MDD, does not clarify their meaning within antidepressant treatment compliance.⁵³

The definition of compliance varies depending on the context in which it is discussed and thus there may be di-

fferent meanings for clinicians and patients.^{52, 54} However, even when compliance may be promoted by the clinicians, it is a voluntary act of the patient and remains under his/her control.⁵⁵ Due to this, its determinants may be multifaceted and complex. Knowing those characteristics of the patient that may predict lack of treatment compliance can contribute to formulating a strategy to elaborate individualized treatment plans, identify those with greater risk of lacks of compliance and develop appropriate interventions to minimize this risk.^{19, 56}

1. Sociodemographic variables.

RECOMMENDATION

Clinicians must keep in mind that young adult patients with MDD and the elderly have less compliance with antidepressant treatment in comparison with the other age groups (GRADE OF RECOMMENDATION C). Furthermore, they should consider that many frequently have less compliance in the long-term treatment of Major Depressive Disorder. (GRADE OF RECOMMENDATION D)

Age

- 2+ Even though some studies do not find differences in age-related compliance,^{14–16} most of the studies have observed that the younger patients have greater risk of lack of adherence to the treatment than patients who are older. Expressed differently, the risk of lack of adherence is reduced as age increases in the patients.^{3, 27, 57}
- 2++ Demyttenaere et al. (2008), in their most recent prospective study, observed that the patients who discontinued antidepressant treatment were significantly younger than those who completed the treatment (35.7 years SD±8.1 vs. 43.1 years SD±11; p=0.0045).¹⁰
- 3 Arnou et al. (2007), in a clinical trial with 681 patients without psychotic symptoms and diagnosed of MDD, who were randomly included in several groups to receive treatment with nefazodone, psychotherapy or the combination of both, also found that among the 156 patients in the "treatment discontinuation," group, those who abandoned were significantly younger than those who completed it.⁵⁸
- 2- Akincigil et al. (2007) in an observational, retrospective study with 4312 patients over 18 years, diagnosed recently of unipolar major depression and who had initiated antidepressant treatment, analyzed compliance in the acute phase (first 16 weeks) and

continuation phase (week 17 to 33), using pharmacy AD drug refilling records. All the patients belonged to private health care insurance systems, from which sociodemographic data and those regarding their disease were obtained. In the acute phase, the compliance rate was 51%, considering that they had the drug in their power for more than 75% of the corresponding period. The major treatment compliance was found in those patients of older ages (between 50-64 years of age OR=2.48 95% CI 1.94-3.15; ≥ 65 years OR= 1.96 95% CI 1.34-2.85), and higher socioeconomic status. AIDS was not a predictive factor of compliance in the continuation phase.²²

- 2+ On the contrary, Bambauer et al. (2007), only found a relationship between lack of compliance in younger age of the patients in the continuation phase of the AD treatment (between 30 - 39 years of age OR=0.90 95% CI 0.79-1.02).⁵⁹
- 2- Busch et al. (2004), also found greater likelihood of adequately complying with the treatment in those patients of older age (OR= 1,01; $p<0.01$).⁶⁰

Age seems to be related with treatment compliance: the older the age the greater the compliance.

Some studies have focused on treatment compliance in the elderly. In this group of patients, Reuben et al. (1999 and 1996) studied the effectiveness of the Comprehensive Geriatric Assessment together with an intervention to improve compliance.^{61, 62} After 15 months of follow-up, it was observed that this therapy could prevent decreasing quality of life and decrease in functionality of the elderly with specific geriatric diseases. One of the limitations of this study was that the participating subjects had two or more medical disorders (urinary incontinence, depressive symptoms, functional deterioration and/or falls).

- 1- Therefore, in the analyses by subgroups, it was not possible to determine a clear pattern of patients in which the functional performance demonstrated better or worse benefit was secondary to the intervention.
- 1- Mittmann et. al. (1997) evaluated antidepressant medication (tricyclics, SSRI, MAOIs, atypical) in a meta-analysis in patients over 60 years of age diagnosed of MDD, considering response to treatment as the primary outcome. Forty-one publications were identified for a typical AD, 16 studies for MAOI, 40 studies for SSRI and 77 studies for tricyclic AD. No significant differences were found between the AD types in regards to treatment interruption. However, one of the primary limitations of this study is that the clinical trials included had a small sample size, they were very he-

terogeneous and the mean duration of the follow-up with only 5 weeks.⁶³

Gender

In relationship to gender, the studies available indicated divergent results.

- 3 Some observed female gender as a predictor of lack of compliance, and others the male one.³
- 3 Brown et al., in an observational, prospective study in 197 patients with unipolar MDD and without other associated psychiatric conditions, observed that compliance at 3 months of treatment was greater in the men and then in women (81% vs 56%; $p=0.03$).²⁷
- 2- In the study of Burra et al.(2007), being a woman (OR=5,12 95% CI 1.09-24.1; $p<0.05$) and only having reached secondary education (OR=4,43 95% CI 1.03-18.9; $p<0.05$) were factors that were significantly related with a lower likelihood of treatment compliance,¹³ while Akicingil et al. (2007),²² Aikens et al. (2005)⁶⁴ and Busch et al. (2004) found that the fact of being a man was significantly related with worst likelihood of treatment compliance (OR=0.91; $p<0.05$) and (OR=0.73; $p<0.01$) respectively.⁶⁰
- 3 Other studies have not found significant differences between genders in compliance.^{14, 58, 65, 66}

Demyttenaere et al. (2001) analyzed the relationship between gender, severity of MDD and discontinuation of antidepressant treatment in 272 adult patients who were given a baseline interview and monthly telephone follow-up. The severity of the MDD was evaluated with the Sheehan Disability Scale, which contemplated self-evaluation of the disability on the scale of 0 to 10 for the occupational, social and family spheres. Approximately 72% of the patients had more than 3 points - moderate dysfunction in the 3 spheres - and complied with the DSM-IV criteria of the MDD. The discontinuation rate, defined as the premature termination of treatment by the patient without knowledge of the treating physician, after 4, 8, 12, 16, 20 and 24 weeks was 12%, 22%, 32%, 42%, 48% and 53%, respectively. Median time to discontinuation of treatment was 22 weeks.

The relationship between sexual dysfunction and risk of discontinuation was not altered by the patient's gender or age. While the risk of abandonment in women was only related with recovery of functions in the family sphere, in men it was related with the recovery of functions in the 3 spheres. Those men with the most significant improvements were especially prone to discontinue treatment. Among the

women, those who discontinued the treatment had had significant improvements within the family sphere regarding those who completed the treatment ($p<0.0001$ after 4, 8, 12, 16 and 20 weeks of treatment).

- 2+ In the men, those who discontinued treatment had significant improvements in family function ($p<0.0001$ from week 4 to 24), in social function ($p<0.0001$ in week 4, 8 and 12) and in the occupational sphere ($p<0.0001$ after weeks 4 and 8).^{15, 16}

Race

There are not many studies that incorporate the analysis of race of the patients into their variables.

- 3 While some studies do not report differences between ethnic or minority groups^{64, 67}
- 1- Arnow et al. (2007) found that the discontinuation rate due to adverse effects was greater in those patients having minority racial groups ($\chi^2=5.05$, $df=1$, $p=0.025$)⁵⁸
- 2- Busch et al., (2004) observed that when comparison was made according to race, and with regard to the white race, the likelihood of treatment compliance in Hispanic patients ($OR=1.20$; $p<0.01$) and Afro-Americans ($OR=0.63$; $p<0.01$) was significantly lower.⁶⁰
- 3 Similar results were found by Burton et al. (2007),³ Brown et al. (2007),²⁷ Bogner et al. (2006)⁴³ with the white race associated to lower risk of lack of compliance than minority groups.
- 3 Ayalon et al., studied antidepressant treatment compliance specifically for patients of the black and Latino races, without finding significant differences in the intentional compliance between both groups. However, the Latinos reported significantly greater lack of compliance than the black patients ($\chi^2 [1.99]=3.87$; $p=0.04$). Patients of the black race also reported fewer symptoms of baseline depression, and they were significantly younger than Latinos, had higher education level, and had taken a greater amount of drugs in the last 4 weeks. However, when all of the significant variables were introduced into a multi-variant logistics model, none of them could explain the differences regarding the compliance found between both races⁶⁸.

It seems that belonging to minority groups negatively influences treatment compliance of MDD, but this obviously could be linked to other more determining factors such as, for example, socioeconomical and cultural ones.

2. Knowledge of the disease, of antidepressant treatment and its possible effects.

RECOMMENDATION

Knowledge of the disease (by the patient), on its biological aspects and the treatment, including the drug adverse effects, favors drug compliance in patients with Major Depressive Disorder. Furthermore, clinicians should keep in mind that beliefs of addiction to drug treatment is related with lower AD medication compliance (GRADE OF RECOMMENDATION C)

In recent years, the number of studies that investigated the relationship existing between the belief system and the different AD treatments has been increasing since the importance of this factor on the lack of AD treatment compliance had begun to be commented on at the beginning of the decade.

- 3 In Germany, a survey that included a list of verification of depressive symptoms and questions related with AD treatment and its preferences, made in a sample of 2224 subjects representative of the German population, disclosed that 16.7% of the subjects were mildly affected, 7.5% moderately affected and 6.5% strongly affected by the depressive symptoms. Only 22.7% of the total of the group affected were receiving treatment with a physician for this reason. A total of 29.2% wanted to receive treatment while 70.8% did not want it. Both the prevalence of the treatment as well as the desire for treatment increased significantly according to the severity of the depressive symptoms ($p<0.001$). However, even in the group with the most severe depressive symptoms, 46.4% of the population showed no desire to undergo treatment.⁶⁹
- 3 In Australia, a survey made in 999 subjects over 18 years of age and representative of the Australian population examined their opinions regarding depression and antidepressant treatment based on two cases that were identified as "major depression" or "depression/suicide." A total of 46.7% of those surveyed considered that AD drugs could be useful in cases of depression while 27.5% considered that they were harmful. In the case of depression/suicide, 52.5% considered that antidepressant treatment could be useful, while 23.4% considered it harmful. Those interviewed who had a university degree considered the AD significantly less harmful (17%) versus those who responded that they were useful (31.2%) or who answered that they did not know (26.8%) $p=0.004$. Those who had considered antidepressant treatment as harmful had been less exposed to the disease, i.e., they had suffered some MDE during their life ($p<0.001$), then those in whom some member

had suffered some MDE in the family or friends setting ($p<0.001$), or in the work setting ($p=0.02$). Those who had considered AD as harmful also rejected to a greater degree the rest of the therapeutic options, including visits to the psychiatrist ($p<0.001$), psychologists ($p<0.001$), and psychotherapy ($p<0.001$); and they were less pessimistic about the results of these patients if they did not seek professional help⁷⁰.

3- Givens et al. (2006), in a qualitative study based on semistructured interviews examined the attitudes of depressed patients over 60 years of age. The most commonly expressed reasons to reject antidepressant treatment were fear of addiction to treatment, resistance to considering depression as a disease, concern about the possibility that the AD would not allow them to have natural feelings of sadness and previous negative experience with AD drugs⁷¹.

2+ Vanelli et al. (2008) analyzed the role that previous experience of the patients with AD drugs had and its relationship with compliance to the current treatment. To do so, they extracted data from 211,565 patients of the anonymous registry of 1157 drugs, in which 38.5% of the patients had not received any antidepressant in the 180 days prior to the prescription. In those patients who had not previously received in AD, the mean days to discontinue treatment was 67, and 184 days in those who had received treatment in the previous 6 months. Interruption rate at 30 days was 38.8% for the patients who had not received previous AD and 18.8% for those who had, and at 180 days, of 74.9% and 48.3%, respectively. The previous use of AD was associated with greater rates of treatment compliance. No significant differences were found regarding the antidepressant indicated⁷².

3 Dijkstra et al (2008), suggested that in relationship to the antidepressant treatment at 9 months of having initiated the medication, only the "goal or time objective of the treatment" is related with compliance. While the objective is less time of treatment duration, there is more likelihood that the AD treatment will be discontinued prior to 9 months ($OR=2.08$ 95% CI 1.41-3.07; $p<0.001$). Their findings reaffirm the theories on psychological determinants of behavior and illustrate that perceptions of the patients on the use or not of the AD influence their decision beyond the psychiatric, environmental, social or clinical factors.⁷³.

3 In a recent study, Aikens et al. (2008) examined in depth the beliefs of 165 patients with MDD regarding the need or harmfulness of AD drugs, considering the results of this previous study –Aikens, 2005– in which these beliefs are the only significant predictor of compliance to treatment, as certain.^{64, 74}.

3 Both recent compliance as well as compliance in general are higher when the perception of the need for antidepressant treatment exceeds the concerns that taking the medication generate. The perception of the need for AD was associated with older age of the patient ($p<0.001$) and greater severity of the depression symptoms ($p=0.03$). Furthermore, in those who perceived a long course of their disease (0.001) and in those who attributed their symptoms to neurochemical unbalances ($p.005$), the need for AD perceived by the patients was significantly greater. On the contrary, in those patients with no background of using AD ($p=0.02$), in those who perceived that their disease was caused by bad luck or chance ($p=0.04$), and in those with worse understanding/knowledge on depression ($p=0.003$), perception of harm of the AD was greater, so that it could be associated to worse treatment compliance.⁷⁴.

1+ Edlund et al. (2008), in a study performed in war veterans, also described how the beliefs on the disease and the treatment affected compliance. Those who were more willing to receive antidepressant treatment did not agree with: "they should manage their depression alone" ($OR=1.29$ 95% CI=1.02-1.63; $p=0.04$), "they would become addicts to the antidepressants" ($OR=1.37$ 95% CI=1.11-1.69; $p=0.003$), "other diseases are more important than depression" ($OR=1.56$ 95% CI=1.22-2.00; $p=0.0004$) and also that "other problems of their life are more important than depression" ($OR=1.33$ 95% CI=1.05-1.67; $p=0.02$). Those who demonstrated their agreement that an antidepressant drug would be useful were more willing to receive treatment ($OR=0.66$ 95% CI=0.50-1.67; $p=0.003$)⁷⁵.

3 Burra et al. (2007), found a significant relationship between less efficacy perceived of the antidepressant treatment and worse beliefs regarding the drugs, with a likelihood of non-compliance to the treatment ($OR=0.27$ 95% CI 0.10-0.71; $p<0.01$)¹³, as Ayalon et al. described it in a subpopulation of black and Latinos in the USA⁶⁸.

3. Perception of the origin of the disease.

RECOMMENDATION

Clinicians should consider that the attribution of the Major Depressive disorder to non-medical causes among the patients is frequently related with lower AD compliance (GRADE OF RECOMMENDATION C).

Patients with greater knowledge of the depressive disease and those who perceive that some chemical unbalan-

ces are part of the origin of the disease, have a lower risk of lack of treatment compliance.

- 3 In a study of Jorm et al. (a survey to know perceptions on depression and AD in Australia), the group that considered the ADs harmful had the opinion that weakness of character was often the cause of depression ($p<0.001$), and in fewer cases that genetics ($p=0.01$), or traumatic events ($p=0.01$) could be the cause of the disease. In addition, in this group, more attitudes of stigmatization of the MDD were observed as the depressed patients had that opinion they could "overcome the depression by themselves" ($p<0.001$) and that the depression was not really the disease ($p<0.001$)⁷⁰.
- 3 In addition, Aikens et al. (2008) found that in those patients who perceived a long course of their disease ($p=0.001$), and in those who attributed their symptoms to chemical unbalances ($p=0.005$), the need for AD perceived by the patients was significantly greater. On the contrary, in those patients with no background of use of AD ($p=0.02$), in those who perceived that their disease was caused by bad luck or chance ($p=0.04$), and in those with a worse understanding/knowledge on depression ($p=0.003$), perception of harmfulness of the AD was greater, which could be associated to worse compliance⁷⁴.

4. Chronic comorbid medical conditions.

RECOMMENDATION

More studies are needed in patients with Major Depressive Disorder and chronic comorbid conditions that evaluate the influence of the latter on AD medication compliance. (GRADE OF RECOMMENDATION C)

Some comorbid conditions have been seen to be associated to greater risk of lack of compliance, and several studies have attempted to demonstrate that this relationship is significant.

- 3 Bogner et al. (2006), using a self-evaluation comorbidity questionnaire (based on the Charlson Comorbidity Index), did not find a significant relationship between presence of cardiopulmonary, metabolic diseases and cancer, among others, and treatment adherence in MDD⁴³.
- 2- On the contrary, Akincigil et al. (2007) found that compliance is less in those patients who have two or more cardiovascular or metabolic conditions in comorbidity (OR= 0.65)²².
- 2+ Bambauer et al. described a significantly higher risk of

lack of continuation compliance (at 6 months) in patients who reported chronic previous use of analgesics (OR=1.16 95% CI 1.04-1.29)⁵⁹.

- 3 Arnow et al. (2007) observed that some patients with MDD who abandoned treatment had a significant association of anxiety disorder with greater frequency in some way regarding those who continued with the treatment (31% vs. 20%; $\chi^2=7.9$; $df=1$, $p=0.005$). On the contrary, there was no significant difference between the patients who completed and abandoned AD treatment when a personality disorder was associated⁵⁸.
- 2- Opposed to these results are those of Akincigil, Busch et al. (2004), who observed that the presence of psychiatric diagnoses associated with MDD increased the possibility of treatment compliance, except for personality disorder (anxious disorders OR=1.21; bipolar disorder OR=1.17; other psychiatric diagnoses OR=1.09; $p=0.001$)⁶⁰.
- 3 A retrospective study of Tai-Seale et al. (2000) in 2012 patients recorded through a medical insurance system observed that anxious depression is associated to a higher likelihood of treatment compliance ($\beta=0.562$, $p<0.01$), and other patients with risk factors for their health ($\beta=0.320$, $p<0.01$). On the contrary, those women with MDD and previous gynecological disorders are more prone to discontinue treatment with AD ($\beta= -0.301$, $p<0.01$), probably because of the effects of AD on sexual performance function⁶⁶.

5. Personality characteristics.

RECOMMENDATION

More studies that evaluate the influence of the characteristics of personality on antidepressant treatment compliance in patients with MDD are necessary (GRADE OF RECOMMENDATION C)

Only one study has been found that describes the characteristics of personality in relationship with antidepressant treatment compliance. Cohen et al. performed an observational, prospective study and 57 patients diagnosed with MDD in order to examine the relationship between personality characteristics of patients measured with the NEO Five-Factor Inventory Revised, and antidepressant treatment compliance in the acute phase evaluated with the MEMS (Medication Event Monitoring System). The scores obtained within the 5 dimensions of NEO were compared with those obtained in a previous study in patients with depression and these were found to be comparable.

The overall relationship between the 5 dimensions and treatment compliance was not significant.

It was analyzed if the NEO dimensions independently were related with treatment compliance and it was found that extroversion was a significant negative predictor of treatment compliance. None of the 4 other dimensions was related with treatment compliance significantly. In addition, the relationship of each aspect of the 5 dimensions of personality was analyzed. A significant relationship was found between activity, feelings and modesty. Activity was a negative predictor of treatment compliance and modesty a positive one. Feelings did not predict compliance.

- 2+ However, this study found very high levels of compliance to treatment that could be due to the close follow-up made during the 3 months of follow-up, and within its limitations, complexity of the assessment of personality and treatment compliance is described. Thus, its results are not conclusive, it being necessary to go deeper into this line of investigation⁷⁶.

6. Consumption of alcohol and other toxic substances.

RECOMMENDATION

Substance and alcohol abuse in patients Major Depressive Disorder are associated to lesser compliance with the medication (GOOD CLINICAL PRACTICE).

Substance and alcohol abuse in patients with MDD are frequent and there are very few studies on this subject in all of the age groups.

- 3 The limited data suggest a negative relationship between alcoholism or drug abuse and antidepressant treatment compliance⁷⁷.
- 2- Busch et al. (2004) studied alcohol and drug abuse as one more among the possible psychiatric comorbidities and found lower likelihood of treatment compliance in those patients with these conditions associated to MDD⁶⁰.
- 2- The same conclusions were obtained by Akincigil et al. (2007) in acute compliance to treatment, or when the MDD was associated to simultaneous abuse of alcohol (odds ratio [OR] = 0.49, 0.36-0.68) or other substances (OR= 0.72, 95% CI 0.56-0.93); and in compliance of continuity in those which alcohol and other substances are grouped (OR=0.80 95% CI 0.57-1.13).²² These results coincide with those of Cooper and Dobscha in populations of patients over 65 years of age^{78, 79}.

III. Factors related with the professional.

RECOMMENDATION

Clinicians should consider if the specialty of the professional who is in charge of the care, the medical -patient relationship (time, confidence, dedication) and care by the multidisciplinary teams has a positive or negative influence in antidepressant treatment compliance in patients with MDD (GOOD CLINICAL PRACTICE).

RECOMMENDATION

Clinicians should keep in mind that the experience and prestige of the professional improve compliance in the long term treatment of MDD. Furthermore, the patients attribute greater credibility and experience in the management of patients with MDD to the psychiatric physicians, favoring better compliance with antidepressant treatment (GRADE OF RECOMMENDATION D).

1. Specialty of the professional.

The study suggests that initiating the treatment by a psychiatrist improves the possibility that the patient will comply with the treatment in the acute phase, although there is less evidence in relationship with the continuation phase.

- 3 Fernández et al., (2006) analyzed the incidence and likelihood of receiving treatment in accordance with the clinical practice guideline (CPG) in patients with psychiatric disorders in Spain, in a retrospective study based on the results all of the ESEMed (European Study of the Epidemiology of Mental Disorders) and any subsample of 133 subjects. They found that the conditions that had most frequently received any treatment were panic disorder (49.3%) and MDD (48.9%). Most of the treatments were initiated in the psychiatric medical visit (35%), followed by those treated jointly by a mental health professional (psychiatrist or psychologist) and a general practitioner (27.8%). More than 25% of the subjects received treatment exclusively by the general practitioner and 7% only by the psychologist. The likelihood of receiving treatment in accordance with the CPG was similar in the specialized sector and in the general medicine with 31.8% and 30.5%, respectively⁷⁷.
- 2- Akincigil et al. (2007), in relationship to compliance during the acute phase, observed that those whose follow-up visits were with the psychiatrist showed better AD compliance. Among those patients who complied with treatment, 41.5% remained compliant during the continuation phase. Of these, in turn, those who had

follow-up visits took place in psychiatry showed significantly better treatment compliance²².

- 2+ The study of Bambauer et al. (2007) analyzed the impact of the medical specialty in antidepressant treatment compliance. Those patients under treatment with psychiatrists had a lower immediate risk of lack of compliance (OR= 0.70 95% CI 0.61 to 0.80) than those who initiated their treatment with a primary care physician. Treatment with some other specialty (different from psychiatry or primary care) was associated to a significantly higher intermediate risk of lack of compliance (OR= 1.39 95% CI 1.22 to 1.60) and lack of continuity compliance measured at 6 months of treatment (OR= 1.40 95% CI 1.24 to 1.59). Treatment with multiple specialties was associated to greater compliance than treatment with a single specialty (OR= 0.83 95% CI 0.75 to 0.92)⁵⁹.

2. Medical-patient relationship (time, confidence, dedication).

RECOMMENDATION

Physicians can improve treatment compliance of the patients, indicating to them how long they have to take the medication, explaining the possible adverse effects and resolving their questions and concerns. .

Physicians can improve treatment compliance of the patients by indicating the amount of time they must take the medication, explaining the possible adverse effects and resolving their questions and concerns.

- 3 Brown et al.(2007), in a survey performed in 191 primary care patients, demonstrated that the possibilities of compliance was three times more in those patients who were told by their physician "how much time the AD treatment would last (OR=3.8, 95% CI 1.6-8.9) and "what to do if they had any doubts regarding the treatment" (OR=3.8, 95% CI 1.4-10.4), in comparison with those who had not received this information²⁷.
- 1- Young et al. (2006), in a randomized study performed with 101 internal medicine or primary care physicians in different types of practice in the USA, using recordings of the medical visit, analyzed the amount and quality of the information provided to 129 patients diagnosed of major depression or adaptive disorders, who had been prescribed any antidepressant drug. The information provided by the medical professional was classified into 11 aspects. Of these 11, a mean of 5.7 aspects (SD±1.6) was explained to the patient and none of the 129 patients received any explanation for all of the aspects related with the treatment. In 96.1% of the cases, the purpose of the treatment was explained, in 90.7% the name of the treatment and in 85.3% the possible adverse effects. Reference was made to treatment duration in only 34.9% of the patients, to the costs in 21.4% and to the barriers of the drug use in 1.6%. Among the instructions that had previously demonstrated an association with treatment compliance, the physician made reference to the fact that the antidepressants should be taken 2 to 4 weeks before the first results could be observed in 69.8% of the visits and that the medication should be taken daily in 68.2% of the visits. The physician only warned 5.4% of the patients that they should continue antidepressant treatment even if they felt better. Only 3.9% of the patients were warned that they should consult their physician again before discontinuing treatment. The older physicians (β : -0.01; $p=0.002$), and those having private practices (β : -0.20; $p=0.02$) provided their patients less information and those who had longer medical visits received significantly more instructions (β : 0.01; $p=0.02$). Furthermore, the patients with MDD received less information and fewer instructions than those with adaptive disorders (β : -0.41; $p=0.01$ and β : -0.51; $p=0.004$, respectively). This makes it necessary to identify effective interventions that can assure that those patients who initiate treatment with AD will have the critical information that can maximize their compliance and the treatment objectives⁸⁰.
- 3 The objective of the Bull et al. (2002) study was to analyze communication between physicians and patients in treatment with SSRI, the information that the physicians provided their patients and its relationship with discontinuation and changes of treatment. A total of 72% of the 137 physicians answered that they regularly recommended to their patients that they should take antidepressant treatment for at least 6 months and only 29 physicians (21%) responded that they had not indicated the treatment duration to their patients at the beginning, since they preferred to wait to observe how they felt. On the contrary, 137 patients (34%) responded that their physicians had advised them to follow the treatment for at least six months while 228 (56%) responded that they had not received any instructions regarding the expected duration of the antidepressant treatment. Those patients in whom their physician had indicated that the duration of the treatment would be less than 6 months had significantly more likelihood of having discontinued the treatment before completing 3 months of its onset (OR= 3.12 95% CI 1.21-8.07). When the possibility of having adverse effects is discussed at the beginning of the treatment, it reduced the possibility of discontinuation of treatment regarding those who had not discussed the adverse effects with their

physician (OR= 0,49 95% CI 0.25-0.95), and the possibility of changing treatment increased (OR= 3.02 95% CI 1.52-6.02). In the same way, those who commented the adverse effects during the treatment with their physician had a greater likelihood of undergoing a treatment change⁶⁵.

- 3 These results coincide with those of Maidment et al. (2002), who found an association between greater compliance and greater amount of information provided in the medical visit to patients over 65 years and with a lower cognitive discapacity, while worse adherence was related with concern by the patient about the antidepressant treatment and the severity of the adverse effects⁸¹.
- 2+ Demyttenaere et al. (2001), within the physician - patient relationship, analyzed the fact that the patients informed their physician on their decision of discontinuing the treatment. Of the 272 patients studied, 24% of them did not inform their physician on their decision to discontinue treatment. Differences in this percentage were observed based on the reason for the discontinuation: 100% of the physicians were informed about the decision when the reason was "the physician told me I could stop it;" 82% were informed in the reason was "*feeling uncomfortable with the treatment*"; 76% were informed if the reason given was "*improvement of the depressive symptoms*," 60% if the reason was "fear of dependency on the AD treatment", if the abandonment was due to "adverse effect of the treatment", there was another 60%. On the other hand, when the reasons were "*absence of AD treatment efficacy*" and "*need to resolve their problems without using drugs*", only 34% and 25% of the physicians, respectively, were informed. The physicians were significantly more informed on the decision of their patients to discontinue the treatment when the latter had agreed with the statement of the Antidepressant Compliance Questionnaire (ACDQ) that were related with the physician-patient relationship: "*The physician understood how I felt perfectly*" (p=0.05), "I am satisfied with the explanations that the physician offered me regarding the reasons for my depression" (p=0.04), "I am satisfied with the time that my physician dedicated to discussing my emotional problems" (p=0.04) and "*My physician assured me that he/she is confident that the antidepressants are the adequate treatment*" (p=0.02).^{15, 16}.
- 3 Bultman et al. (2000), performed a study in 100 patients with antidepressant treatment. A telephone survey was made to evaluate the style and information provided by the physician in the first visit and a second follow-up visit and its relationship with an-

tidessant treatment compliance. The results obtained were the following: a) an initial "collaborative" system with the physician predicts better perceptions regarding the antidepressants ($\beta=0.35$, $p<0.0004$); b) knowledge of the treatment regime predicts satisfaction of the patient with the antidepressant ($\beta=0.19$, $p<0.02$); c) more possible beliefs regarding the AD predict satisfaction of the patient with the medication ($\beta=0.39$, $p<0.0003$); d) satisfaction of the patient with the antidepressant predicts fewer missed doses of the treatment ($\beta= -0.25$, $p<0.03$)⁸².

- 3 Interventions aimed at improving adherence through the perception of the patients can maximize their effectivity if they are oriented towards those who underestimate the severity of their symptoms or those patients who believe that the symptoms will be temporary, even when their previous experience has shown the contrary, or the patients who believe that their symptoms are caused by chance, those who previously have not taken ADs or those who are confused by their symptoms⁷⁴.

Furthermore, the physicians should discuss the need for the antidepressant treatment, probable duration of their treatment, the differences between feelings of sadness and depression and the reality of the new AD drugs and their limited sedative effects with their patients.

3. Multidisciplinary teams.

- 1+ Peveler et al. (1999), in a randomized study on the effect of psychological counseling provided by nurses vs. the administration of information in leaflets in a medical office, demonstrated that assigning the counseling regarding the disease to the nursing service was an important predictor of treatment adherence at 6 weeks (OR=2.1 95% CI 1.1 to 4.0) and at 12 weeks (OR=2.7 95% CI 1.6 to 4.8) while information through leaflets did not have a significant effect. In this study, a short psychosocial intervention by the nursing staff significantly improved adherence⁸³.
- 2+ Furthermore, Clever et al. (2006) analyzed the impact of involving the patient in the decision making, through an intervention designed to be made by the nursing teams in patients with depression. The basic objectives of the nursing intervention were: evaluate key symptoms of depression, educate and activate the patients and offer feedback to the primary care physicians. The degree in which the patients considered that they were "involved in the decision-making" (IDM, Involvement in Decision Making) was evaluated on a 5-point scale, going from 1 (very little involvement) to 5 (very much involvement). The IDM

was positively and significantly associated with the individual evaluations of the patients regarding the explanations given by their physicians on the health problem, tests and treatment, and global communication ($p<0.001$). Clinical care was appropriate to the CPG with significantly greater frequency in patients who had higher values on the IDM scale. In those patients assigned to the intervention, the likelihood of receiving care in accordance with GCP increased 4% and 5% for each increase of 1 point on the IDM (range 0.34-0.51; $p=0.009$), while in patients assigned to a "non-intervention," the likelihood increased from 5% to 6% (range 0.24-0.46, $p=0.007$). Furthermore, the IDM were positively and significantly associated to the resolution of the MDE globally, and when discriminated by intervention and non-intervention groups. In those patients, the relationship between the IDM and adequacy of treatments to GCP and results of the MDE suggests that active patients combined with a multidisciplinary health care system prepared would produce the best results⁸⁴.

IV. Social aspects associated to antidepressant treatment compliance.

RECOMMENDATION

Clinicians should keep in mind that the support of the work setting favors better compliance with the antidepressant treatment. Furthermore, social-health care campaigns frequently are effective in the usual clinical practice (GRADE OF RECOMMENDATION D). More studies are needed to determine the influence of other social aspects on antidepressant treatment compliance. (GRADE OF RECOMMENDATION D).

1. Family aspects (spouse, children, work situation, educational level)

The risk of having MDD is greater in persons who live alone or are unemployed while it is less than those with university degree, self-employed workers, or retired persons.

- 3 Berner et al. (2008), in a survey performed in 2224 subjects in Germany, observed that those persons who were widowed or divorced were significantly more depressed than those who were married or single ($p<0.05$). They also revealed that those having low educational level were more depressed ($p<0.05$), and that the severity of the depressive symptoms had a constant reduction as the yearly income increased ($p<0.001$). Those persons who lived in the large cities were significantly more affected by depression than those who lived in small cities ($p<0.001$)⁶⁹.

- 3 Anseau et al. (2008), in a survey conducted in 13,699 patients in Belgium, demonstrated that those who lived alone and had significantly more risk of suffering MDD alone or associated to generalized anxiety regarding those who lived with a partner or in family, and those living in community (22%, 16.7% and 13.6%, respectively, $p<0.0001$). The educational level significantly influenced the frequency of appearance of MDD associated to the GAT, this being particularly high in subjects without primary education and lower in those who had completed university education (22.1% vs. 12.8%, $p<0.0001$). Furthermore, the prevalence of both disorders together was significantly greater in unemployed patients versus retired ones (27.7% vs. 13.3%, $p<0.0001$)⁵³.

Socioeconomic status

- 2- Akicingil et al. (2007) observed greater adherence during the acute phase as the range of yearly income increased: between 50,000 – 70,000 USD/year with an OR=1.22 (95% CI 1.05-1.42) and income $\geq 70,000$ USD/year with an OR=1,30 (95% CI 1.11-1.53), regarding those whose income was $\leq 50,000$ USD/year. This tendency was maintained when adherence was analyzed during the maintenance phase²².
- 1- Furthermore, Arnow et al. (2007) observed that the patients who had discontinued the treatment had significantly lower income than those who had completed it ($z=-2.0$; $p=0.048$) and this difference was clearer in patients who were in combined therapy: drug therapy and psychotherapy ($z= -2.85$; $p=0.004$).⁵⁸ In this way, better social economic status seems to predict better treatment adherence and less risk of discontinuing it.
- 3 Within the socioeconomic situation, it seems to be important to make the distinction proposed by Bambauer et al. (2007) between lack of adherence related with the cost of the medication, which they define as that situation in which any of the following behaviors occurs in the patient:

- a) skip the doses to prolong the duration of the medication;
- b) take less amount than indicated to prolong the duration of the medication;
- c) they did not buy the maintenance prescription as it is very expensive.

They stratified a sample of 13,835 patients into those 65 years or older and those under 64 year. A total of 38% of the non-elderly patients and 19% of the elderly ones stated they did not comply with the

antidepressant treatment due to the costs. Lack of adherence related with costs was significantly associated in the case of the elderly to older age, female gender, Afro-American race, yearly income, and drug coverage (medical insurance). It was related for both groups with the number of associated diseases, involvement of the daily life activities and, in the case of drug coverage, only for those interviewed who had no medical coverage⁸⁵.

Family situation

- 3 The study of Busch et al. (2004) observed that those patients who were married (OR=1.20; $p<0.01$) and had higher income (OR=1.00; $p<0.05$) had a greater likelihood of adequately adhering to the treatment.⁶⁰ Bull et al. (2002) observed that separated, divorced or widowed patients have two times more tendency to discontinue treatment than those who were married⁶⁵.

Educational level

- 3 Fernández et al. (2006) observed a greater likelihood of receiving adequate treatment to CPG in Spain for MDE in those patients who lived in large cities (OR=2.97, 95% CI 1.3-6.8) and with high educational level (OR=3.36 95% CI 1.1-9.8)⁷⁷.
- 3 Burra et al. (2007) observed that having a lower level of studies or one equal to that of secondary education (OR=4.43 95% CI 1.03-18.9; $p<0.05$) was related significantly with a lower likelihood of adherence¹³.

Socio-health care campaigns

- 2+ Bambauer et al. (2006) evaluated the impact of a coordinated program between pharmacies and physicians who immediately notified the physicians of those patients who had not refilled their AD prescription at 10 days of the indicated time, without finding significant results⁸⁶.
- 1+ Furthermore, Kutcher et al. (2002), in a randomized study to evaluate the impact of an adherence stimulus program by information letters on depression and antidepressant treatment in patients under treatment with sertraline, did not find significant differences after 29 weeks of intervention between the group assigned to the program and the control group. Even when the global satisfaction with sertraline improved in the patients of the group assigned to the program, neither treatment efficacy variables nor adherence improved⁸⁷.

- 1- Brook et al. (2005) demonstrated that an educational program during the continuation phase of the antidepressant medication conducted by a group of pharmacists in different regions of Holland, including informative videos for the patients with new MDE who received treatment did not significantly improve antidepressant treatment compliance⁸⁸.

- 1- Bosmans et al. (2007) made an economic evaluation on this same educational program, considering the resources necessary for its establishment in the clinical practice. They did not find that it was more cost-effective than the usual cares after 6 months of follow-up. 89 Vergouwen et al. (2005) evaluated the effectiveness of 2 interventions: "Depression care programme" (DCP) and "Systematic follow-up programme" (SFP) on antidepressant medication compliance (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) in patients with MDD in primary care. The most important characteristics of these educational programs are described in table 2. After 6 months of follow-up, no significant differences were found in the compliance rates between the groups that received DCP vs. the SFP group, so that the systematic regular follow-up of depressed patients seems to be an intervention by itself⁹⁰.
- 1+ Adler et al. (2004) evaluated antidepressant medication compliance in patients with MDD and comparative group that received special cares ("pharmacist intervention") vs. a group that received standard cares in primary care. At the end of 6 months, an analysis was made by subgroups in which the intervention showed clear benefit in those patients who had not received antidepressant medications at the time of entering the study, but no significant impact was observed in those who had already received antidepressant medication⁹¹.
- 1- Hoffman et al. (2002) evaluated the impact of an educational program through monthly correspondence in patients who received antidepressant medication at 30, 90 and 180 days. Reminder letters were sent to the patients regarding the importance of antidepressant drug compliance in addition to providing a list of advices regarding the treatment: they were told that 2 to 4 weeks would pass before any effect would be observed, that the therapy should be continued even if they felt better, that they should consult a physician before discontinuing the medication, they should take it daily as prescribed, maintain regular visits with the professionals who facilitated the treatment and call if they have any more questions, etc. In this study, it was observed that after the first month of follow-up, both groups had similar compliance rates (58.9% for the intervention group and 57.4% for the control group). However, the difference in compliance at

3 in 6 months was modest, but significant, and in favor of the intervention. On the other hand, the study also had some limitations, the most important being the inclusion of all patients who received new antidepressant medication, independently of their diagnoses. Thus, it is difficult to generalize the impact of this intervention on patients with a specific diagnosis (for example, MDD). On the other hand, two interventions were studied, one aimed at professionals who administered the treatment and the other at the patients who received the antidepressant medication. Thus, it cannot be determined if both interventions together are necessary to achieve an improvement in medication adherence or if only one of them is necessary to achieve this objective⁹².

2+ Aubert et al. (2003) evaluated the impact of telephone counseling and reminders by e-mail in the adherence of 505 patients under antidepressant treatment. The program participants received for telephone calls and 5 E-mails focused on the importance of treatment adherence, adherence barriers, quality of life, depressive symptoms and satisfaction of the patient with the program. The patients included in the program were significantly more adherent to treatment during the acute phase (89.9% vs. 67.7%, $p < 0.001$) and continuation phases (81.1% vs. 57.6%, $p < 0.001$). Furthermore, there was a significantly greater tendency to continue treatment after 7 months from its onset (77.8% vs. 49.5%, $p < 0.001$), and they refilled their drugs within the times more in agreement with that of the medical indication (± 0 days vs. ± 18 days, $p < 0.001$)⁹³.

1+ Also, Akerblad et al. (2003) observe that none of the 2 interventions (educational program and drug monitoring) produced a significant increase in compliance, even though both intervention groups showed a numerically higher rate of compliance compared with the control group and significantly more patients assigned to the education program responded to treatment, after 6 months of follow-up, compared with those who received the usual cares. The complying patients (independently of the 2 intervention shoes) had greater response to treatment than the non-compliers⁶.

V. Factors related with the Organization of the System.

1. Characteristics of the health care service (centralization, multidisciplinary, accessibility, waiting time).

RECOMMENDATION

Clinicians should consider that accessibility to the health care services (ease of being attended if there are side effects or complications during the treatment) favor compliance during maintenance of the antidepressant medication (GRADE OF RECOMMENDATION D)

RECOMMENDATION

Clinicians should keep in mind that a greater number of professionals per inhabitant as well as improvement of the management and refilling of the prescriptions favors better long-term treatment compliance of the Major Depressive Disorder. (GRADE OF RECOMMENDATION D)

2- Akincigil et al. (2007) observed worse adherence in the AD treatment continuation phase in those patients with comprehensive medical insurance coverage (in this case, represented by the North American HMO system) regarding Indemnity Plan Enrollees (OR=0.62, 95% CI 0.42-0.92)²².

3 The study of Busch et al. (2004) analyzed antidepressant medication adherence according to the available CPG up to date of the study, in 4 war veteran patients in the USA. Only those patients seen by physicians in non-psychiatric clinics had a better likelihood of adherence in comparison with those patients seen by nonmedical professionals. When the analyses model was adapted for the variable "type of health care Center," better adherence was determined in patients who received the antidepressant medication prescription from a medical professional, within a scenario of a psychiatric clinic⁶⁰.

Table 2

Characteristics of two types of programs to improve MDD treatment compliance⁹⁰.

Intervention	AD dose based on the evidence	Improvements in the education to the patient	Improvements in the education to the PC physician	Active participation of the PC physician and patient in the treatment is promoted	Support	Systemic follow-up
DCP	Yes	Yes	Yes	Yes	Yes	Yes
SFP	Yes	No	No	No	No	Yes

DCP: Patient depression care programme.

SFP: Systematic follow-up programme.

- 3 Tai-Seale et al. (2000) observed that in those patients whose health care plan contemplated the visit of a social worker, there was no improvement in treatment adherence ($\beta = -0.569$, $p = 0.01$). This contradicts the theories that state that social workers would control for improving quality, efficacy and continuity of the treatment, improving adherence⁶⁶.

VI. Factors related with the Therapy.

In most of the patients with MDD, treatment during the acute phase (6-12 weeks) may seem to be insufficient and it has been described that between 30% and 50% of the patients who respond to short-term treatment will develop a relapse in the year following the discontinuation of the therapy.⁹⁴ MDD treatment has 3 phases: the acute phase (12 weeks) whose objective is to relieve the symptoms of the depression and treat the adverse effects of when they occur in order to achieve better compliance. The continuation phase (4-9 months) prevents relapses and the maintenance phase (10 months on) is aimed at the prevention of recurrences. In patients with high risk of recurrence, treatment with a duration of 1 year is recommendable, in order to reduce the likelihood of recurrence and restore the quality of life of the patient⁹⁵.

1. Predominance of the efficacy of tolerability of the AD in treatment compliance.

RECOMMENDATION

Clinicians should keep in mind that weight gain secondary to treatment negatively affects and, to a greater degree in women, antidepressant treatment compliance, in regards to other adverse effects (digestive problems, anxiety, sedation). Weight gain is one of the most frequent factors in young women and those of middle age, that affects compliance. However, it may be an important factor associated to compliance in patients of any age (GRADE OF RECOMMENDATION C).

Somnolence secondary to treatment negatively affects AD medication compliance in patients with MDD, principally in relationship to work activity of the patient (activities that require greater attention and concentration) and when there is a concomitant medication. This does not seem to vary based on age and gender of the patient, and its impact on compliance is less than sexual dysfunction and weight gain (GRADE OF RECOMMENDATION C).

One of the most frequent causes of discontinuation given are those of side effects of the medication⁹⁶.

- 2++Demyttenaere et al. (1998) compared amitriptyline with fluoxetine, using the MEMS to differentiate between "drop out" (premature discontinuation) and non-compliance (specific missing of medication dose) in outpa-

tients at 9 weeks. Although the efficacy was comparable between both treatment groups, a significantly larger proportion of patients discontinued treatment as a result of lack of efficacy or adverse events in the amitriptyline group (45.2%) than in the fluoxetine one (17.1%). The authors state that the relationship between efficacy, adverse events and compliance is complex. Premature discontinuation and noncompliance can be determined by different factors²¹.

- 2++Melartin et al. (2005), in a prospective study, observed that while the treatment was administered adequately in most of the patients during the acute phase, almost half of the patients (49%) discontinued treatment prematurely during the continuation phase. This "dropout" from the treatment at the beginning of the second phase of the therapy was conditioned by a negative attitude of the patients regarding antidepressant medication, fear of dependency or adverse effects of the therapy, among other variables⁹⁷.

- 2+ One study by Goethe et al. (2007) evaluated 460 adult patients diagnosed of MDE. In this work, they observed that the most bothersome side effects were, going from greater to lesser frequency, decrease in sexual desire, insomnia, weight gain, gastric symptoms and headaches. In other studies, the causes given by the patients for treatment discontinuation were: side effects (12.8%), "the doctor told me to stop taking the medication" (12.6%), "The SSRIs do not help" (11.1%) and the MDE ended" (3%), among others. The logistic regression analysis found that the risk of discontinuation doubled when there were "extremely uncomfortable" side effects ≥ 1 (OR 2.15; 95% CI 1.27-3.64). On the other hand, weight changes were associated to greater adherence as well as the use of benzodiazepines. However, this point is difficult to interpret because weight change was not classified in the study as gain or loss.
- Considering that these side effects occur in general in more than 90% of the patients, even in this study, only 2 side effects were associated with treatment discontinuation: anxiety and weight gain⁹⁸.

2. Influence of adverse effects in premature withdrawal from the treatment.

One of the factors having the greatest influence in compliance is tolerability and efficacy of the antidepressant medication. This fact is clearly determined by the drug profile of the ADs.

Tricyclic antidepressants (TAD), selective serotonin reuptake inhibitors (SSRI), selective serotonin/norepinephrine reuptake inhibitors (SSNRI), selective norepinephrine reup-

take inhibitors (SNRI) have different tolerability profiles based on their relative selectivity for several pharmacological receptors. It is well known that the adverse events associated with the TADs are due to an interaction with alpha-adrenergic, acetylcholine, histamine and dopamine receptors.

- 3 This profile causes a wide range of adverse effects, including sedation, hypotension, mouth dryness, tachycardia, urinary incontinence, weight gain and exacerbation of psychosis.⁹⁹⁻¹⁰¹
- 2+ In spite of their greater tolerability, the SSRIs may cause adverse events which, under certain circumstances, would cause the patients to discontinue the medication, including: nausea, anxiety/nervousness, insomnia and sexual dysfunction. For the SNRI, such as venlafaxine, the profile of adverse events is similar to the SSRIs, but they also include adrenergic effects.¹⁰² The treatment, at the correct dose, with the adequate antidepressants and for sufficient time, has an important impact on antidepressant medication compliance. Lack of an immediate effect is one of the primary reasons for premature "discontinuation" of the pharmacotherapy while the early appearance of adverse effects may increase this problem even more¹⁰³.
- 1+ Mirtazapine acts on the serotonergic and noradrenergic systems blocking the presynaptic alpha-adrenergic and alpha-heteroreceptor receptors, respectively, as the 5 HT₂ and 5 HT₃.¹⁰⁴ This antidepressant has a tolerability profile that may include mouth dryness, vertigo, sedation, increase in appetite, weight gain and headache, although it rarely provokes sexual dysfunction. The most commonly associated adverse effects with the NRI reboxetine are typically adrenergic: mouth dryness, constipation, headache, insomnia and sweating¹⁰⁵.
- 2++ Some studies and meta-analyses have evaluated the "discontinuation rate" of antidepressant medication due to adverse events and lack of efficacy. Montgomery et al. (1995) developed a meta-analysis of 67 published, randomized and controlled studies of TAD vs. SSRI, comparing the discontinuation rates due to adverse effects or lack of efficacy as a marker of treatment compliance. The study revealed that the SSRIs are generally better accepted than the TAD. Fewer patients discontinued treatment with SSRI (21.3%) compared with TAD (25.6%). The discontinuation rate due to adverse effects was only 19.4% for the SSRI and 27.2% for the TADs¹⁰⁶.
- 2++ A second meta-analysis of 62 published, randomized and controlled studies compared the rates of discontinuation for SSRI and TAD and observed similar results:

discontinuation rate due to adverse events was 14.4% and 18.8% for SSRI and TADs, respectively¹⁰⁷.

In summary, in general the SSRIs are better tolerated with a lower "discontinuation rate" than the TADs. The discontinuation rates due to adverse effects associated with SNRI and NRI reboxetine are similar to those reported for SSRI.

- 1+ Beasley et al. (2000), in a systematic review and meta-analysis obtained from the analysis of 25 clinical trials in patients diagnosed of MDD who received fluoxetine (20 to 80 mg/day) or TADs, observed that in spite of the fact that fluoxetine was well tolerated in the acute treatment phase in adults, especially at the dose of 20 mg/day, the discontinuation rates due to adverse effects were similar for patients who received this dose of fluoxetine compared with the controls. The adverse events leading the treatment discontinuation were also evaluated, the most frequent ones being insomnia, nausea, and nervousness compared with the controls¹⁰⁸.

3. Differences between the different antidepressant treatments– TAD, SSRI, SNRI, NARI and Bupropion, in relationship to compliance.

RECOMMENDATION

Los clínicos deberían tener en cuenta que los ISRS frecuentemente se relacionan a un mayor cumplimiento con el tratamiento en pacientes con Trastorno Depresivo Mayor, seguido de los ISRN, Bupropión, NaSSA. Los ATC frecuentemente se relacionan a un menor cumplimiento. (GRADO DE RECOMMENDATION D)

- 1- Some studies have compared treatment compliance with the SSRIs and the TADs showing that the SSRIs have fewer and more tolerable adverse effects than the TADs. However, no significant differences have been found in its effect on treatment compliance in MDD¹⁰⁹.
- 1+ Mao et. al. (2008) evaluated patients between 18 and 65 years of age diagnosed of major depression (moderate to severe) and compared 2 interventions: escitalopram 10 mg/d vs. fluoxetine 20 mg/d for 8 weeks. The primary objective in this clinical trial was the change of the HAM-D-17 scale (efficacy), no significant differences being found between the treatment groups. Anti-depressant medication compliance (short-term) was evaluated by accountability of the tablets and self-registry, compliance being high in both intervention groups (121/123 in escitalopram

and 115/117 in fluoxetine), without significant differences between both treatment arms. The percentage of patients who dropped out of the study due to adverse events was also similar (5% in escitalopram and 4% in fluoxetine)¹¹⁰.

- 2+ Mullins et al. (2005), in a retrospective cohort study, described the therapy of switching antidepressants and discontinuation pattern in patients who received 3 types of SSRIs (Zoloft®, Paxil®, Celexa®), but not their generic presentation, comparing the switch in use from one SSRI to another one and the discontinuation rates between patients who initiated therapy with these SSRIs. A greater rate of dropout among the patients who received Paxil® (paroxetine) compared with those who received Zoloft® (sertraline) and Celexa® (citalopram) was observed. The clinical explanation for this difference and compliance needs to be evaluated in subsequent studies¹¹¹.

4. Influence in sexual dysfunction on compliance

RECOMMENDATION

Clinician should consider that sexual dysfunction in men, secondary to the treatment, has a negative affect, and to a greater degree, on antidepressant medication compliance, regarding other adverse effects (sleep disorders, weight gain, gastrointestinal problems). Sexual dysfunction is one of the factors that affects antidepressant medication compliance more frequently in young and middle aged males (it may even lead to treatment discontinuation) without the patient telling his physician and thus it is generally not appropriately diagnosed (GRADE OF RECOMMENDATION C)

- 1+ Sexual dysfunction (SD) has been especially associated with the use of clomipramine, SSRI and SNRI. The available evidence suggests that the SD would be closely related with the serotonergic action mechanism. Treatment with bupropion, moclobemide or mirtazapine does not seem to provoke, or even alleviates sexual problems, without affecting its antidepressant efficacy¹¹².
- 2+ Data obtained from large series surveys of between 3500 and 10,000 patients in different countries of the world indicate surprising and very high percentages of discontinuations due to sexual dysfunction: 50.8% in the "GAMIAN Survey." Montejo et al. (1997, 2001) administering the Psychotropic Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX), evaluated the incidence of the SD secondary to antidepressant medication in more than 1,000 patients with normal sexual function prior to the use of the antidepressant and compared the frequency and intensity of sexual

dysfunction among patients who received different ADs. The study found that SD was underestimated by the clinicians and was the most frequent side effect (>60%) among the patients who received SSRI, clomipramine and venlafaxine. A total of 36% of the patients considered discontinuing the treatment for this reason. Long-term tolerability should be adequately evaluated in order to permit the patient and partner to reach the best possible quality of life¹¹³.

- 1+ Thase et. al. (2006), in a multicenter clinical trial, evaluated patients with diagnosis of major depression, comparing the use of bupropion XL vs. venlafaxine XR for 12 weeks, using the SD as the primary outcome and efficacy and tolerability as secondary outcomes. Bupropion XL and venlafaxine XR demonstrated similar efficacy. However, regarding sexual functioning, a significant favorable difference for bupropion XL was observed when compared with venlafaxine XR. In the case of men, there were differences after week 5 of the treatment and this was maintained until the end of the follow-up. In women, the difference was only seen at weeks 5 and 6 of the treatment. The adverse effects that most frequently lead to premature discontinuation were insomnia, nausea, headaches and fear in the group that received venlafaxine XR; while in the group that received bupropion XL, the most frequent adverse events leading to medication discontinuing were vertigo and anxiety¹¹⁴.

5. Administration guidelines related with better compliance.

RECOMMENDATION

Clinicians should consider that the administration of a single dose (monodose) of the medication favors compliance in patients with Major Depressive Disorder. (GRADE OF RECOMMENDATION D)

- 1- MDD treatment compliance may vary among the different types of medications and therapeutic regimes. Compliance with a weekly dose of fluoxetine was shown to be mildly better (86%) than with a daily dose of fluoxetine (79%) during the continuation phase for MDD treatment¹¹⁵.
- 2+ Stang et al. (2007), in an observational, retrospective study, found that patients with MDD who received the once daily formulation of bupropion (XL) had significantly greater compliance than those who received it in its twice-daily formulation (SR). In addition, this difference in compliance according to the formulation of bupropion was maintained in the multivariate analysis, after controlling for potential co-variables

related with MDD treatment compliance. This analysis assumes that, independently of the formulation, any patient who initiated treatment with bupropion should continue the therapy for the complete follow-up. (9 months). However, this duration of the treatment may not be adequate for all the patients. This study did not make it possible to obtain information on the reasons for lack of compliance¹¹⁶.

- 2+ McLaughlin et al. (2007) evaluated the impact of 2 administration regimes of bupropion on compliance during 9 months of follow-up, calculating the medication possession rate (MPR). In the multivariate logistic regression analysis that compared the likelihood of obtaining an MPR greater than or equal to 0.7 and controlling for other factors, the use of bupropion XL obtained a significant improvement in the persistence of the therapy compared with bupropion SR¹¹⁷.

6. Psychotherapy and/or Psychoeducation and their relationship with improvements in antidepressant treatment compliance

RECOMMENDATION

Clinicians should consider that psychoeducation may improve long-term treatment medication compliance of MDD, followed by cognitive behavior therapy and supportive psychotherapy (GRADE OF RECOMMENDATION D)

Some specific psychotherapies (cognitive behavioral therapy, educational programs and others) designed to improve MDD treatment compliance have not been sufficiently or rigorously studied (in spite of its long history). Thus, they do not provide scientific evidence having high validity and reliability on the efficacy of these interventions. However, it seems that compliance may improve with interventions that support the prescription of antidepressant medication.

- 1- Pampallona et al. (2004) performed a systematic revision and meta-analysis that evaluated the persistence in treatment and efficacy of the drug treatment in combination with antidepressant medication vs. drug treatment alone. The study determined that efficacy of the combined therapy was significantly greater than drug treatment alone. However, in the analysis of subgroups, when those who responded to treatment were excluded, and the OR of the "drop-outs" from the therapy were measured, the summary measurement of Association was OR=0.86 (95% CI 0.86-1.24), indicating a non-significant difference in the distribution of patients who discontinued or did not respond to treatment and relationship to combined therapy vs. drug treatment alone¹¹⁸.

- 2+ Peveler et al. (1999) compared two methods (psycho-social counseling and information leaflets) to improve antidepressant treatment adherence (dothiepin or amitriptyline) in patients who initiated treatment in primary care. It was observed that only half of the participants in the study had criteria for MDD. After 12 weeks of follow-up, in the analysis by subgroups, it was found that psychosocial counseling administered by a nurse between weeks 6 and 8 of the treatment had a favorable and significant effect on compliance in MDD patients ($\chi^2 = 6.33$, $df = 1$, $p = 0.012$). On the other hand, the use of a leaflet containing information on the medication, adverse effects and what to do if the patient forgets to take a dose did not improve compliance in these patients⁸³.

Most of the studies evaluated a variety of interventions, so that it was not possible to determine which component of the intervention (or combination of components) improved adherence. Additionally, the studies analyzed the data related with more than one affective disorder (MDD and others), without describing the effectivity of the psychotherapy in each specific condition, or if the psychotherapy offered comparative improvements in some subgroups of affective disorders regarding others.

- 1- Dekker et al. (2005) compared 2 interventions: short (8 weeks of psychotherapy) and long (16 weeks of psychotherapy), both groups receiving antidepressant medication for 6 months. Compliance was similar for the groups being compared (short and long psychotherapy), reaching a compliance rate with the antidepressant treatment of 76%, without there being statistically significant differences between both groups¹¹⁹.

- 1- Loh et al. (2007), in a clinical trial, evaluated an education program based on shared decision-making in several phases, in which the physician was trained by this technique through modules designed for this purpose. The intervention did not show differences in compliance regarding the group that received the usual cares. Compliance was evaluated by means of the report of the patient and his/her physician, although no objective measurement methods were used in this study¹²⁰.

- 1- Singh et al. (1997) evaluated, through a comparative clinical trial, an exercise program (progressive resistance training, PRT) vs. an education program for 10 weeks in patients over 60 years with MDD, considering changes in the severity of symptoms as the primary object. All the subjects included in the study completed the 10 weeks of follow-up. Measurement of compliance in the exercise group was 93%, and in the control group 95%. Unfortunately,

the effects of these programs on compliance for long-term therapy and this group of patients were not evaluated¹²¹.

CONCLUSIONS

Patients with Major Depression and without comorbidity with other mental disorders, those who are in the acute treatment phase and those who have a recurrent episode frequently have better antidepressant treatment compliance.

Patients with severe depression and those who have anxious symptoms frequently have better antidepressant treatment compliance.

Knowledge about the disease and of the biological aspects of depression among the patients, as well as training they need to receive drug treatment and the therapeutic options available improve compliance with the antidepressant treatment.

More studies are needed to determine the influence of the social aspects on antidepressant medication compliance.

Somnolence is a factor that negatively affects compliance with the antidepressant medication, mainly in relationship to work activity of the patient and if there is concomitant medication. This does not seem to vary based on age or gender of the patient and its impact on compliance seems to be much less than sexual dysfunction and weight gain.

Weight gain is one of the side effects affecting compliance, more frequent in young women and middle aged women. However, it also may be an important factor associated to compliance in women of any age.

Sexual dysfunction is one of the side effects that affects compliance with antidepressant treatment, more frequently in young and middle-aged males. Many patients do not inform their physician and therefore are not appropriately diagnosed.

Psychoeducation may improve long-term treatment compliance of MDD, followed by cognitive-behavioral psychotherapy and supportive psychotherapy.

ABREVIATONS

- **ACDQ:** Antidepressant Compliance Questionnaire
- **AD:** Antidepressants
- **CES-D:** Center for Epidemiologic Studies Depression Scale

- **DALY:** Disability adjusted life years
- **DCP:** Depression care program
- **DESS:** Discontinuation-Emergent Signs and Symptoms Scale
- **ESEMeD:** European Study of the Epidemiology of Mental Disorders
- **GAT:** Generalized anxiety disorder
- **CPG:** Clinical practice guidelines
- **IDM:** Involvement in decision-making
- **MADRS:** The Montgomery-Åsberg Depression Rating Scale
- **MDD:** Major depressive disorder
- **MDE:** Major depressive episode
- **MEMS:** Medication Event Monitoring Systems
- **NASA:** Norepinephrine Antagonist Serotonin Antagonist
- **SD:** Sexual dysfunction
- **SFP:** Systematic follow-up program
- **SIGN:** Scottish Intercollegiate Guidelines Network
- **SNRI:** Selective Norepinephrine Reuptake Inhibitors
- **SSNRI:** Selective Serotonin/Norepinephrine Reuptake Inhibitors
- **SSRI:** Selective serotonin reuptake inhibitors
- **TAD:** Tricyclic antidepressants

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