Clinical Practice Guideline on the Management of Major Depression in Adults

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH SHN
MINISTRY OF HEALTH AND CONSUMER AFFAIRS

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y CONSUMO

Plan de Calidad para el Sistema Nacional de Salud

avalia-t
Axencia de Avaliación de Tecnoloxías Sanitarias de Galicia

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This CPG is healthcare decision aid. It is not mandatory, and it is not a substitute for the clinical judgement of healthcare professionals.

More than 6 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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Presentation

Healthcare practice is becoming more and more complicated due to many different factors. One of the most relevant factors is the exponential increase of scientific information.

To make clinical decisions that are adequate, safe and effective, practitioners need to devote a lot of effort in continuously updating their knowledge.

In 2003, the Interterritorial Council of the Spanish SNS created the GuiaSalud Project whose final aim is to improve clinical decision-making based on scientific evidence, via training activities and the configuration of a registry of Clinical Practice Guidelines (CPG). Since then, the GuiaSalud project has assessed dozens of CPGs in agreement with explicit criteria stipulated by its scientific committee. It has registered them and has disseminated them over the Internet.

At the beginning of 2006, the G.D. of the Quality Agency of the National Health System prepared the Quality Plan for the National Health System, which was divided into in 12 strategies.

The purpose of this Plan is to increase the cohesion of the National Health System and help guarantee maximum quality health care for all citizens regardless of their place of residence.

As part of the Plan, different agencies and expert groups in prevalent pathologies related to health strategies were entrusted with the preparation of eight CPGs. This depression guideline is the fruit of this assignment.

The definition of a common methodology to prepare the CPG for the SNS was also requested and this has been prepared as a collective effort of consensus and coordination among the Spanish CPG expert groups. This methodology was used as the basis to prepare this Depression guideline and the other CPGs driven by the Quality Plan.

The GuiaSalud Project was renewed in 2007 and the Clinical Practice Guideline Library was created. This project developed into the preparation of the CPGs and included other Evidence-Based Medicine services and products. It also aims to favour the implementation and assessment of the use of CPGs in the National Health System.

Depression in adults represents an important health problem due to its high prevalence, to the handicaps and changes in quality of life it generates as well as its enormous economic impact. It is also managed in a variety of ways, with different therapeutic, referral and follow-through approaches.

This clinical practice guideline addresses depression in adults and it is the result of the work of a large group of professionals belonging to different disciplines who provide health care for patients with depression. The members of the drafting group have spent many hours preparing the recommendations which will undoubtedly help improve the health care provided both in primary and in specialised care. The scientific societies involved and patients' associations directly involved in this health problem have collaborated in the review process of the guideline.

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Answers to many of the questions that arise when caring for an adult patient with depression will be found in this guideline. These questions are given in the form of systematically prepared recommendations and with the best available evidence. We hope that it will also result in higher quality care for these patients and their families, which is the goal we pursue.

Dr. Alberto Infante Campos
General Department of the SHN Quality Agency

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Spanish Association of Neuropsychiatry. Spanish Association of Clinical Psychology and Psychopathology.

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Declaration of interests

All the members of the Working group, as well as the people who have participated on the external review, have made the declaration of interests that is presented in the corresponding appendix of the complete version of the guideline.

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Questions to be answered

1. Screening and suicide risk factors in major depression of adults

Would screening improve the results in major depression?
Are there suicide risk factors in patients with major depression?

2. Pharmacological treatment of depression

Is there any effective and safe drug for the treatment of mild, moderate or severe major depression?
Is any drug better than another for the treatment of major depression? What is the time-course for assessing the efficacy of a drug?
How long pharmacological treatment should be maintained after remission of depressive symptoms?
What pharmacological strategies are indicated for resistant depression?

3. Psychotherapy

Is any type of psychotherapy effective for patients with major depression?

4. Other treatments

Is electroconvulsive therapy effective for the treatment of major depression?
Is guided self-help effective for any sub-group of patients?
Are support groups effective for patients with major depression?
Is physical exercise effective for patients with major depression?
Is acupuncture effective for patients with major depression?
Is treatment with St John's Wort effective?

5. Quality indicators

What are the indicators that allow monitoring quality in the management of depression?

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Summary of recommendations

Screening and suicide risk factors in the major depression of adults

✓	Screening of depression is not generally recommended, given that there are reasonable doubts about its effectiveness for modifying the course of the illness if it is not accompanied by follow-up measures.
✓	The possibility of a depressive pathology in persons with risk factors must be taken into account.
B	The questionnaires to be used should include at least two questions referring to the person's mood and ability to enjoy.
✓	In any patient with a major depressive disorder, it is advisable to explore ideas of death and intent to inflict self-harm.
✓	The clinical history of a patient with major depression must always include previous attempts to inflict self-harm.
✓	In patients with a high risk of suicide, it is advisable to seek frequent, additional support and to assess sending them urgently to a mental health specialist.
✓	Hospitalisation should be considered for patients with a high risk of suicide.

Pharmacological treatment of depression

A	Antidepressant drugs represent a first line of treatment for moderate or severe depression.
✓	For mild depression, other therapeutic strategies can be considered before antidepressant drugs.
D	The use of drugs is recommended for those patients with mild depression and a history of moderate or severe episodes of depression.
D	The use of drugs is recommended for mild depression when other medical illnesses or associated comorbidity may be present.
✓	It is advisable to set up an appointment within 15 days for any patient with depression who does not receive pharmacological treatment.
A	SSRIs are recommended as drugs of first choice in the treatment of major depression.
B	In the event that an SSRI drug is not well-tolerated due to the appearance of adverse effects, it should be switched to another drug of the same group.
A	An SSRI should be prescribed for patients who may receive treatment with any tricyclic antidepressant and who do not tolerate it.
✓	TCAs are an alternative to SSRIs if a patient has not tolerated at least two drugs from this group or is allergic to them.
✓	New drugs could be used in the event of intolerance to SSRIs, thereby using the profile of their adverse effects as a guideline.

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B	Specific patient profiles could warrant different drugs, thereby using the adverse effects rather than their efficacy as a guideline.
A	Venlafaxine should be considered as a second line of treatment in patients with major depression.
✓	Before starting antidepression treatment, a healthcare professional should adequately inform the patient about the expected benefits; the frequent, infrequent and patient-specific side effects that could arise, in both the short and the long-term; and especially about the duration of the treatment.
✓	It is especially advisable to inform about a possible delay in the therapeutic effect of antidepressants.
✓	Patients receiving antidepressant drug treatment must be closely monitored, at least during the first 4 weeks.
✓	All patients who show moderate major depression and who are treated with antidepressant drugs must be assessed again before 15 days after initiating treatment.
✓	All patients who show severe major depression and who receive outpatient treatment with antidepressant drugs must be assessed again before 8 days after initiating treatment.
A	Pharmacological treatment must be maintained in all patients for at least 6 months after remission.
B	In patients with any previous episode or the presence of residual symptoms, the treatment must be maintained for at least 12 months after remission.
✓	In patients with more than 2 previous episodes, the treatment must be maintained for at least 24 months after remission.
B	The dose of the drug used during the maintenance phase must be similar to the dose used to achieve remission.
✓	In patients with a partial response at the third or fourth week of treatment, it is advisable: - To wait for the clinical evolution until week eight. - To increase the dose of the drug up to the maximum therapeutic dose.
✓	For a patient who does not improve with the initial drug treatment for depression, it is advisable: - To revise the diagnosis of depressive disorder. - To verify that the treatment is being followed. - To confirm that the antidepressant is being taken at the right time and dose.
B	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: - Switching from an antidepressant to any family, including another serotonergic. - Combining antidepressants. - Augmenting the initiated treatment with lithium or triiodothyronine.
B	It is not advisable to increase the SSRI dose if there is no response after 3 weeks of treatment.

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C	The association of SSRI with mirtazapine or mianserin could also be a recommendable option, but thereby taking into account the possibility of greater adverse effects.
B	There is insufficient information available to recommend an increase in the dose of tricyclic antidepressants in non-responders.
✓	In the event of resistance to various treatments according to the aforementioned guidelines, assess the use of MAOIs.
✓	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.

Psychotherapy

✓	Psychological interventions should be provided by professionals who have experience at managing depression and who are experts in the applied therapy. This is especially important in the most severe cases.
B	In mild and moderate depression, specific and brief psychological treatment (such as problem-solving therapy, cognitive behavioural therapy or counselling) in 6 to 8 sessions during 10-12 weeks should be considered.
B	The preferred psychological treatment for moderate, severe or resistant depression is cognitive behavioural therapy. Interpersonal therapy can be considered as a reasonable alternative.
B	For moderate and severe depression, suitable psychological treatment should include 16 to 20 sessions during at least five months.
B	For moderate depression, either antidepressant drug treatment or suitable psychological intervention can be recommended.
B	Cognitive behavioural therapy should be offered to patients with moderate or severe depression who reject drug treatment or for whom avoiding the secondary effects of antidepressants is a clinical priority or who express that personal preference.
B	Couples therapy should be considered, if applicable, in the event that a suitable response is not obtained with previous individual intervention.
B	Cognitive behavioural therapy should be considered for patients who have not had a suitable response to other interventions or who may have a prior history of relapses or residual symptoms, despite treatment.
B	Cognitive behavioural therapy should be considered for patients who have recurrent depression and who have relapsed despite antidepressant treatment or who express a preference for psychological treatment.

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A	For patients whose depression is resistant to pharmacological treatment and/or who have multiple episodes of recurrence, a combination of antidepressants and cognitive behavioural therapy should be offered.
A	A combination of cognitive behavioural therapy and antidepressant medication should be offered to patients with chronic depression.
C	Whenever cognitive behavioural therapy is applied to more severe patients, the techniques based on behavioural activation should be given priority.
C	Psychological interventions other than the aforementioned could be useful for dealing with comorbidity or the complexity of the family relationships frequently associated with the depressive disorder.

Other treatments

A	Electroconvulsive therapy should be considered as a therapeutic alternative in adults with severe major depression.
✓	ECT is especially indicated for patients with severe major depression (with a high risk of suicide or severe physical impairment) in resistant depression and by informed choice of the patient.
✓	In general, guided self-help is not recommended for patients with severe major depression.
B	However, for patients with mild or moderate depression, professionals could consider recommending guided self-help programmes based on cognitive behavioural therapy.
✓	Participation in support groups is not considered an effective treatment measure in patients with the major depression disorder, either alone or combined with other therapeutic measures.
C	Programmes of structured and supervised exercise of moderate intensity, with a frequency of 2-3 times per week, with a duration of 40-45 minutes and for a period of 10 to 12 weeks should be recommended to patients with mild-moderate depression.
✓	The existing scientific evidence does not allow recommending the use of acupuncture as a treatment for major depression.
B	The use of St John's Wort is not recommended as a treatment option for patients with major depression.
✓	Health professionals should inform patients who consume it about the possible risks and benefits.

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Quality indicators

	Quality indicators: - Underdiagnosis of major depression. - Follow-up on treatment with antidepressants. ✓ - Maintenance of treatment with antidepressants. - Efficient use of antidepressant drugs. - Psychotherapeutic treatment in severe major depression. - Psychotherapeutic treatment in mild major depression.

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1. Introduction

Prevalence and health repercussions of depression

According to the World Health Organization (WHO), depression affects about 121 million people in the world, and less than 25% of them have access to effective treatments. It warns that one out of every five people will develop depressive symptoms in their lifetime, and this number increases if there are other concurrent factors, such as medical illnesses or stressful situations[1]. Moreover, it is expected that in 2020, depression will become the second most common cause of disability, after cardiovascular diseases[2].

The prevalence of the illness varies according to the studied country. The American *National Comorbidity Survey Replication* observed that 16.2% of people showed a major depressive disorder at some point in their lives (lifetime prevalence) and that 6.6% showed it in the last 12 months (one-year prevalence)[3], while the Green Book produced by the Commission of the European Communities estimates that the annual prevalence in the European population of 18 to 65 year-olds is 6.1%[4].

An epidemiological study performed on a representative sample of the population observed a lifetime prevalence of mental disorders of 19% and a one-year prevalence of 8.4%, and it revealed that the major depressive episode is the most frequent mental disorder, with a lifetime prevalence of 10.5% and a one-year prevalence of 3.9%[5]. However, among hospitalised patients, the prevalence of depression increases to 18.9%[6], and some groups, such as illegal immigrants, are especially sensitive to it, with a percentage of 40.7%[7].

In the WHO's opinion, suicide constitutes a major public health problem (to a large extent preventable), and it translates into almost one million victims per year, in addition to very high economic costs. In Spain, the number of suicides committed has increased in recent years, going from 1652 in 1980 (1237 men and 415 women) to
3399 in 2005 (2570 men and 829 women). The suicide mortality rate in the last year was 15.79/100,000 in habitants (12.03/100,000 in men and 3.76/100,000 in women), and important differences are observed when taking into account the age group in which suicide occurs: 12.48 at 25-29 years; 17.43 at 50-54 years; 31.68 at 70-74 years; 49.45 at 80-84 years; and 79.96 at 90-94 years[8].

According to the Ministry of Health and Consumer Affairs, in 2005 the expense on antidepressants exceeded 600 million Euros, 6 times higher than in 1994. By number of containers, selective serotonin reuptake inhibitors (SSRIs) represented 69.5%, versus 30.5% for other antidepressants. The variation of SSRIs with respect to 2004 was +1.07% by number of containers and –0.36% by cost, versus an 11.39% increase in the use of other antidepressants (the majority, new molecules) by number of containers and 6.33% by cost[9].

On average, patients with depression lose 11 days for every 6-month period, while individuals without this condition only lose two or three days[10]. Due to its high prevalence, the cost of its treatment, its role as one of the main risk factors of suicide (about fifty-eight thousand people commit suicide each year in the European Union, a figure that exceeds that for annual deaths due to traffic accidents, homicides or HIV/AIDS) and its impact on personal productivity, depression plays a huge economic role, not only in the health system but also in society.

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Variability of clinical practice

The 14.7% of patients who go to primary care consultations for any reason show depression but only 72% of those patients are diagnosed, and 34% receive treatment with antidepressants[11]. Detection is positively associated with the level of education, the severity of the symptoms, the degree of disability and the complaint of explicitly psychological symptoms, while treatment with antidepressants is associated with the civil status, the severity of the depression, the frequency of visits to the primary care physician and the complaint of psychological symptoms[12]. Thus, a considerable percentage of patients with depression is not recognised, and many of those who are recognised do not receive suitable treatment[11-13]. Both the detection rates and the treatment rates are greater in the more severe forms of depression[12], and moreover, up to 26.5% of patients diagnosed with depression by the family physician do not meet the formal criteria for this diagnosis[14].

A recent study by the Atlas de Variaciones en la Práctica Médica[15] examines, in 156 health areas of 15 Autonomous Communities, the admissions due to psychiatric conditions in acute hospitals of the public network of the National Health System during 2003 and 2004. The results show that affective psychoses, which include major depression, presented in Spain a standardised rate of hospital admissions per 10,000 inhabitants between 0.09 (the lowest health area) and 12.52 (the highest health area), while in Galicia this variability is smaller, varying between 1.65 and 4.37.

In general, there is a high variability in the management of depression[16], which has been demonstrated among primary care professionals in the various rates of referral, average duration of visits, attitude towards a lack of therapeutic response and follow-up on patients with depression[17].

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2. Scope and objectives

The development of this clinical practice guideline on the management of depression in adults is justified by the demand generated from various areas of the health system that are involved in taking care of this pathology, at both the healthcare level and at the service management level, in view of both the health and social magnitude of the problem.

This guideline has been developed with the objective of offering recommendations to professionals for taking care of patients with depression, developing indicators that can be used to evaluate the practice of professionals and helping patients to make informed decisions. These recommendations have been developed by a multi-disciplinary team formed by professionals who are involved in caring for these types of patients and who, prior to developing the work, have filled out a declaration of interests (see the corresponding appendix of the complete version of this guideline).

The **main users** at whom the guideline is directed are all those health professionals involved in the management of depression, as well as patients and carers.

The **objectives** of this clinical practice guideline are:

~ Improve the healthcare given to patients with depression in the field of primary health care and hospital care.

~ To provide recommendations to health professionals for caring for patients with depression.

~ To develop indicators that can be used to assess the practice of professionals.

~ Help patients to make informed decisions.

The CPG **includes** the following:

~ The care that patients with depression can expect to receive from health professionals within the healthcare system.

~ The information that they can expect to receive about their problem and the treatment, including pharmacological therapy, psychotherapy and electroconvulsive treatment.

Conversely, the CPG **does not include** recommendations about:

~ The organisation of healthcare services.

~ Depression in childrens under 18 years and puerperal depression.

~ Dysthymia and bipolar and adjustment disorders.

~ Transcranial magnetic stimulation, vagus nerve stimulation and phototherapy as treatments for depression.

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3. Methodology

The methodology used is included in "Development of Clinical Practice Guidelines in the National Health System. Methodological Manual"[18].

• Creation of the development group of the guideline.

In addition to the scientific coordinator, a development group of nine members was formed: 3 psychiatrists, 2 psychologists, 1 mental health nurse, 1 expert in methodology and 2 specialists from the Axencia de Avaliación de Tecnoloxías Sanitarias (avalia-t). All members of the development group submitted a declaration of interests. The possible training needs of the guideline development group were covered by a specific programme prepared by avalia-t, which consisted of six workshops.

The duties of the various members who participated on the guideline are shown in the following table:

Table 1: duties of the different members who participated on the guideline

	Coordinator	Clinicians	Methodologists and specialists of avalia-t	Documentalist	External reviewers
Development of clinical questions	+++	+++	++	+	-
Bibliographical search	+	-	+	+++	-
Evaluation and synthesis	++	+	+++	-	-
Recommendations	++	+++	++	-	-
Drafting	++	++	+++	+	+
External review					+++

• Development of the scope and objectives of the guideline.

They were determined in conjunction with the Mental Health Authority of the Autonomous Community of Galicia. The clinical questions of the guideline followed the PICO format (Patient-Intervention-Comparison-Outcome).

• Search of the scientific information

A first search of the literature was performed without time limit in order to locate all existing CPGs in the main bibliographical databases (see the corresponding appendix in the full version of the guideline) and to make a first estimate of the volume of material to be reviewed. To complete the guideline search, a general Internet search was performed using several search engines, thereby reviewing the pages of different national and international organisations, scientific societies, etc., with quality parameters and indicators and that could be of interest.

The selection of the depression guides was made from all guidelines that were based on trials or on the consensus of experts and published after the year 2000. Neither those that covered depression in specific groups (post-partum, the elderly, etc.) nor adaptations of other, existing guidelines were included. The search resulted in locating 15 clinical practice guidelines, and except for one of them (for which the complete text was not available[19]), they were all appraised by four technicians independently using the AGREE[20] instrument *("Appraisal of Guidelines Research and Evaluation")* (Appendix 9). The overall appraisal of the guidelines was established by consensus among the evaluators, always following the recommendations of the

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AGREE instrument. The guideline that received the highest score was prepared by the *National Institute for Clinical Excellence* (NICE)[21], assessed as "highly recommended", given that all areas earned scores above 60%. The overall assessment of most of the remaining guidelines was "recommended with modifications", with scores of between 30 and 60%.

The NICE guideline was used as the starting point for all the questions discussed in it. When a NICE question was responded with recommendation level 'A', that recommendation was immediately adopted. In all other cases, the search was updated or the question was prepared again. As a general rule, specific strategies were used.

• Selection, evaluation and synthesis of the scientific information.

After reading the summaries of the articles appearing in the search, those that met the inclusion and exclusion criteria specified in the corresponding appendix were selected. Subsequently, they were given a critical reading, and data were analysed and extracted. Both the critical reading and the data extraction were selected independently by two reviewers following the recommendations of SIGN[22] (*Scottish Intercollegiate Guidelines Network*).

• Formulation and rating of the recommendations.

The recommendations were formulated based on the "formal assessment" or "reasoned opinion" of SIGN. The scientific information has been classified and the recommendations have been rated according to the SIGN system. Controversial recommendations or recommendations in the absence of evidence were resolved by the consensus of the guideline development group, using the "appropriate use method" or "RAND/UCLA method"[23].

• External review and final recommendations.

The expert collaborators who participated in reviewing the draft of the guideline were selected at the proposal of the corresponding scientific societies.

Comprehensive information of the methodological process of the CPG is available at the web page of Guiasalud, www.guiasalud.es, as well as at the web page of avalia-t.

• Update of the Guideline.

The updating of this guideline is scheduled every three years, unless the publication of relevant scientific knowledge dictates that it should be done before that time, basically in those aspects or specific questions where the recommendations may be substantially modified.

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4. Definition and diagnosis of major depression

- Would screening improve the results in major depression?
- Are there suicide risk factors in patients with major depression?

4.1. Definition

Major depression is a syndrome or grouping of symptoms where there is a predominance of affective symptoms (pathological sadness, lassitude, irritability, subjective feeling of distress and impotence in the face of life's demands), although to a greater or lesser extent, symptoms of a cognitive, volitional or even somatic type are present, wherefore we could also talk about an overall impairment of the psychic life, with special emphasis on the affective sphere. The basis for distinguishing these pathological changes from ordinary changes is given by the persistence of the clinical symptoms, their severity, the presence of other symptoms and the degree of functional and social impairment that accompanies it.

Many cases of depression are clearly noticeably in clinical practice, although it is rarely easy to establish its separate diagnosis with respect to other psychopathological situations. For example, there is high association between depressive disorder and anxiety, and with different combinations in its manifestations. Depression can also occur simultaneously with alcohol abuse or the abuse of other toxic substances and with some cerebral organic and systemic diseases[1].

Even though the causes of depression remain unknown, various factors could take part in its origin, such as certain genetic factors, childhood experiences and current psychosocial adversities (social context and personality aspects). Difficulties in social relations, gender, socio-economic status or cognitive dysfunctions could also play an important role as risk factors in the development of depression, although it is most likely that it is an interaction of biological, psychological and social factors[25,26].

4.2. Diagnosis

The diagnostic possibility of a depressive disorder can be approached based on scarcely-specific observational factors, such as deterioration of personal appearance and look, psychomotor retardation, low tone of voice, sad facies, easy or spontaneous weeping, decreased attention, verbalisation of pessimistic ideas, hypochondriacal ideas, alterations of sleep and non-specific somatic complaints.

Even though the initial age of major depression varies in different studies, it can be established between 30 and 40 years of age, and it reaches a maximum peak of incidence between 18 and 44[27]. The illness can appear differently according to age; thus, young people show fundamentally behavioural symptoms while the elderly have a greater frequency of somatic symptoms[28].

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There are several, reliable diagnostic instruments, such as the MINI self-evaluation scale (*Mini International Neuropsychiatric Interview*)[29, 30], which allow identifying those individuals who show depressive symptoms and make it possible for a clinician to carry out a diagnostic interview. Many of these instruments are useful at Primary Care centres.

The first episode of a major depression can occur at any time, and in some cases during the first months of appearance patients can experience a set of symptoms such as anxiety, phobias, minimal depressive symptoms and panic attacks[21]. The tendency towards recurrence is very frequent in this pathology[31]. A severe depressive episode may or may not also be accompanied by psychotic symptoms, in which delusional ideas, hallucinations or stupor appear, in addition to the criteria established for defining a severe depressive episode.

Depressive symptoms can be assessed and ordered according to operational diagnostic criteria, and those used the most – both in the clinic and in research studies – are the ICD-10[32] and DSM-IV[33] classifications. Their importance stems from using uniform diagnostic criteria among different professionals.

Table 2. General diagnostic criteria of a depressive episode according to ICD-10

A. The depressive episode should last for at least two weeks.
B. The episode is not attributable to psychoactive substance use or to any organic mental disorder.
C. Somatic Syndrome: some depressive symptoms are widely regarded as having special clinical significance, and in other classifications they are called melancholic or endogenomorphic ~ Marked loss of interest or pleasure in activities that are normally pleasurable ~ Lack of emotional reactions to events that normally produce a response ~ Waking in the morning 2 hours or more before the usual time ~ Depression worse in the morning ~ Evidence of psychomotor retardation or agitation ~ Marked loss of appetite ~ Weight loss of at least 5% in the last month ~ Marked loss of libido
Source: Adapted from WHO. Tenth Revision of the International Classification of Diseases. ICD-10. Mental and behavioural disorders. Madrid: Meditor 1992.

The ICD-10 uses a list of 10 depressive symptoms and divides the major depression into mild, moderate or severe (with or without psychotic symptoms) (Tables 2 and 3). In any of these cases, at least two of the three symptoms considered typical of depression must always be present: depressive mood, loss of interest and ability to enjoy and increase in fatigability, and the episode must last at least two weeks.

The DSM-IV uses a list of 9 depressive symptoms, it also requires that the episode last at least two weeks, and it divides the major depressive table into mild, moderate or severe, with specific codes for partial/full remission or unspecified remission. The diagnosis is established with the presence of at least five of the symptoms, and one of them must be a depressive mood state or the loss of interest or ability for pleasure.

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Table 3. Severity criteria of a depressive episode according to ICD-10

A. General criteria for depressive episode 1. The depressive episode should last for at least two weeks 2. The episode is not attributable to psychoactive substance use or to any organic mental disorder
B. Presence of at least two of the following symptoms: 1. Depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by environmental circumstances and sustained for at least two weeks. 2. Marked loss of interest or ability to enjoy activities that were previously pleasurable. 3. Decreased energy or increased fatigability.
C. An additional symptom or symptoms from the following list should be present, to give a total of at least four: 1. Loss of confidence and self-esteem and feelings of inferiority 2. Unreasonable feelings of self-reproaches or excessive and inappropriate guilt 3. Recurrent thoughts of death or suicide or any suicidal behaviour 4. Complaints or evidence of diminished ability to concentrate or think, accompanied by indecisiveness or vacillation 5. Change in psychomotor activity, with agitation or inhibition 6. Sleep disturbance of any type 7. Changes in appetite (decrease or increase), with corresponding weight change
D. There may or may not be the somatic syndrome*
Mild depressive episode: Two or three of the symptoms of criteria B are present. A person with a mild episode is probably capable of continuing with the majority of their activities. **Moderate depressive episode**: At least two of the symptoms of criteria B are present, in addition to symptoms of criteria C until there is a minimum total of 6 symptoms. A person with a moderate episode will probably have difficulties continuing with their ordinary activities. **Severe depressive episode**: There must be 3 symptoms of criteria B, in addition to symptoms of criteria C until there is a minimum of 8 symptoms. People with this type of depression have symptoms that are marked and distressing, mainly the loss of self-esteem and feelings of guilt or worthlessness. Suicidal thoughts and acts are common, and a number of somatic symptoms are present. Psychotic symptoms can appear, such as hallucinations, delusions, psychomotor retardation or severe stupor. In this case, it is called a severe depressive episode with psychotic symptoms. The psychotic phenomena such as hallucinations or delusion may or may not be mood-congruent.
Source: WHO. Tenth Revision of the International Classification of Diseases. ICD-10. Mental and behavioural disorders. Madrid: Meditor 1992.

This clinical practice guideline assumes the classification and definitions of depression included in the tenth edition of the International Classification of Diseases (Mental and Behavioural Disorders), ICD-10[32], with codes F32 (depressive episodes) and F33 (recurrent depressive disorder), and by the *American Psychiatric Association* (DSM- IV)[33], with codes 296.2X (depressive disorder) and 296.3X (depressive disorder, recurrent).

4.3. Risk factors

Major depression is a multi-factor and complex process whose probability of development depends on a broad group of risk factors, and to date it has not been possible to establish neither the totality thereof or the multiple interactions existing between them. The weight of each factor in relation to the circumstances and to the moment in life in which they develop is unknown.

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Variables that increase the risk of depression include personal, cognitive, social, family and genetic factors[34]. Poverty, chronic illnesses (both physical and mental[21]), the possible association with the consumption of alcohol and tobacco and work circumstances have been highlighted within the role attributed to personal or social circumstances, given that the unemployed, the disabled and people on sick leave due to illness or maternity show signs of depression with greater frequency[5]. Civil status and chronic stress seem to be related to a greater likelihood of developing depression[21], and it has been observed that exposure to adversities throughout life is involved in the onset of depressive and anxiety disorders[36].

The offsprings of patients with depression constitute a high-risk group, for both somatic and psychiatric illnesses, which begin at an early age and persist throughout adult life[37]. Thus, first-degree relatives of patients with a major depressive disorder have double the possibility of showing depression than the general population[38], a proportion that is also considerable in second-degree relatives[39]. The pattern of how the symptoms are presented can also be different, and an anxiety disorder has been found as the earliest sign[40]. However, these family studies cannot, by themselves, establish what amount of risk comes from genetic factors and what amount comes from the shared family environment. Moreover, with the progressive knowledge of the human genome, it has become possible to identify the chromosomic location of genes that determine vulnerability for disorders such as major depression. One factor that could have an influence on its development is the presence of a polymorphism of the gene that codes the serotonin transporter, thereby causing a decrease in the transport of this neurotransmitter[41].

The neurotic traits of the personality are associated with a greater incidence of cases and relapses of major depression[42, 43], and this personality trait probably lends greater susceptibility to developing depression when faced with the adversities of life[44]. In general, anxiety disorders are risk factors for the development of the first episode of major depression[41, 42], and dysthymia has also been seen as an important predictor of the subsequent development of major depressive symptoms. Furthermore, it has been observed that patients, mainly males, with previous panic attacks, had a greater risk of developing major depression. This correlation has not been found with other psychiatric disorders[46]. An association between migraines and depression has been described, such that patients with major depression showed a greater risk of suffering from migraines, and in turn those who had migraines (and not another type of headache) had a greater risk of major depression[47]. Also, the presence of heart disease and various endocrine illnesses such as diabetes, hypo or hyperthyroidism, Cushing's syndrome, Addison's disease and hyperprolactinemic amenorrhea seem to increase the risk of depression[21].

Finally, and in order to create a predictive model of depression, a prospective study is being carried out in various European countries, based on taking surveys focussed on depression risk factors in Primary Care[48].

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4.4. Depression screening

A high percentage of patients with depression are neither diagnosed nor treated[11, 49, 50], wherefore some authors propose screening of the population in order to assure that everyone is identified and receives suitable treatment.

It is important to question if screening improves the results in patients with major depression and if it should be done broadly (all the general population, all patients who go to a doctor's appointment) or in a limited manner (only those patients for whom there is a specific type of risk).

In a recent meta-analysis[51], performed to evaluate the diagnostic validity of the questionnaires in depression screening, the authors observed that the tests of a single question have a sensitivity of 32% and a specificity of 96%, with a positive predictive value (PPV) of 56% and a negative predictive value (NPV) of 92%, while the tests of two or three questions have a sensitivity and specificity of 74%, with a PPV of 38% and an NPV of 93%. The authors conclude that the ultra-short tests (between one and four questions) seem to be, in the best of cases, a method for excluding the diagnosis of depression and should be used only when there are sufficient resources for a second analysis of initially positive cases.

In the NICE[21] Depression CPG, the depression screening section is based on two systematic reviews. The first one summarises the work of the *U.S. Preventive Services Task Force* and identifies 14 randomised clinical trials in which the effect of routine screening of depression in adults was evaluated[52]. The second reviews a group of nine trials similar to the previous one, although not identical[53]. The NICE conclusions were the following:

- ~ Routine screening for depression may be effective in identifying an increased number of cases but there is only limited evidence that screening alone may have any beneficial effect on depressive symptomatology, even when integrated into an accessible treatment programme.
- ~ For screening, a questionnaire with two questions is as effective as a more elaborate questionnaire, and it adapts better to the characteristics of Primary Care.
- ~ None of the reviewed studies specifically handled people considered to be at high risk for developing depression.
- ~ And its recommendations for clinical practice were the following:
- ~ Screening of depression should be undertaken in Primary Care for risk groups, such as those with a past history of depression, significant physical illnesses causing disability or other mental problems such as dementia.
- ~ Healthcare professionals should bear in mind the potential physical causes of depression and the possibility that depression may be caused by medication and consider screening if appropriate.
- ~ Depression screening should include the use of at least two questions referring to a person's mood and to the ability to enjoy.
- ~ Research is needed into the cost-effectiveness of routine screening of populations known to be at high risk of depression.

In 2004, the *Canadian Task Force on Preventive Health Care*[53] published an update of their recommendations after a review by Pignone *et al*[52]. This task force recommends screening for major depression in adults in Primary Care, as long as it is linked to effective treatment and follow-up. Finally, the Cochrane Collaboration published a review on the subject in 2001

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(updated in 2005[54, 55]), although it only contributes one trial with respect to the NICE depression CPG[21]. The authors conclude that screening questionnaires have a minimum impact on the detection, treatment or outcome of depression, and this strategy should not be adopted alone.

Summary of the evidence

1+	Tests with more than one question (between two and three) are the most suitable for depression screening. (51).
1-	The studies currently available show that while there are valid instruments for identifying or excluding cases of depression, there are insufficient trials on their ability to favourably modify the evolution and prognosis of the illness (21, 52, 53).
1-	The screening of major depression without a programme of accessible treatment and suitable follow-up does not seem to be effective (21, 52, 53).

Recommendations

✓	In general, screening of depression is not recommended, given that there are reasonable doubts about its effectiveness to modify the course of the illness if it is not accompanied by follow-up measures.
✓	The possibility of a depressive pathology in persons with risk factors must be taken into account.
B	The questionnaires used should include at least two questions referring to the person's mood and ability to enjoy.

4.5. Risk of suicide

Depression is one of the factors most-related to suicidal behaviour[56], which is the result of a confluence of a large number of situations and factors that combine together to generate a range that would go from a simple passing thought to actually committing suicide. There are many variables that intervene in causing suicidal behaviour, and they include biological factors as well as sociodemographic, psychiatric and psychosocial variables[57-59].

One of the main problems that arises when interpreting the findings of studies about suicidal behaviour is their low representativity, given that suicide is an infrequent behaviour.

The NICE guideline includes the importance of the severity of the major depressive episode as a suicide risk factor, whereas other authors point out the importance of hopelessness[60]. Two prospective studies with 18-24 months of follow-up observed different percentages of attempted suicide or suicide completion, varying between 8%[61] and 16.6%[62], without therein specifying the severity of the depressive disorder. In the first study[61], the risk of suicide was significantly greater in periods of partial remission and during the episode than in the period of full remission. After a multivariate analysis, the most important factors were the duration of the depressive episode, suicide attempts and not having a partner. The second study took on the risk factors associated with suicidal behaviour, thereby observing that a family history of previous suicides, a background of drug addiction

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or tobacco use, borderline personality disorders and family separation at an early age multiply the risk of suicidal acts by three in men with major depression. In women, the risk of suicide was greater in those who had made previous attempts and those with suicidal ideation, and the risk of suicide increased by three with each previous attempt.

Table 4. Suicide risk factors in people with major depression

~ History of previous suicide attempts. ~ History of familial suicide. ~ Axis II comorbidity (diagnosis by DSM-IV axes): Borderline personality disorder. ~ Impulsiveness. ~ Hopelessness. ~ Traumatic early life events. ~ Life stress. ~ Low social-couple support. ~ Masculine sex. ~ Abuse of – dependence on alcohol or other drugs.
Source: own preparation.

Impulsive and aggressive behaviour as a suicide risk factor was studied in a case-control study (male depressed suicide completers compared to living depressed male subjects). The authors observed that abuse of or dependence on alcohol or other drugs and that the borderline personality disorder increase the risk of suicide in patients with major depression, in addition to high levels of impulsiveness and aggressiveness[63].

Finally, a retrospective study with 21 years of follow-up that included 785 patients with depression found that the only significant predictor variables of suicide after a univariate analysis were suicidal tendency, assessed with 7 points in the *Schedule for Affective Disorders and Schizophrenia* (SADS), and a history of previous suicide attempts[64].

Summary of the evidence

3	The risk of suicide increases during the major depression episode and during the period of partial remission (61).
3	Prior attempts to inflict self-harm by a patient are significantly associated with the probability of a future, completed suicide (61, 62, 64).
3	The abuse of or dependence on alcohol or other drugs, the borderline personality disorder and high levels of impulsiveness and aggressiveness increase the risk of suicide in males with a major depressive disorder (63).
3	Even though the clinical information is scarce and heterogeneous, there is evidence that suggests that there is a difference in the suicide risk factors in patients with major depression with respect to sex, age, severity and duration of the episode, civil status and comorbidity (alcoholism or drug addiction) (62).

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Recommendations

✓	In any patient with a major depressive disorder, it is advisable to explore ideas of death and the intention to inflict self-harm.
✓	The clinical history of a patient with major depression must always include previous attempts to inflict self-harm.
✓	In patients with a high risk of suicide, it is advisable to seek frequent, additional support and to assess sending them urgently to a mental health specialist.
✓	Hospitalisation should be considered for patients with a high risk of suicide.

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5. Pharmacological treatment

- Is there any effective and safe drug for the treatment of mild, moderate or severe depression?
- Is any drug better than another for treating major depression? What is the time-course for assessing the efficacy of a drug?
- How long pharmacological treatment should be maintained after remission of the depressive symptoms?
- What pharmacological strategies are indicated for resistant depression?

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5.1 Overall efficacy

A systematic review of 35 randomised clinical trials (RCTs) (with 2013 patients and several degrees of depression), in which low doses of tricyclic antidepressants (TCAs) (75-100 mg) were compared
with a placebo, showed that low doses of these drugs were 1.65 and 1.47 times more likely than the placebo to achieve a response at four and at six-eight weeks, respectively. The standard dose of TCA did not yield a greater response, yet there was an increase in the number of dropouts due to secondary effects[65].

Another subsequent systematic review (9 RCTs, 751 patients with a initial diagnosis of a depressive episode) assessing the effectiveness of TCAs versus "active placebos" found a statistically significant difference in favour of the active drug, although the analysis of the results showed a small slight, combined estimate of the effect in favour of the antidepressant, and there was heterogeneity in the outcomes due to a highly positive trial[66].

A meta-analysis of patients attended in primary care (15 RCTs of low quality, without reflecting the severity of the depression and using TCA in ten trials and SSRI in the rest or an association of the latter with TCA), demonstrated that drugs were more effective than placebo[67].

The NICE guideline does not recommend the use of drugs in mild depression because of their low risk-benefit ratio. It recommends considering them after the failure of other therapeutic strategies if there are associated psychological or medical problems or there is a prior history of moderate or severe depression[21].

A large number of studies show efficacy in the response to placebo in moderate depression[21], although there are authors who postulate the existence of over-estimation of the effect due to population skewing[68]. Greater response and remission rates have been observed in the use of escitalopram and citalopram at high doses (20 mg and 40 mg, respectively) in 3 RCTs with a total of 1321 patients over 8 weeks[69-71]. Likewise, a meta-analysis that included 6 RCTs with 1978 patients with a score of 15 on the *Hamilton Rating Scale for Depression* (HAM-D) demonstrated the efficacy of duloxetine versus placebo[72]. The remission rates were higher than placebo only with higher doses than those currently recommended for this drug (p 0.02). Paroxetine, as an active comparator, also showed clinical efficacy and remission rates that were higher than placebo. In the treatment of moderate major depression, reboxetine was superior to the placebo in 5 of 12 short- and long-duration controlled studies and comparable in efficacy to active comparators in 3 out of 3 controlled studies[73]. There are studies with prolonged release formulations, as in the case of

venlafaxine, which also showed statistically significant response and remission rates in comparison with placebo[74].

For severe depression, NICE includes solid data with respect to the SSRI response rate versus placebo, although the data are weak with respect to remission rates[21]. For reboxetine, the response rates in both hospitalised patients and in outpatients were higher than placebo (between 20 and 52%), as were its active comparators (desipramine, fluoxetine, imipramine). It also demonstrated significant differences in the remission rate[76].

Summary of the evidence

	There are insufficient data to allow an assessment of low doses of tricyclic antidepressants in the treatment of major depression.
4	There are no quality data about the risk-benefit ratio of drug treatment for mild depression (21).
1++	The use of antidepressant drugs improves moderate and severe depression (21).
1+	New antidepressants show high response and remission rates to compared to placebo (21, 69-76).

Recommendations

A	Antidepressant drugs represent a first line of treatment for moderate or severe depression.
✓	For mild depression, other therapeutic strategies can be considered before antidepressant drugs.
D	The use of drugs is recommended for those patients with mild depression and a history of moderate or severe episodes of depression.
D	The use of drugs is recommended for mild depression when other medical illnesses or associated comorbidity may be present.
✓	It is advisable to set up an appointment within 15 days for any patient with depression who does not receive pharmacological treatment.

5.2 Comparative efficacy of drugs

The use of drugs for depressive disorders was generalised starting in the 50s after the discovery of imipramine and amitriptyline, the first ones to be effective. Amitriptyline inhibits the reuptake of serotonin and noradrenaline, thereby increasing their synaptic concentration, and it continues to be a standard drug in comparison studies of TCAs with other drugs. SSRIs appeared later, among which fluoxetine was the first that was shown to be effective, and it is the most used up to now[77]. SSRIs are a heterogeneous class of drugs that cause the selective inhibition of serotonin reuptake, with a different strength than existing compounds. There are also differences in the secondary pharmacological actions, such as blocking the reuptake of noradrenaline and dopamine, the agonist action of the serotonin 2C receptors, the antagonist action of the cholinergic muscarinic receptors, etc. In recent years, a number of antidepressants, that act on adrenergic and serotonergic

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neurotransmission, with various pharmacological characteristics have appeared. Table 5 shows the main antidepressants available in Spain.

Despite this therapeutic arsenal, around 38% of patients do not respond to treatment with SSRIs and new antidepressants during 6-12 weeks, and 54% do not reach remission[78].

TCA versus SSRI

The NICE[21] depression guideline includes most of the studies published about TCAs, with sufficient samples to determine its efficacy in comparison with other types of antidepressants, its tolerability and its adverse effects. The comparisons included by NICE were amitriptyline with citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amoxapine, desipramine, imipramine, lofepramine, minaprine, nortriptyline, trimipramine, maprotiline, mianserin, trazodone, phenelzine and mirtazapine.

Even though a statistically significant difference was observed in favour of amitriptyline versus other antidepressants (both individually and by class), it was not relevant. Moreover, clinically significant differences between amitriptyline and other antidepressants (of all groups) were not observed when TCAs were compared as a group with other antidepressants, thereby taking into account the response percentages, the reduction of symptoms and remissions. In hospitalised patients, statistically significant, although not clinically relevant differences were observed in the response percentage between TCAs and other antidepressants, and a significant difference at decreasing symptoms was observed in favour of TCAs in comparison with other antidepressants. However, in outpatients, there seems to be a clinically significant difference in favour of other antidepressants, measured using the response rate, but not in reducing symptoms.

In a subsequent Cochrane review, neither statistically significant nor clinically relevant differences at decreasing symptoms were found in the response rates between fluoxetine and TCAs, or between the former and antidepressants in individual comparisons[77].

Table 5. Main antidepressants available in Spain.

Drug	Classification	Average Daily dose	Frequency	Particulars
Amitriptyline	TCA	50-200 mg	Two or three times/day	More dropouts due to adverse effects than SSRIs.
Clomipramine	TCA	100-150 mg	Several times per day	
Imipramine	TCA	50-200 mg	Several times per day	
Nortriptyline	TCA	75-100 mg. Up to 150 mg in hospitalised patients	Several times per day	
Maprotiline	Related to TCA	25-150 mg	One or several times per day	Blurry vision and drowsiness
Trazodone	Related to TCA	150-400 mg and up to 600 mg for hospitalised patients	Several times per day	More sedation, postural hypotension and nausea

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Mianserin	Related to TCA	30-200 mg	One or several times per day	More drowsiness than other TCAs. Useful in combined treatments.
Citalopram	SSRI	20-60 mg	Once per day	Nausea, dry mouth, sweating and tremors. Fewer dropouts.
Escitalopram	SSRI	10-20 mg	Once per day	
Fluoxetine	SSRI	20 mg - 60 mg 90 mg (weekly)	Every 12-24 hours or once per week	More sweating, nausea and weight loss.
Fluvoxamine	SSRI	100-300 mg	One or several times per day	Nausea, nervousness and sweating.
Paroxetine	SSRI	20-50 mg	Once per day	Weight increase, major sexual dysfunction and discontinuation syndrome.
Sertraline	SSRI	50-200 mg	Once per day	More diarrhoea than the rest of the group.
Bupropion	NDRI, others	150-300 mg	Once per day	Fewer problems of erectile dysfunction and less weight loss.
Duloxetine	SNRI	60 mg	Once per day	No relapse prevention studies (6 months).
Mirtazapine	SNRI, others	15-45 mg	Once per day	Faster response, more weight gain.
Reboxetine	NARI	8-12 mg	Several times per day	Vegetative symptoms. Tachycardia and mild hypotension related to the dose.
Venlafaxine	SNRI	75-325 mg 75-225 mg (delayed)	Several times per day or every 24 hours (delayed)	Potentially more serious side effects. Requires close cardiovascular monitoring.

Source: own preparation. TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors; NARI: selective noradrenaline reuptake inhibitors; SNRI: serotonin and norepinephrine reuptake inhibitors; NDRI: Norepinephrine and dopamine reuptake inhibitors.

Acceptability and tolerance of treatment

Fluoxetine had fewer early dropouts due to secondary effects than amitriptyline and other TCAs[21].

Comparison between SSRIs

There are numerous published RCTs that compare fluoxetine with other SSRIs and other SSRIs between each other, although the studies tend to have a short duration, have different populations, have limited internal validity (many losses) and tend to be financed by the company that owns the patent to one of the studied drugs. In some meta-analyses included in the review by the *Agency for Healthcare Research and Quality* (AHRQ)[78], statistically significant differences were found in the efficacy of some drugs, although these differences were small and probably not clinically relevant. The patients treated with escitalopram seem to respond in a greater proportion than those treated with citalopram, with a number-needed-to-treat (NNT) of 14 in order to obtain an additional responder at 8 weeks. The patients treated with sertraline had an additional reduction of 0.75 points in the HAM-D-17 compared to those treated with fluoxetine,

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and the NNT for gaining an additional responder at 6-12 weeks was 14. No statistically significant differences were found in improvement of the symptomatology or in the response rates between fluoxetine and paroxetine, or between paroxetine and sertraline[78]. These findings concur with a previous Cochrane review[77] in which statistically significant differences were found in efficacy and tolerability between fluoxetine and other antidepressants, although with an uncertain clinical significance and without being able to draw definitive conclusions for clinical practice.

Acceptability and tolerance of treatment

Efficacy studies do not indicate any substantial difference between SSRIs and new antidepressants regarding adherence to treatment. The most frequent and common side effects are the following: constipation, diarrhoea, vertigo, headaches, insomnia, nausea and drowsiness. Nausea and vomiting were the most frequent reasons for dropping out in efficacy studies[78].

Even though SSRIs and new, second-generation antidepressants have similar adverse profiles and even though the strength of the trials is high[77, 78], there are differences:

When analysing the patients who dropped out of the trial for some reason, no statistically significant difference was found between fluoxetine and each SSRI, with the exception of a possible advantage for sertraline.

Sweating was more frequent in patients treated with fluoxetine than in those treated with paroxetine, and nausea was more frequent in patients treated with fluoxetine than in those treated with fluvoxamine. As a class, SSRIs caused less weight loss than fluoxetine[77]. Paroxetine caused more weight gains than fluoxetine and sertraline[78].

In most of the studies, sertraline showed an incidence of diarrhoea around 8% higher than the drugs with which it was compared (citalopram, fluoxetine, fluvoxamine, nefazodone and paroxetine), including second-generation drugs of other groups. Nevertheless, it is not clear that these findings can be extrapolated to other second-generation antidepressants[78].

Discontinuation syndromes (i.e. headache, vertigo, nausea) occurred in 0 to 86% of patients (referring to all second-generation drugs). Within SSRIs, the patients treated with paroxetine showed the highest incidence of this problem, while fluoxetine had the lowest incidence[78].

In head-to-head trials, paroxetine showed higher indices of sexual dysfunction than fluoxetine, fluvoxamine and sertraline[78].

There is scarce information about the comparative risk of rare but serious adverse events such as suicide, convulsions, hyponatraemia, hepatotoxicity and serotonin syndrome, which prevents solid conclusions from being proposed, although clinicians must keep in mind that these risks exist during the course of any treatment with a second-generation antidepressant[78].

Comparison between SSRIs/new antidepressants

A Cochrane review[77] did not find any statistically significant difference between fluoxetine and any heterocyclic antidepressant using a continuous outcome measurement. However, there are some studies that compared fluoxetine with bupropion, mirtazapine and trazodone; sertraline with venlafaxine and mirtazapine; paroxetine with duloxetine and venlafaxine; and citalopram with mirtazapine; and even though statistically significant differences were found in some comparisons, they were not clinically relevant.

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The patients treated with venlafaxine had an additional effect (statistically not significant) of a 1.31-point reduction in the HAM-D 17 scale compared to those treated with fluoxetine. The NNT to gain one additional responder in 6 to 12 weeks with venlafaxine was 12[78]. This analysis agreed with another prior study in which venlafaxine was statistically more effective than fluoxetine, both in a dichotomous and continuous outcome[77]. However, venlafaxine has higher drop-out rates, it requires monitoring of the blood pressure, it shows a higher cardiovascular risk, and an overdose is more dangerous[21].

The efficacy of reboxetine is similar to that of paroxetine[79] and citalopram (except in specific groups), and it has fewer problems of sexual dysfunction than both[79-81], although with more dropouts than citalopram due to adverse effects[80, 81].

Even though it is generally believed that the onset of the effect of antidepressant drugs does not occur until after 4 to 6 weeks have elapsed, there are hardly any studies designed with this variable as a measure of outcome, and some even contradict this belief. Thus, one meta-analysis observed that more than half of the patients who respond at 8 weeks begin to improve at the second week, and 75% in the fourth. Moreover, the lack of a response at
4-6 weeks is associated with a 73-88% likelihood that they will not start to respond in the eighth week[82]. Another review[83] observed that the therapeutic response to SSRIs is greater in the first week, with a progressive decrease in the following weeks, and a third study[84] observed that between 60% and 62% of the improvement takes place within the first 2 weeks of treatment.

Seven low-quality studies with a possibility of skewing found that mirtazapine has a faster onset of action than citalopram, fluoxetine, paroxetine and sertraline. The NNT to get one additional responder after 1 or 2 weeks of treatment was 7, yet after 4 weeks of treatment, most of the response rates were similar. Patients treated with escitalopram reached remission
7 days before those treated with venlafaxine. Likewise, those treated with citalopram showed a faster onset of effect than with fluoxetine, and there were no differences between them in the percentage of responders[78].

Acceptability and tolerance of treatment

When considering the total number of patients who dropped out during the trials, no statistically significant differences were found between fluoxetine and the various heterocyclic antidepressants[77]. Patients treated with fluoxetine or sertraline had greater sexual dysfunction than those who took bupropion[78], while reboxetine had a high rate of dropouts, although it interfered less with sexual function.

Mirtazapine caused a considerably greater weight increase than other drugs (between 0.8 and 3 kilos after 6-8 weeks of treatment) and a greater number of patients who dropped out due to adverse reactions. Citalopram and escitalopram caused more nausea, tremor and flatulence than mirtazapine[78]. In turn, paroxetine caused greater weight gains than fluoxetine and sertraline[78]. On the other hand, an important observational study revealed that patients treated with venlafaxine showed a greater risk of suicide than those treated with citalopram, fluoxetine and dothiepin[85].

Suicide is an infrequent event, and clinical trials tend to be short-duration and have a small sample size, wherefore they don't have sufficient statistical strength to detect differences[85, 86]. Meta-analyses, apart from including short-duration studies, do not tend to include suicide or the presence of any self-inflicted injury as a measure of outcome. There also are no meta-analyses that demonstrate a greater frequency of ideas, attempts or completed suicides in adult patients treated with antidepressants, although it is demonstrated in patients under 24 years of age[86-88]. The low frequency of this event and the fact that depression itself can have the same outcome as the treatment are the greatest

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problems when interpreting the outcomes related to this subject, which means that the subject is not closed[86].

Comparison of new drugs between each other

There are few studies (some with insufficient statistical strength) for detecting significant or clinically relevant differences, wherefore the outcomes are not conclusive. In general, the differences found were of a modest magnitude, and their clinical implications are still undefined. Thus, the AHRQ[78] review found comparative studies between mirtazapine and trazodone without statistically significant differences regarding efficacy, and between venlafaxine and trazodone, with some results favourable to venlafaxine and a different profile of adverse effects: better sleep and more dizziness with trazodone and more nausea with venlafaxine.

After this review, a comparative study between mirtazapine and venlafaxine (with extended release) was published, which pointed out an early response with mirtazapine, independent from its sedative effect[89]. Another study between trazodone (extended release) and sertraline was published, which did not show differences in the main outcomes, but it did show some in the adverse effects, such as a greater tendency towards sleepiness with trazodone and gastrointestinal disorders with sertraline[90].

No trials comparing directly duloxetine with venlafaxine were found, except one meta-analysis in which the efficacy and safety of extended-release venlafaxine and duloxetine were compared indirectly, without finding significant differences[74].

Finally, indirect comparison studies were consistent with those that compared a drug with a drug, without detecting differences in the relative response risk measured with the HAM-D-17 scale.

Summary of the evidence

1++	TCAs, as a group, are as effective as SSRIs in the treatment of major depression. However, they show worse tolerability and a greater number of adverse effects, which cause a higher premature dropout from the treatment by patients than in relation to SSRIs (21, 77).
1-	Regarding efficacy, there are some statistically significant differences between SSRI drugs, although they are clinically scarcely relevant. The adverse effect profiles are similar among SSRIs, although there are differences in specific adverse effects (78).
1-	The different efficacy found between new antidepressant drugs was of a modest magnitude, and its clinical implications remain undefined. Moreover, among new drugs there are differences in the profile of adverse effects (7, 78).
1+	The onset of improvement generally begins in the first or second week of treatment, and the lack of a response at 4-6 weeks is associated with a 73-88% likelihood that there will be no onset of a response at 8 weeks (78, 82).
1++	Around 38% of patients do not respond to treatment with second-generation antidepressants after 6-12 weeks, and 54% do not reach remission (78).

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1+	New antidepressants represent another therapeutic alternative, without relative advantages in efficacy, although with differentiated profiles of adverse effects (74, 78).
1-	Patients treated with venlafaxine had more and potentially more dangerous adverse effects than those treated with fluoxetine, and only one additional, non-significant clinical effect (21).

Recommendations

A	SSRIs are recommended as drugs of first choice in the treatment of major depression.
B	In the event that an SSRI drug is not well-tolerated due to the appearance of adverse effects, it should be switched to another drug of the same group.
A	An SSRI should be prescribed for patients who may receive treatment with any tricyclic antidepressant and who do not tolerate it.
✓	TCAs are an alternative to SSRIs if a patient has not tolerated at least two drugs from this group or is allergic to them.
✓	New drugs could be used in the event of intolerance to SSRIs, thereby using the profile of their adverse effects as a guideline.
B	Specific patient profiles could warrant different drugs, thereby using the adverse effects rather than their efficacy as a guideline.
A	Venlafaxine should be considered as a second line of treatment in patients with major depression.
✓	Before starting antidepression treatment, a healthcare professional should adequately inform the patient about the expected benefits; the frequent, infrequent and patient-specific side effects that could arise, in both the short and the long-term; and especially about the duration of the treatment.
✓	It is especially advisable to inform about a possible delay in the therapeutic effect of antidepressants.
✓	Patients receiving antidepressant drug treatment must be closely monitored, at least during the first 4 weeks.
✓	All patients who show moderate major depression and who are treated with antide-pressant drugs must be assessed again before 15 days after initiating treatment.
✓	All patients who show severe major depression and who receive outpatient treatment with antidepressant drugs must be assessed again before 8 days after initiating treatment.

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5.3 Duration of treatment

The risk of recurrence in major depression is high. Thus, half of all patients have a new episode after suffering the first one, 70% after suffering two and up to 90% after suffering three[91]. Therefore, an important question when treating major depression is the time that the drug treatment must be maintained after recovery in order to prevent recurrence.

There are few studies designed specifically to assess this question, and there is no definitive agreement on the recommendations of other guides[21, 91, 92].

In general, patients who leave antidepressive treatment have a greater risk of recurrence than those who continue to take antidepressants, and theoretically, the patients with a greater risk of recurrence would be those who would benefit the most from an extended programme[93]. Moreover, the more extended the treatment, the less difference there is between treated patients and controls in the risk of recurrence. In other words, the benefit of extending treatment decreases over time[94, 95]. The goal of this question is to adjust the time of duration of the treatment after recovery to the type of patient.

In one double-blind study, 395 patients whose symptoms had previously remitted after 12-14 weeks of treatment with fluoxetine were assigned to one of the following options: 50 weeks of placebo; 14 weeks of fluoxetine, followed by 36 weeks of placebo; 38 weeks of fluoxetine, followed by 12 weeks of placebo, or 50 weeks of fluoxetine. The conclusion was that the treatment must be maintained a minimum of 26 weeks after recovery, given that the percentage of relapses was significantly greater in the patients with placebo treatment at 14 and 38 weeks. These differences between placebo and fluoxetine were smaller as the weeks elapsed, until there were no statistically significant differences at 62 weeks[94]. In another double-blind study, these differences were statistically significant in favour of maintaining drug treatment for 12 months[96].

The information derived from a joint analysis of short-term studies (6-12 months) found a lower NNT in those treated for 12 months than in those treated for 6, which seems to advise maintaining treatment for one year after a first episode[92].

The variable that is associated with a greater risk of recurrence and a greater benefit from maintaining treatment is the number of previous episodes[99, 100], and neither the response pattern[97] nor the recovery time after the start of treatment seem to have any relevance.

Finally, NICE recommends maintaining treatment with antidepressive drugs for at least 6 months after remission of the episode, at which time the patient is assessed for the possibility of extending treatment, thereby taking into account the number of previous episodes and the presence of residual symptoms[21].

Summary of the evidence

1+	The more extended the drug treatment, the lower the risk of recurrence (92, 94, 96).
1+	The benefit of this extension decreases over time, and the optimum period is not clear (94, 95).
1+	Patients with previous episodes of depression benefit the most from this extension due to their high risk of recurrence (99, 100).

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Recommendations

A	Pharmacological treatment must be maintained in all patients for at least 6 months after remission.
B	In patients with any previous episode or the presence of residual symptoms, treatment must be maintained for at least 12 months after remission.
✓	In patients with more than 2 previous episodes, treatment must be maintained for at least 24 months after remission.
B	The dose of the drug used during the maintenance phase must be similar to the dose used to achieve remission.

5.4 Pharmacological strategies in resistant depression

There is no general agreement about when a depression should be considered resistant. In the consensus of the Fundación Española de Psiquiatría y Salud Mental [*Spanish Foundation of Psychiatry and Mental Health*], resistant depression is discussed when a patient does not improve after treatment using a drug with verified antidepressive action at therapeutic doses and during an adequate time[98]. NICE defines it as depression in which the symptoms remain after two or more trials with antidepressants, and it considers those patients who do not respond to a single treatment trial as non-responders in acute treatment[21]. Following more restrictive criteria, other authors define resistant depression as the failure to reach remission after a suitable treatment trial with three different classes of antidepressants in suitable doses and time[91,93].

In the STAR*D[100] report, after an initial, suitable treatment with citalopram, only 27.5% reached remission. Subsequently and successively, three more treatments were given in the event of intolerance or therapeutic failure, thereby obtaining an accumulated remission rate of 67%[99, 100]. This seems to indicate that response rates decrease to the extent that more therapeutic trials are performed, wherefore there is a degree of resistance. Moreover, after four successive attempts of treatment, up to 32% of patients had not satisfactorily improved.

These figures indicate that, in clinical practice, resistance is a frequent fact, wherefore it is very important to know the different therapeutic options that we have and the outcomes that we can expect. In this chapter, and due to its clinical relevance, we will consider the options available for those patients who do not respond as from the first treatment.

The various pharmacological strategies to be adopted against a depressive episode that is resistant to treatment can be grouped into the following categories:

Dose increase

In a systematic review[101] that included studies that analysed the increase of antidepressants in patients with resistant depression, among other strategies, the following results were obtained:

- In those patients treated with 20 mg/day of fluoxetine for 8 weeks who showed a partial response, no differences were observed with respect to the efficacy between a dose increase to 40-60 mg/day, a combination with desipramine or augmentation with lithium.

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~ In 4 studies that analysed the efficacy of a dose increase of different SSRIs (fluoxetine, paroxetine, sertraline) in patients who were non-responders to a first trial of 3 weeks of treatment with SSRI at medium doses, it was observed that a dose increase did not significantly improve the results versus maintaining the dose and that dose increase caused a rise in the dropout rate due to adverse effects. However, there are data that point to the fact that in patients with severe depression, it is necessary to begin with high doses as from the start of treatment.

~ In another study with non-responder patients after 6 weeks of treatment with sertraline at a dose of 100 mg/day, the response rate after 5 more weeks of treatment was lower when the dose was increased to 200 mg than when the initial dose was maintained or it was augmented with 30 mg of mianserin.

~ The only heterocyclic antidepressant studied in resistant depression was maprotiline, and unfavourable data were obtained.

Antidepressant switch

A comparative study of sertraline versus imipramine in patients with resistant depression did not obtain sufficient evidence to determine if a switch between both drugs favoured a response by reducing the depressive symptoms, although the switch to sertraline reduced the risk of early dropout[102].

Likewise, another study compared venlafaxine to paroxetine, and it obtained a significant difference in favour of venlafaxine regarding the likelihood of reaching remission[103].

Regarding the use of monoamine oxidase inhibitors (MAOIs), there are no data on using them in resistant depression due to a lack of randomise studies. There are only indications of a response in patients who have resistant depression with atypical symptoms and in major depressions and melancholia[104].

After not obtaining a therapeutic response with citalopram, no significant differences were observed with three treatment alternatives: venlafaxine, sertraline and bupropion[100]. Another study also did not show that nortriptyline or mirtazapine improved remission rates after two failed treatments, the first with citalopram and the second with an increase of the dose or adding bupropion[105].

Finally, one study compared tranylcypromine with the association of venlafaxine and mirtazapine after the failure of three different treatments, without observing differences in the remission rates, although it did observe differences in the dropout rates due to tolerance, which were less with the combination of venlafaxine and mirtazapine[106].

Combinations of antidepressants

The systematic review prepared by NICE included several studies that compared the outcomes of patients who took two antidepressants versus a single-therapy at a standard dose or high doses[21]. The combinations were the following:

a) SSRI plus mianserin vs. SSRI.

b) several antidepressants plus mirtazapine vs. several antidepressants.

c) amitriptyline plus moclobemide vs. amitriptyline.

d) sertraline plus mianserin vs. high doses of sertraline.

a) fluoxetine plus desipramine vs. high doses of fluoxetine.

The clinical data obtained on a mixed population of patients provide some evidence that augmenting an antidepressant with another seems to improve the outcomes of the response,

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remission and final score of the assessment scales used in comparison with an antidepressant in monotherapy at a standard dose, although the data were insufficient for high doses. Given that most studies used mianserin, the analyses oriented towards this drug. Conversely, there are data to the effect that a combination of antidepressants is associated with greater adverse effects than a single antidepressant (at a standard or high dose), although conclusions cannot be drawn about the number of patients who dropped out early from the treatment.

Finally, Dodd *et al*[107] published a systematic review in 2005 that included seven studies with a small sample size, in which different combinations of antidepressants were tried versus monotherapy. The studied combinations were fluoxetine plus mianserin or plus desipramine, phenelzine plus amitriptyline or mirtazapine plus sertralin or plus another antidepressant. The authors observed certain indications that it was useful to combine antidepressants with different action mechanisms, although with reservations and recommending that other studies of higher quality be performed.

Augmentors

NICE[21] includes ten studies that compared an antidepressant plus lithium vs. an antidepressant plus placebo, and the antidepressants included were clomipramine, desipramine, imipramine, nortriptyline and citalopram. The results found significant differences in the response rates in favour of augmentation with lithium, and no data were found to indicate that the remission rates improved. Even though augmentation with lithium seems to be less tolerated by patients, there is insufficient evidence to determine if it is due to adverse effects.

Regarding the use of anti-epileptic drugs as augmentors in resistant depression, the data existing in literature are insufficient. Thus, there are no controlled studies with carbamazepine, although there are some observational studies, and numerous adverse effects are found. There are no positive data with lamotrigine, the data are insufficient with valproate, and there are no data with other drugs of this group, such as gabapentin or topiramate[21].

Augmentation with pindolol was analysed in 6 studies in which an antidepressant plus pindolol was compared to an antidepressant plus placebo[21]. The authors conclude that even though there are data indicating that remission is favoured by adding pindolol, the effect is not evident in terms of response or in the average score of the scales. No effects were observed in the initial assessments of patients with resistant depression, and there are no long-term assessment data. The data were insufficient with respect to tolerability, and there are no clear data about the optimum dose and the duration of treatment.

One study in which desipramine or imipramine plus triiodothyronine or placebo was used observed significant differences in the response rates, even though the information was insufficient with respect to the reduction of the depressive symptoms[108]. Due to its adverse effects, triiodothyronine must be used with caution in patients with a cardiovascular pathology, and care must be taken when associating it with tricyclic antidepressants[21]. The results of antidepressant augmentation with triiodothyronine or lithium showed similar results in the remission rates, although the dropouts due to intolerance were higher with lithium[109].

Five studies analysed the augmentation of antidepressants with benzodiazepines (BZDs) or with placebo, but the data were insufficient for determining if they have any augmenting effect in terms of efficacy and tolerability[21].

One study compared the augmentation of fluoxetine plus buspirone versus placebo. No augmenting effect by buspirone was observed, and the data regarding differences in tolerability were insufficient[110]. Another study comparing methylphenidate associated with

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various antidepressants, did not detect significant differences with respect to placebo[111]. Finally, augmentation with buspirone versus augmentation with bupropion[112] in patients who did not remit with citalopram did not show differences with respect to remission rates, although there were significant and relevant differences regarding dropouts due to secondary effects.

Regarding the use of atypical antipsychotics, NICE only found one study that compared fluoxetine plus olanzapine or placebo[21] showing significant differences in the response rate, although with insufficient evidence regarding the reduction of the likelihood of early dropout from treatment. In turn, olanzapine associated with fluoxetine was not superior to fluoxetine alone in patients who did not respond to venlafaxine when assessing the average score of the Montgomery-Asberg (MADRS) depression rating scale, either in the remission or in the response rates[113].

A final study randomised non-responder patients after eight weeks of treatment with fluoxetine into groups with an increase of the fluoxetine dose, with a combination of fluoxetine and olanzapine and with olanzapine alone at different doses. The authors found significant differences in favour of the association antidepressant and olanzapine in terms of an average variation of the MADRS score and also in secondary measurements such as the remission and response rates. However, the dropout rates were higher with the combination of fluoxetine and olanzapine[114].

Summary of the evidence

Dose increase	
1-	A dose increase in patients with a partial response was only assessed after eight weeks of treatment with fluoxetine, and it was not studied for other drugs (101).
1+	Increasing the dose for patients who do not respond after three weeks of treatment with fluoxetine, paroxetine or sertraline does not improve the results and increases the dropout rate (101).
1+	In patients who are treated with sertraline for six weeks and who show no response, the dose increase is not more effective than maintaining average doses or augmenting with mianserin (101).
	There is no evidence of an increase of the dose of tricyclics in non-responder patients, and the evidence pertaining to maprotiline (tetracyclic antidepressant) is insufficient.
Antidepressant switch	
1+	Switching imipramine for sertraline and vice versa does not improve the evolution of depression (108).
1-	In non-responder patients, while switching from an SSRI to venlafaxine does increase the remission rate, it is no better than switching to another SSRI or to bupropion, and no differences were observed regarding secondary effects (102, 105).
1-	After two failed treatment attempts, no differences were observed in the remission between mirtazapine and nortriptyline (104).

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Combination of antidepressants	
1+	The combination of different antidepressants, with a greater strength for mianserin or mirtazapine with an SSRI, could be beneficial for the response and remission rates and for reducing depressive symptoms, although the risk of secondary effects is increased (21, 105).
Augmentors	
1-	There is evidence of an augmenting effect by lithium when it is associated with treatments using tricyclic or serotonergic antidepressants (21).
1-	There is insufficient information about the use of valproic acid, there are no controlled trials with carbamazapine, and the outcomes using lamotrigine in resistant depression depression are not positive (21).
1-	There is insufficient data for recommending augmentation with pindolol (21).
1-	The augmentation of antidepressants with triiodothyronine or lithium was similar, although the former is better tolerated, even though it must be used with caution in patients who have a cardiovascular history (107).
1-	The association of antidepressants with benzodiazepines does not seem to improve resistant depression regarding remission or response, and neither does buspirone or methylphenidate (21, 108-110).
1-	The augmentation data with olanzapine are contradictory, in addition to the fact that secondary effects and dropouts were increased (21, 111, 112).

Recommendations

✓	In patients with a partial response at the third or fourth week of treatment, it is advisable to: - Wait for the clinical evolution until week eight. - Increase the dose of the drug up to the maximum therapeutic dose.
✓	For a patient who does not improve with the initial pharmacological treatment for depression, it is advisable to: - Revise the depressive disorder diagnosis. - Verify that the treatment is being followed. - Confirm that the antidepressant is being taken at the right time and dose.
B	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: - Switching from an antidepressant to any family, including another serotonergic. - Combining antidepressants. - Augmenting the initiated treatment with lithium or triiodothyronine.
B	It is not advisable to increase the dose of an SSRI if there is no response after three weeks of treatment.

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C	The association of an SSRI with mirtazapine or mianserin could also be a recommendable option, but thereby taking into account the possibility of greater adverse effects.
B	There is insufficient information available to recommend an increase in the dose of tricyclic antidepressants in non-responders.
✓	In the event of resistance to various treatments according to the aforementioned guidelines, assess the use of MAOIs.
✓	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methyl-phenidate or atypical antipsychotics.

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6. Psychotherapy

- Is any type of psychotherapy effective for patients with major depression?

There are different types of psychological treatments for a wide variety of health problems, including depression. These treatments vary according to the theoretical foundation on which they are based, the level of formal development of their techniques, the available studies that allow endorsing their efficacy and their use by health professionals of the health system.

The randomised clinical trials that are used assessing drugs have also become a key piece for psychotherapy, although with a series of specific difficulties[115]:

~ There are a series of common factors that are well-recognised in all psychological treatments, which are related to the therapeutic relationship (such as unconditional acceptance, the expectation of change, etc.) and are potentially important to the treatment outcome, as well as a series of active ingredients that are not easy to specify. Moreover, psychotherapies are constantly evolving, and new techniques are developed within the same approach or through approximations between different orientations. This can mean a source of innovation and flexibility in routine clinical practice in the interest of each patient, but in a clinical trial, treatment manuals that clarify exactly what has been done in the trial are essential.

~ It is necessary to control the dependent variables of the therapist, especially their psychotherapeutic training and clinical experience, as well as their adherence to the treatment manual through independent evaluations.

~ It is impossible to blind the treatment for whoever is administering it (psychotherapist), and it is relatively problematic to mask the active treatment condition for the independent external evaluator.

~ The same psychological treatment can be provided in different formats (for example, individual or group), and the duration can also be variable, which should probably be evaluated separately, given that it could affect the outcome and efficiency.

~ Several variables have been proposed for the patient (personality, biographical history, education level, etc.) or for the depressive disorder (type and severity, previous recurrence, etc.), which could have a greater likelihood of affecting the outcome of psychotherapy than the outcome of biological therapies.

~ In recent years, clinical practice guidelines are consistent in recognising the efficacy of psychological therapies in the treatment of depression, especially those that have been specifically designed, such as cognitive behavioural therapy and interpersonal psychotherapy[21,29,97].

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6.1 Cognitive Behavioural Therapy (CBT)

Cognitive therapy was originally developed by Beck and formalised at the end of the 70s in order to be applied to depression[116], and it has become the most-frequently studied mode of psychological therapy in depression[117]. Intervention focuses on the modification of dysfunctional behaviours, distorted negative thoughts associated with specific situations and disadaptive attitudes related to depression. The therapist adopts an educational style and seeks the patient's cooperation so that he can learn to recognise his patterns of negative thinking and re-evaluate this thinking. This approach requires that the patient practice his new skills between sessions through tasks at home and that he try new behaviours. It is commonly acknowledged that all cognitive therapy interventions include more or less behavioural techniques, which is where it gets the name of cognitive behavioural therapy.

Moreover, the CBT includes a range of different interventions that share the basic theoretical assumption that most human behaviour is learned. Thus, these interventions seek to implement certain skills in depressed persons, such as problem-solving therapy, assertive training or behavioural couples therapy. Behavioural activation is one of the ingredients of Beck's cognitive therapy, which emphasises the relationship between activity and mood and which has been the object of renewed attention[118]. Nevertheless, these other interventions have been evaluated with less intensity than Beck's cognitive therapy, and they are summarised briefly below.

CBT adopts a structured format, it is limited in time, and it is based on the cognitive-behavioural model of affective disorders. It has been evaluated in a diversity of contexts (primary care, specialised care, hospitalised patients), compared mainly with pharmacological treatment and with different patient samples[119]. The most frequent duration varies between 15-20 sessions of 50 minutes each and at a weekly frequency, although there are also studies that adopt briefer formats for less serious cases (from 6 to 8 sessions), and it is assumed that the duration of therapy can be extended in the event of greater severity or associated comorbidity.

NICE[21] synthesises the available evidence based on 30 trials referring to patients whose depression varies from moderate to very severe, with the following conclusions:

- ~ CBT is as effective as antidepressant drugs in reducing the symptoms at the end of treatment. While the effect is maintained for one year after ending CBT, the same thing does not always occur with antidepressants. This therapy seems to be better tolerated than antidepressants, especially in patients with severe or very severe depression, and its benefits are maintained to a greater extent than antidepressant medication.
- ~ Adding cognitive behavioural therapy to antidepressant medication is more effective than treatment with antidepressants alone, especially in those patients with severe symptoms. In general, there is no indication that adding antidepressants to cognitive behavioural therapy is useful, although effects on specific symptoms, such as sleep, have not been explored. There is insufficient information to assess the effects of combined treatment on relapse rates.

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~ There is evidence coming from an wide study on chronic depression[120] that a combination of CBT and antidepressant medication is more beneficial in terms of response and remission than either of those treatments separately.

~ In patients with residual symptoms who take antidepressants, adding CBT seems to be useful, given that it reduces the relapse rates during follow-up, although this advantage is not always evident at the end of treatment.

~ With respect to the mode of providing treatment, there are data that suggest that group cognitive behavioural therapy is more effective than other group therapies, but there are few studies that compare the group mode and the individual mode of cognitive behavioural therapy to each other. A group mode of cognitive behavioural therapy based on mindfulness seems to be effective at maintaining the response in people who have recovered from depression, especially in those who have had more than two previous episodes[121].

An important study subsequently published endorses CBT as a therapeutic strategy in resistant depression. In the STAR*D[122] project, after an unsatisfactory response to citalopram, patients who accepted being randomly assigned to an alternative drug strategy or to CBT generally had a comparable outcome. Adding another drug produced a faster outcome than adding CBT to citalopram, although the switch to CBT was better tolerated than the switch to another antidepressant. The degree of acceptance of CBT (less than a third of patients) has been considered relatively low, although there are aspects of the experimental design that could have skewed the choice, as the authors themselves acknowledge, in addition to the fact that the cost of the therapy had to be paid for in the event that it was not covered by the patients' health insurance, which would not occur in the case of pharmacological options.

Regarding recurrent depression, it has been seen that increasing the duration of CBT can reduce relapse and recurrence, especially in high-risk patients[123]. This protector effect seems to be robust, regardless of whether or not CBT is provided alone or in combination with medication or if the combination is applied simultaneously or sequentially. Furthermore, another clinical trial reports a reduction of the relapse/recurrence rate from 72% to 46% (in a period of 2 years) in patients with multiple previous episodes by adding 16 hours of CBT to the usual treatment after remission[124].

In samples of patients with greater severity and comorbidity (more than 80% of the cases showed an additional diagnosis on Axis I or II of the DSM, 30% with melancholic depression), a controlled clinical trial with placebo showed that CBT reaches efficacy that is comparable to pharmacological treatment (which included dispensing suitably increased doses or augmentation, if necessary), although this degree of effectiveness seems to be linked to a high level of experience of the cognitive behavioural therapist[119].

This recommendation of CBT as first-line treatment in severe depression expands prior recommendations referring to mild and moderate depression[125]. It has been included in the decision algorithm of the clinical practice guidelines of Australia and New Zealand[92], although they suggest drug therapy in advance, but not in the ICSI[91] or NICE[21], which preferably recommend combined therapy in depression that is initially shown to be severe.

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Summary of the evidence

1++	In general, CBT is as effective as treatment with antidepressants in dealing with major depression (21).
1+	In mild depression, the brief CBT formats (from 6 to 8 sessions) are as effective as the more extended ones (21).
1+	The combination of antidepressant treatment and CBT offers outcomes that are superior to either of these treatments alone in chronic or severe depression (21, 118).
1+	CBT seems to be tolerated better than antidepressants, especially in the most severe cases (120).
1+	CBT has an independent protector effect that is cumulative to maintenance medication against relapses/recurrence, and the cases with multiple previous episodes or with residual symptoms are those that benefit the most due to their high risk of relapse (121, 122).

6.2 Interpersonal Therapy (IPT)

IPT was originally developed by Klerman[126] to be applied as maintenance treatment for depression, although it was subsequently used as independent treatment, and it currently has been expanded to a variety of different disorders. IPT mainly deals with current interpersonal relationships, and it focuses on the immediate social context of the patient. The original format of the therapy has 3 phases over 12-16 weeks, with weekly sessions during treatment of the acute phase. The symptoms and distress are related to the patient's situation in a formulation that includes one or more of the following areas of life: grief, interpersonal disputes, role transition and interpersonal deficits. The therapy sessions are structured, and they focus on facilitating an understanding of the most recent events in interpersonal terms and on exploring alternative ways of managing these situations.

The number of rigorous randomised clinical trials in which IPT has been evaluated is scarce. For NICE, there are data that suggest that IPT is more effective than the placebo and the usual care by the primary care physician. Moreover, the effectiveness of IPT can be increased when combined with an antidepressant, and it can also be effective as a maintenance strategy for patients whose depression has remitted previously with drug treatment[21].

A meta-analysis compared the efficacy of IPT with CBT[127], and it observed that the former obtains a certain clinical advantage regarding the likelihood of a response, although two of the three considered studies showed considerable methodological limitations, wherefore a prudent assessment must be made. The study also compares combined therapy (IPT and medication) to medication alone, without obtaining efficacy differences either in acute treatment or in maintenance treatment.

In two previous studies, Hollon *et al*[123] emphasise the potential importance of improvement in social adjustment attributed specifically to IPT in comparison with medication and in the event of similar symptomatological remission, a variable that has, unfortunately, not been subsequently examined.

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Finally, a recent trial[128] concludes that a weekly session of IPT can be sufficient to prevent recurrence in major depression for two years, but only in the cases in which remission has been achieved with this psychological intervention. Conversely, it would be ineffective if drug therapy had been needed during the course of follow-up in order to reach remission. Wherefore, the outcomes are difficult to interpret due to the design and the characteristics of the sample (women who initially did not want to treat their depression with drugs).

Summary of the evidence

1-	IPT has been shown to be effective in the treatment of major depression with respect to placebo, although reaching improvement can be slower than with antidepressants (21).
2+	Treatment with IPT could be associated with additional improvements in social functioning at the end of the therapy (121).
1-	Combined IPT and medication treatment offers better results than IPT alone at reducing relapse rates (126).

6.3 Other psychological therapies

There are no data that allow recommending ***dynamic psychotherapy*** as treatment for depression, which is a relatively non-directive form of therapy derived from psychoanalysis. Quality studies are infrequent, and those that exist offer unsatisfactory or inconclusive outcomes. Nevertheless, in these studies, dynamic psychotherapy tends to be used as an element of comparison with another, more valued form of treatment, wherefore there continue to be doubts about whether or not they have been suitably implemented[123].

In ***behaviour therapy***, depression is conceived as the result of a low rate of reinforced behaviour or behaviour that can be reinforced. Here, the therapy is structured, and it focuses on behavioural activation, the objective of which is to get the patient to develop more gratifying behaviours through tasks of gradual exposure and the planning of pleasing activities that are congruent with the patient's objectives, role-playing for dealing with behavioural deficits, etc. Some of these purely behavioural techniques constitute a part of the aforementioned CBTs. NICE[21] acknowledges growing interest in behavioural activation as a therapy in its own right, but it concludes that the information is insufficient for establishing conclusions due to the fact that the published studies have been scarce and without a placebo control group. A recent, randomised and controlled clinical trial compared CBT, paroxetine and behavioural activation (with augmented techniques for decreasing avoidance behaviours and cognitive rumination). The outcomes suggested the utility of behavioural activation techniques, and in the subgroup of the most severe patients, it obtained outcomes that were similar to antidepressant medication and superior to CBT[118].

Problem-solving therapy is a structured and brief form of intervention that is centred on learning to face specific problems frequently associated with depression, and it is considered to be within the scope of behavioural therapies[129]. It has demonstrated its efficacy over placebo in mild depression and within the context of primary care[21], although there are no reliable, long-term outcomes. It also seems that professionals who are not specialists in mental health could be satisfactorily trained on these techniques[21]. A recent

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meta-analysis based on 13 randomised clinical trials affirms that intervention is effective despite the high heterogeneity of the effects, which reflects a possible variability in the outcomes or highly diverse samples[130].

Counselling is a generic term used to describe a wide range of psychological interventions with different theoretical orientations (psychodynamic, systemic or cognitive-behavioural). The majority focus on the therapeutic relationship itself, in a process that attempts to offer the patient the opportunity to explore and discover more satisfactory ways of life. Counsellors usually receive training on listening with respect, empathy and authenticity, on reflecting on the patients' feelings and on helping to comprehend the meanings of those feelings. There is certain evidence of its efficacy in primary care and for patients with a recent onset of mild to moderate depression[21].

Couples therapy is a psychological intervention format in which the depressed patient and his or her partner usually participate. It is based on a transactional model of the relationship in which the behaviours of both partners have mutual influence and interact with the depressive symptomatology, which in turn generates changes in the behaviours of those involved. The style of the therapy varies according to the theoretical approach followed by the therapist (for example, cognitive-behavioural or systematic), and it attempts to successfully change the communication between them both and to provide them with new skills for the interpersonal relationship. In the summary provided by NICE[21], it highlights that there are certain data to the effect that couples therapy is effective treatment against depression when compared with a wait-list condition, and it seems to be better tolerated than antidepressants, although no comparisons with the latter have been established regarding efficacy. Some reviews point out that certain formats of couples therapy have reached efficacy that is similar to individual CBT in dissatisfied couples with one of the partners depressed, but only couples therapy seems to improve the dyadic adjustment. Thus, marital stress could provide an indication for prescribing this type of therapy[123, 131].

Summary of the evidence

1-	In mild depression, no treatment has been shown to be more effective than problem-solving therapy or different forms of counselling (support, advice, orientation) (21, 128).
2	In mild or mild-moderate depression in which couple difficulties simultaneously exist, couples therapy seems to offer additional advantages over other forms of treatment by improving the marital adjustment (121, 129).

Recommendations

✓	Psychological interventions should be provided by professionals who have experience at managing depression and who are experts in the applied therapy. This is especially important in the most severe cases.
B	In mild and moderate depression, specific and brief psychological treatment (such as problem-solving therapy, cognitive behavioural therapy or counselling) in 6 to 8 sessions during 10-12 weeks should be considered.
B	The preferred psychological treatment for moderate, severe or resistant depression is cognitive behavioural therapy. Interpersonal therapy can be considered as a reasonable alternative.

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B	For moderate and severe depression, suitable psychological treatment should include 16 to 20 sessions during at least five months.
B	For moderate depression, either antidepressant drug treatment or suitable psychological intervention can be recommended.
B	Cognitive behavioural therapy should be offered to patients with moderate or severe depression who reject drug treatment or for whom avoiding the secondary effects of antidepressants is a clinical priority or who express that personal preference.
B	Couples therapy should be considered, if applicable, in the event that a suitable response is not obtained with previous individual intervention.
B	Cognitive behavioural therapy should be considered for patients who have not had a suitable response to other interventions or who may have a prior history of relapses or residual symptoms, despite treatment.
B	Cognitive behavioural therapy should be considered for patients who have recurrent depression and who have relapsed despite antidepressant treatment or who express a preference for psychological treatment.
A	For patients whose depression is resistant to pharmacological treatment and/or who have multiple episodes of recurrence, a combination of antidepressants and cognitive behavioural therapy should be offered.
A	A combination of cognitive behavioural therapy and antidepressant medication should be offered to patients with chronic depression.
C	Whenever cognitive behavioural therapy is applied to more severe patients, the techniques based on behavioural activation should be given priority.
C	Psychological interventions other than the aforementioned could be useful for dealing with comorbidity or the complexity of the family relationships frequently associated with the depressive disorder.

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7. Other treatments

- Is electroconvulsive therapy effective for the treatment of major depression?
- Is guided self-help effective for any sub-group of patients?
- Are support groups effective for patients with major depression?
- Is physical exercise effective for patients with major depression?
- Is acupuncture effective for patients with major depression?
- Is treatment with St John's Wort effective?

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7.1 Electroconvulsive therapy

Electroconvulsive therapy (ECT) induces, for a therapeutic purpose, generalised seizure activity through electrical stimulation of the central nervous system. Even though years ago it was a reviled and even prohibited technique, today it is performed under certain circumstances, under anaesthetic control and with muscle relaxation, wherefore secondary effects have been reduced to the point where they are comparable to those of general anaesthesia.

Even though electroconvulsive therapy has been used in clinical practice for more than 50 years, there continues to be controversy about the pathologies for which it could be indicated, as well as its efficacy, how it is administered, the possible complications and its indication as maintenance treatment. Despite all this, ECT has proven is efficacy in various studies, and it is used in severe depressive episodes, with or without psychotic symptoms, and in resistant depression. It should also be considered as first-line treatment in acute situations of suicidal risk or for patients who have severely deteriorated medically[21, 132].

There are no absolute contraindications for electroconvulsive therapy, although there are situations of relative risk, such as the presence of brain injuries that occupy space (tumours or haemorrhages) or any other situation in which intercranial pressure is high; recent cardiovascular problems (such as acute myocardial infarction or vascular malformations); treatment with MAOIs or lithium; and the existence of increased risk for general anaesthesia[133]. Regarding side effects, they depend basically on the patient's previous conditions, their personal susceptibility, the technique used (bilateral or unilateral), the number of sessions used and the frequency of administration. These side effects can be immediate (mental confusion, amnesia and headache) or more persistent (euphoria and cognitive disorders)[132].

In 1999, the Sociedad Española de Psiquiatría [*Spanish Society of Psychiatry*] promoted the formulation of a Spanish consensus on electroconvulsive therapy, in which it was agreed that maintenance ETC could benefit 10-15% of patients with severe affective disorders in which relapses occur (even with adequate drug treatments) during the 6 months following the ECT[134].

The ECT section of the NICE[21] Depression CPG is based on a systematic review prepared by the University of Sheffield and subsequently published in 2005[21, 135], and it in turn includes two systematic reviews of quality randomised clinical trials. The first, prepared by the Cochrane Collaboration, studied the efficacy and safety of ECT in schizophrenia[136] and the second, performed by the *UK ECT Group*, studied the efficacy of ECT on the depressive illness[137]. It also included a systematic review of non-randomised studies on

the patients' point of view about this technique[138]; two clinical studies in which ECT was compared with transcranial magnetic stimulation; ten studies in which ECT combined with drugs was compared to ECT plus placebo; a prospective cohort study in which patients of advanced age who had received ECT were compared to those who had not received it[139]; and a systematic review of a series of cases on using ECT during pregnancy[140, 141]. The NICE CPG considers ECT to be an effective treatment for depression in adults and it reaches the following conclusions:

~ Real ECT is more effective than sham ECT, although the parameters of the electrical stimulus have an important influence on efficacy.

~ Bilateral ECT is more effective than unilateral ECT, and unilateral ECT at a low dose is not more effective than sham ECT.

~ ECT has the risk that side effects of the cognitive type may appear. Even though the evidence is limited, it seems that the duration of these effects does not go beyond six months, although there are no longer-term studies.

~ ECT is probably more effective than short-term pharmacotherapy, although the evidence of this affirmation is based on studies of inadequate variable quality and doses.

~ The combination of ECT with pharmacotherapy was not shown to have a greater short-term effect than ECT alone.

~ There is limited information to the effect that ECT is more effective than repetitive transcranial magnetic stimulation.

~ Certain data suggest that tricyclic antidepressants could improve the effect of ECT and that the continuation of treatment associated with lithium reduces the rate of relapses in patients who have responded to ECT after an acute episode.

~ Finally, the meta-analysis prepared by Kho *et al*[142] and based on 16 clinical trials included in most of the preceding reviews supports the aforementioned conclusions.

Summary of the evidence

1+	There are numerous controlled studies that demonstrate that electroconvulsive therapy is an effective and safe treatment in adult patients with severe major depression (133, 135, 140).
1+	The parameters of the electrical stimulus have a major influence on the efficacy of the technique, and bilateral ECT is more effective than unilateral ECT (133, 135, 140).
1+	ECT is a safe technique, and its side effects on memory are usually slight and temporary (133, 135, 140).
1+	ECT is more effective in the short-term than pharmacotherapy, and the combination of ECT with pharmacotherapy has not shown to have a greater short-term effect than ECT alone (133, 135, 140).

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1+	Tricyclic antidepressants improve the effect of ECT, and continuing with antidepressant treatment associated with lithium could reduce the rate of relapses in patients who have responded to ECT after an acute episode (133, 135, 140).

Recommendations

A	Electroconvulsive therapy should be considered as a therapeutic alternative in adults with severe major depression.
✓	ECT is especially indicated for patients with severe major depression (with a high risk of suicide or severe physical impairment), in resistant depression and by informed choice of the patient.

7.2 Guided self-help

Guided self-help is an ambiguous term that includes self-help as such and guided self-help. Self-help is directed at improving the clinical outcome by training patients on the pertinent skills for overcoming and managing their health problem. It includes the use of written materials (bibliotherapy), computer programmes or material recorded in audio/video format so that, for the purpose of modifying their attitudes and behaviour, they successfully solve or improve their problems.

In turn, guided self-help is more complete and uses these self-help materials in conjunction with minimum guidance offered by a professional "to monitor progress, clarify the procedures, respond to general questions or provide general support or stimulus"[143].

Reading the existing literature on this subject brought several questions to light:

~ First of all, the self-help material for depression is scarce, it is in English, and it always alludes to two texts of reference: *Feeling Good, The New Mood Therapy*, by David Burns, whose version in Spanish is called *Sentirse bien*[144]; and *Managing anxiety and depression*[145], which has been translated into Spanish under the title of *Manejando su ansiedad y depresión*. A single article refers to a third book titled *Control your depression*[146]. We are unaware if these books have been validated in Spanish and if they are actually used as bibliotherapy material in consultations.

~ Most studies refer to the fact that the therapist is the one to deliver the reading material, with minimum intervention. Moreover, there was considerable variation in the range of patients to whom bibliotherapy was offered.

~ There is considerable heterogeneity about the diagnosis and classification of depression, and on many occasions neither criteria nor scales considered to be of reference in this guideline are used.

~ The use of different nomenclatures and, occasionally, combinations of techniques was observed, which limits the assessment.

NICE assessed guided self-help through nine randomised clinical trials, and it concluded that guided self-help generates a significant clinical reduction of depressive symptoms in comparison to non-intervention. In patients with mild or moderate depression, it could be as effective as some forms of individual therapy and more effective than group psychotherapy, although there isn't

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sufficient data to the effect that this benefit is maintained in the long term[21]. The recommendations that it makes are the following:

~ In patients with mild depression, health professionals should recommend guided self-help programmes based on cognitive behavioural therapies.

~ Guided self-help, in addition to providing suitable written material, must include support and follow-up by health professionals for six to nine weeks.

Bibliotherapy in the treatment of depression was assessed in a meta-analysis[147], and it was observed that using bibliotherapy translated into at least a 25% reduction in scores of depression tests when compared to non-treatment, although there was no significant relationship between the maintenance time of the treatment and the final clinical outcome. Up to now, there are no clinical trials that demonstrate that bibliotherapy is helpful in patients with severe depression.

A randomised controlled trial[148] examined if the fact that adding self-help material (books, brochures, algorithms, etc.) to the standard treatment of depression using antidepressants by primary care physicians was associated with any additional improvement of the clinical outcomes. The outcomes showed no significant reduction between the patients treated only with antidepressants and those who also received self-help. However, significant differences were observed in favour of the intervention group with respect to knowledge of the treatment, of the illness, of how to make changes in their lives and of the effects of the medication. The patients were shown to be satisfied with receiving self-help, and most general physicians found it to be useful.

Summary of the evidence

1+	Compared to non-intervention, guided self-help is effective at reducing the symptoms of mild to moderate depression, although its long-term effect is unknown (21).
1+	No significant differences were observed when the pharmacological treatment of depression was compared to adding or not adding self-help (146).

Recommendations

✓	In general, guided self-help is not recommended for patients with severe major depression.
B	However, for patients with mild or moderate depression, professionals could consider recommending guided self-help programmes based on cognitive behavioural therapy.

7.3 Support groups

A **mutual support group** is understood as a group specifically created to help its members face a critical life situation, such as chronically mental ill persons, and to inform, guideline and support families, thereby offering resources for supporting the anxiety and bearing the prejudices linked to the ignorance of certain illnesses. These "non-professional" groups and networks work autonomously and arise in society when formal healthcare organisations do not satisfy certain needs. The most well-known examples are alcoholics anonymous groups and self-help programmes for food disorders. These groups are considered to be mainly self-sufficient and usually have no professional interference.

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Conversely, **support groups** tend to be called together by a professional and are composed of people who share some type of problem that alters or modifies aspects of their normal functioning. Belonging to these groups provides new links and social relationships for their members, thereby allowing interaction with people who have common problems, deficiencies and/or experiences. A group can begin by being a support group and over time become a mutual support group that operates autonomously, although this group may likewise and occasionally require the help of a professional or of an institution and operate for a certain period of time like a support group.

Occasionally, these groups can be guided by **paraprofessionals** who are trained or supervised by professionals. They are defined as mental health workers, paid or volunteers, without training regarding psychological treatment for anxiety and depression, and who substitute professionals in treating patients with these disorders[149].

In this section, the NICE[21] guideline only included one randomised clinical trial that used befriending of women with depression. It consisted of especially trained volunteers who got to know, speak with and accompany women with depression for at least one hour a week, which women were also allowed another type of treatment. The outcomes showed that friendship is significantly effective at achieving the remission of depressive symptoms in comparison with controls. NICE concludes with the recommendation that in patients with chronic depression, friendship could be considered an adjuvant to pharmacological or psychological treatment.

In a prospective cohort study not included by NICE[150], the use of depression support forums through the Internet was assessed. The patients that customarily used these forums (more than five hours a week) showed a better resolution of their depressive symptoms. However, the high probability of skewing of this study must be considered, given that it used patients who had different states and who were socially isolated.

Support and socialisation groups seem to constitute protector factors in older persons with depression, while sensory limitations, such as blindness and deafness, the absence of a home and low financial income behave like depression risk factors[151]. Finally, a satisfaction study showed that up to 64% of the participants in depression support groups declared that this type of therapy met their expectations[152].

Summary of the evidence

	Studies about support and self-help groups are scarce and of insufficient quality to determine if they can be beneficial or not in patients with major depression.

Recommendations

✓	Participation in support groups is not considered an effective treatment measure in patients with the major depressive disorder, either alone or combined with other therapeutic measures.

7.4 Physical exercise

It is well-known that exercise improves the mood and the general sensation of well-being, wherefore it has been attempted to determine up to what point it can be useful as treatment in patients with major depression. A depressed patient who exercises regularly successfully develops his self-esteem and develops better and greater support from others, which favours his relationships with the environment.

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NICE[21] performed a systematic review on the likelihood of remission, reduction of symptoms and adherence to treatment in patients with depression who took exercise, versus not exercising and versus different available treatments (pharmacological, psychotherapeutic, social support and meditation), thereby including a total of nine clinical trials. In general, the exercise programmes used had a relatively high frequency (at least 3 times per week), lasting from 45 minutes to one hour and in periods of 10 to 12 weeks. The conclusions were that in subjects with depression, in particular mild or moderate depression, structured and supervised exercise had a clinically significant impact on improving the symptoms, even though there was no evidence of long-term benefits for preventing relapses or of the utility of maintenance exercise programmes. There also was insufficient evidence to assess its usefulness as an alternative or in combination with other treatments, although a recent study – with few patients – points out that endurance exercise associated with antidepressant drugs is better than antidepressant drugs alone[153].

One trial with considerable methodological limitations (small sample size, poor definitions of exercise time and intensity, low number of participants among those potentially eligible and no assessment of comorbidities) and not included in the NICE guideline compared physical exercise to educational activities in patients without clinical improvement after six weeks of pharmacological treatment at suitable doses[154]. The authors observed that exercise twice a week provides a greater reduction of depressive symptoms, even though the exercise may be light.

Another systematic review[155], which only included three studies with patients with major depression, observed that physical exercise programmes significantly reduce the symptoms of depression, although the conclusions are limited by the heterogeneity of the three assessed studies and their methodological limitations.

The efficacy of exercise in patients with mild and moderate major depression and their dose-response ratio was evaluated in a trial in which only 5% of the potentially eligible patients initiated it[156]. The authors conclude that aerobic exercise at the traditionally recommended doses (17 kcal/kg/week, taken 3 to 5 times per week) improves the symptoms of depression, while exercise at low doses (7 kcal/kg/week) has no effect at all.

Finally, in patients over 60 years of age, intense exercise also seems to be more effective than low intensity exercise or the usual care by the primary care physician[157].

Summary of the evidence

2++	For patients with major depression, in particular mild to moderate depression, a structured and supervised programme of exercise could be effective intervention, with significant clinical impact on depressive symptoms (21).
2+	Although the acceptance rate of exercise programmes is low, once one is started, adherence is similar to other types of therapies, and short-term benefits are detected (21).
2++	The greatest beneficial effect of exercise is obtained when it is given in association with pharmacological or psychotherapeutic treatment (151).
	No evidence has been found about the usefulness of exercise for maintenance therapy or for the prevention of relapses.

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Recommendations

C	Programmes of structured and supervised exercise of moderate intensity, with a frequency of 2-3 times per week, with a duration of 40-45 minutes and for a period of 10 to 12 weeks should be recommended to patients with mild-moderate depression.

7.5 Acupuncture

Acupuncture is a technique that consists of inserting thin needles in various parts of the body, and it is based on traditional Chinese medicine. There are a wide variety of techniques, which include the classic or traditional, auricular, trigger points and single points.

The use of acupuncture was not discussed in the NICE[21] CPG. We identified three systematic reviews and one subsequent clinical trial with which we used to deal with the question. The first review[158] included 7 randomised clinical trials, six of which included only patients with major depression (a total of 466 patients). The second review, published by the Cochrane Collaboration[159], included seven randomised clinical trials (a total of 517 patients), five of which were included in the first[158]. A final review[160] included nine randomised clinical trials, eight of which included only patients with major depression (614 patients). All the clinical trials of the first review[158] were included in the latter, and only one from the Cochrane review[158] was not included.

The inclusion criteria considered in the reviews were randomised clinical trials that compared acupuncture (specific for depression or not) to simulated acupuncture, pharmacological treatment or no treatment, and all the trials included in the three reviews were considered to be poor quality.

In general, the reviews coincide in that there is insufficient scientific evidence to determine if specific acupuncture for depression is more effective than non-specific acupuncture or no treatment, or if acupuncture plus medication is more effective than acupuncture plus placebo. Moreover, the aforementioned methodological aspects mean that the outcomes must be interpreted with caution.

A final, double-blind, randomised clinical trial not included in the previous reviews and performed on 151 patients diagnosed with major depression compared traditional Chinese acupuncture to manual stimulation and to a control group[161]. It concluded that, even though acupuncture seems to improve the treated patients with respect to the wait-list patients, there are no data as to different efficacy between the two types of acupuncture, and it concluded that acupuncture with manual stimulation is not effective as monotherapy in major depression.

Summary of the evidence

	The available trials lack suitable methodological rigour, wherefore it is not possible to determine if acupuncture, whether specific for depression or not, alone or in combination with other treatments, has a beneficial effect in patients with symptoms of major depression.

Recommendations

✓	The existing scientific evidence does not allow recommending the use of acupuncture as a treatment for major depression.

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7.6 St John's Wort

The extract of *hypericum perforatum*, commonly called St John's Wort, is a product that has been used for centuries, and it has at least seven components that can contribute to its pharmacological effects[162]. Their action mechanism is not entirely clear[163]. Easy access, its low cost and the general belief that it has no side effects[164] have caused a considerable increase in the use of herbal products for treating depression.

The NICE[21] CPG on managing depression selected forty trials pertaining to the use of St John's Wort in treating depression, out of which only 19 finally met the criteria for inclusion. The comparison groups were the placebo (10 articles), tricyclic antidepressants (four articles), serotonin reuptake inhibitors (six articles) and antidepressants related to tricyclics (one article). The conclusions were that St John's Wort seems to be more effective than the placebo at obtaining a response, both in moderate depression and in severe depression, and there are no differences when compared to other antidepressants. Despite the fact that St John's Wort could be beneficial in cases of mild and moderate depression, the authors of the guideline recommend that health professionals do not prescribe it due to the uncertainty of the appropriate dose, the variation in the nature of the existing preparations and the potential interactions with other drugs, such as oral contraceptives, anticoagulants and anticonvulsants. Moreover, patients who may be receiving St John's Wort should be suitably informed about the aforementioned.

A subsequent Cochrane review identified 37 trials that compared St John's Wort with placebo or with other antidepressants[165]. This review includes most of the trials of the NICE review[21]. In adults with mild to moderate depression, St John's Wort improved symptoms more than placebo and than standard antidepressants. When jointly analysing the six most recent trials, all of large size, with an improved design and including only patients with major depression, the observed benefits of *hypericum* over placebo were minimal. This leads to considering a possible over-estimation of the effect in the older studies and in those of a smaller sample size. The authors conclude that the comparison of St John's Wort to placebo only seems to have fewer benefits in patients with major depression, that there possibly is no benefit in patients with prolonged depression and that there is no evidence as to its effectiveness on major depression. A third systematic review[166] in which the outcomes of two meta-analyses were compared, one that included 15 studies published between 1979 and 2000 and the second in which three new studies are added to the previous ones, does not contribute relevant data to the review prepared by the Cochrane Collaboration[165].

Summary of the evidence

	St John's Wort or *hypericum perforatum* is an herbal product frequently used for treating depression due to its easy access and low cost. However, there is uncertainty about the appropriate dose, and complications can appear when using it due to the variation of the nature of the existing preparations and to the potential interactions with other drugs (160).
1+	Current scientific information about the efficacy of St John's Wort for treating depression is heterogeneous, and there may be an over-estimation of its effect. In patients patients with major depression, only minor benefits would be obtained, and possibly none in patients with a prolonged duration of their depression (21, 163).

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Recommendations

B	The use of St John's Wort is not recommended as a treatment option for patients with major depression.
✓	Health professionals should inform patients who consume it about the possible risks and benefits.

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8. Quality indicators

- What are the indicators that allow monitoring quality in the management of depression?

It is important to know if the expected objectives are reached by complying with the recommendations considered to be the most important. Therefore, it is hereby proposed to assess some of the process variables that take part and the most relevant clinical outcomes. When assessing the clinical management of depression, it is advisable to measure the three key areas related to quality, for which some indicators are initially proposed, due to their apparent validity, reliability and feasibility of use in primary care consultations and in the scope of the various healthcare areas.

Five of the proposed indicators are listed and described below, which are quantitative measures that can be used as a guideline and which, if they are obtained with certain frequency, allow analysing the evolution over time, meaning that they allowing the indicators to be monitored.

Proposed indicators:

Area	Focus of the assessment	Indicator name
Diagnosis	Process	Underdiagnosis of major depression.
Treatment	Process	Follow-up of treatment with antidepressants
Treatment	Outcome	Maintenance of treatment with antidepressants
Treatment	Process	Efficient use of antidepressant drugs
Treatment	Process	Psychotherapeutic treatment in severe major depression
Treatment	Process	Psychotherapeutic treatment in mild major depression

Dimensions of the considered quality:

Quality dimension	Indicator name
Diagnostic effectiveness	Underdiagnosis of major depression
Therapeutic effectiveness	Follow-up of treatment with antidepressants
Therapeutic effectiveness	Maintenance of treatment with antidepressants
Therapeutic effectiveness	Efficient use of antidepressant drugs
Therapeutic effectiveness	Psychotherapeutic treatment in severe major depression
Therapeutic effectiveness	Psychotherapeutic treatment in mild major depression

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Indicator name	**UNDERDIAGNOSIS OF MAJOR DEPRESSION**
Justification	It is estimated that 28% of the patients who suffer from major depression are not diagnosed. Even though this percentage is lower in the most severe forms of depression, it is important to increase the number of patients who are diagnosed. This indicator allows alerting about a possible situation of underdiagnosis of new episodes of major depression.
Formula	$\frac{\text{Recorded number of adult patients diagnosed with major depression}}{\text{Number of adult patients who, according to estimates of epidemiological studies, are expected to suffer from major depression}} \times 100$
Description of terms	**Adult patients**: patients over 18 years of age. **Recorded diagnosis of depression**: written record of the diagnosis in the patient's medical history that he suffered from an episode of a major depressive disorder in the reference time period (prevalent cases). **Patient's medical history**: it will be considered to be the information coming from the medical history of Primary Care and/or hospital care and on paper support and/or electronic format. **Epidemiological studies**: to make estimates of expected cases, the epidemiological study that has the best available quality and that has been performed on populations with the greatest sociodemographic similarity will be selected. The number of expected patients will be obtained based on standardised estimates by age and sex.
Geographic area of reference	The geographic area of reference will be indicated in order to define the resident population in this geographic area during the study period and that, if diagnosed with major depression, would be considered a case.
Time period of reference	The adult patients from the geographic area who are diagnosed in the reference period, generally the last 12 months, will be included.
Exclusion criteria	Patients under 18 years of age, patients who do not reside in the geographic area of study and patients who, despite having a recorded diagnostic history of major depression, have not had an active episode in the period of study will be excluded.
Type of indicator	Process.
Data sources	Patient's medical history, epidemiological studies.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Indicator name	**FOLLOW-UP OF TREATMENT WITH ANTIDEPRESSANTS**
Justification	The continuous treatment of major depression with antidepressants during 6 months or more helps to consolidate the response to treatment and reduces the risk of relapse. To decrease the number of patients who do not suitably complete the treatment period, it is recommended that follow-up contact be made with them. This indicator allows monitoring follow-up on the treatment with antidepressants.
Formula	$\frac{\text{Recorded number of adult patients diagnosed with major depression for which there is follow-up contact within the maximum period of 1 month after indication of treatment with antidepressant drugs}}{\text{Recorded number of adult patients diagnosed with major depression for which treatment with antidepressant drugs was indicated}} \times 100$
Description of terms	**Adult patients**: patients over 18 years of age. **Indication of treatment with antidepressant drugs**: written record in the patient's medical history that, after diagnosis of a major depressive disorder, starting treatment with antidepressant drugs has been indicated. New indications of treatment after new episodes in patients with a prior history of a major depressive disorder will also be counted. **Patient's medical history**: it will be considered to be the information coming from the medical history of Primary Care and/or hospital care and on paper support and/or electronic format. **Follow-up contact**: in addition to personally attended, follow-up medical consultations, it could be considered that a patient has made follow-up contact by another system, as long as it has thus been recommended and previously agreed upon by the attending physician.
Geographic area of reference	The geographic area of reference will be indicated in order to define the resident population in this geographic area during the study period and that, if diagnosed with major depression, would be considered a case.
Time period of reference	All diagnosed adult patients from the geographic area for whom treatment with antidepressant drugs has been indicated in the period of reference, generally the last 12 months, will be included.
Exclusion criteria	Patients under 18 years of age and patients not residing in the geographic area of the study are excluded. Other exclusions: patients confined to bed, transfers to other areas, death and diagnosis date within a period of less than one month.
Type of indicator	Process.
Data sources	Patient's medical history.

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Indicator name	**MAINTENANCE OF PHARMACOLOGICAL TREATMENT WITH ANTIDEPRESSANTS**
Justification	The maintenance of treatment of major depression with antidepressants during 6 months or more helps to consolidate the response to treatment and to reduce the risk of early relapse. This indicator allows knowing the maintenance of treatment with antidepressants.
Formula	$\frac{\text{Recorded number of adult patients diagnosed with major depression who maintain treatment with antidepressant drugs for 6 months}}{\text{Recorded number of adult patients diagnosed with major depression for which treatment with antidepressant drugs was indicated}} \times 100$
Description of terms	**Adult patients**: patients over 18 years of age. **Indication of treatment**: recorded indication of pharmacological treatment with antidepressants after diagnosis of an episode of a major depressive disorder. The new episodes of patients with a prior history of a major depressive order will also be counted. The indication must be made during the time period of reference. **Recorded in the patient's medical history**: the information coming from the medical history of Primary Care and/or hospital care and on paper support and/or in electronic format will be considered. **Time period of reference**: all adult patients from the geographic area who are diagnosed in the reference period, generally the last 12 months, will be included. **Geographic area**: the geographic area of reference will be indicated in order to define the resident population in this geographic area and that, if diagnosed with major depression, would be considered a case. **Indication of treatment**: all new indications of pharmacological treatment with antidepressants made during the time period of reference will be included. **Maintenance of treatment**: it will be considered that a patient has maintained treatment for 6 months and that the treatment has been adequate if it is thus recorded in the medical history.
Geographic area of reference	The geographic area of reference will be indicated in order to define the population that resides in this geographic area during the study period and that, if diagnosed with major depression, would be considered a case.
Time period of reference	All adult patients from the geographic area who are diagnosed in the reference period, generally the last 12 months, will be included.
Exclusion criteria	Patients under 18 years of age and patients not residing in the geographic area of the study are excluded. Other exclusions: transfers to other areas, deaths, withdrawal of medication by medical prescription and diagnosis date within a period of less than 6 months.
Type of indicator	Outcome.
Data sources	Patient's medical history.

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Indicator name	**EFFICIENT USE OF ANTIDEPRESSANT DRUGS**
Justification	SSRI antidepressants are better tolerated and safer than TCAs. New dual drugs or serotonin reuptake inhibitors and noradrenaline are not more effective, although they are more expensive and potentially more dangerous. This indicator allows monitoring efficient use of treatments with antidepressants.
Formula	$\frac{\text{Recorded number of adult patients diagnosed with major depression that are treated with SSRI drugs in the first attempt.}}{\text{Recorded number of adult patients diagnosed with major depression for which treatment with antidepressant drugs was indicated}} \times 100$
Description of terms	**Adult patients**: all adult patients over 18 years of age, with a recorded diagnosis of major depression and the start of the indication of pharmacological treatment with antidepressants during the time period of reference will be counted. **Recorded diagnosis of depression**: written record of the diagnosis in the patient's medical history that a new episode of a major depressive disorder was diagnosed in the reference time period. The new episodes of patients with a prior history of a major depressive order will also be counted. **Patient's medical history**: it will be considered to be the information coming from the medical history of Primary Care and/or hospital care and on paper support and/or electronic format. **Indication of treatment**: all new indications of pharmacological treatment with antidepressants made during the time period of reference will be included. **Indication of treatment with SSRI drugs in the first attempt**: it will be considered that treatment with SSRI drugs in the first attempt has been indicated for a patient if it thus recorded in the medical history.
Geographic area of reference	The geographic area of reference will be indicated in order to define the resident population in this geographic area and that, if diagnosed with a major depressive disorder, would be considered a case.
Time period of reference	All adult patients from the geographic area who are diagnosed in the reference period, generally the last 12 months, will be included.
Exclusion criteria	Patients under 18 years of age and patients not residing in the geographic area of the study are excluded.
Type of indicator	Process.
Data sources	Patient's medical history.

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Indicator name	**PSYCHOTHERAPEUTIC TREATMENT IN SEVERE MAJOR DEPRESSION**
Justification	Some psychotherapeutic treatments have been demonstrated to play a relevant role in the treatment of major depression. In the severe form, the combination of antidepressants and psychotherapy is considered to be the most effective option. This indicator allows monitoring the degree of coverage of psychotherapeutic treatment in combination with pharmacological treatment.
Formula	$\frac{\text{Recorded number of adult patients diagnosed with severe major depression and treated with psychotherapy in combination with antidepressants.}}{\text{Recorded number of adult patients diagnosed with severe major depression.}} \times 100$
Description of terms	**Patients with combined antidepressant and psychotherapy treatment**: the patient receives both simultaneously and in coordination between the professionals who dispense the treatments. **Patients treated with psychotherapy**: those who receive any of the duly validated treatments. **Adult patients**: adult patients over 18 years of age, with a recorded diagnosis of major depression and the start of the indication of psychotherapeutic treatment during the time period of reference will be counted. **Recorded diagnosis of depression**: written record in the patient's medical history that a new episode of a severe major depressive disorder was diagnosed in the time period of reference. New episodes in patients with a prior history of major depression will also be counted. **Patient's medical history**: it will be considered to be the information coming from the medical history of Primary Care and/or hospital care and on paper support and/or electronic format. **Indication of treatment**: all new indications of psychotherapeutic treatment with antidepressants made during the time period of reference will be included.
Geographic area of reference	The geographic area of reference will be indicated in order to define the resident population in this geographic area and that, if diagnosed with a major depressive disorder, would be considered a case.
Time period of reference	All patients who are diagnosed in the reference period, generally the last 12 months, will be included.
Exclusion criteria	Patients under 18 years of age and patients not residing in the geographic area of the study are excluded.
Type of indicator	Process.
Data sources	Patient's medical history.

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Indicator name	**PSYCHOTHERAPEUTIC TREATMENT IN MILD MAJOR DEPRESSION**
Justification	Some psychotherapeutic treatments have been demonstrated to play a relevant role in the treatment of major depression. This indicator allows monitoring the degree of coverage of psychotherapeutic treatment in mild major depression.
Formula	$\frac{\text{Recorded number of adult patients diagnosed with mild major depression that are treated with brief psychotherapy.}}{\text{Recorded number of adult patients diagnosed with mild major depression.}} \times 100$
Description of terms	**Patients treated with psychotherapy**: those who receive any of the duly validated treatments. **Brief Psychotherapy**: psychotherapeutic treatment that does not exceed 6-8 sessions, for 10 to 12 weeks. **Adult patients**: patients over 18 years of age, with a recorded diagnosis of major depression and the start of the indication of psychotherapeutic treatment during the time period of reference will be counted. **Recorded diagnosis of depression**: written record in the patient's medical history that a new episode of a mild major depressive disorder was diagnosed in the time period of reference. New episodes in patients with a prior history of major depression will also be counted. **Patient's medical history**: it will be considered to be the information coming from the medical history of Primary Care and/or hospital care and on paper support and/or electronic format. **Indication of treatment**: all new indications of psychotherapeutic treatment made during the time period of reference will be included.
Geographic area of reference	The geographic area of reference will be indicated in order to define the resident population in this geographic area and that, if diagnosed with a major depressive disorder, would be considered a case.
Time period of reference	All patients who are diagnosed in the reference period, generally the last 12 months, will be included.
Exclusion criteria	Patients under 18 years of age and patients not residing in the geographic area of the study are excluded.
Type of indicator	Process.
Data sources	Patient's medical history.

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9. Dissemination and implementation

Formats of the Guideline, dissemination and implementation

The CPG consist of two versions, the complete and the summarised versions, in addition to information for patients. The complete version and the information for patients can be accessed through both the web page of Axencia de Avaliación de Tecnoloxías Sanitarias (avalia-t) and Guía Salud. The dissemination and implementation strategies would be the following:

~ Official presentation of the guideline by the health authorities and delivery to every potential professional user.

~ Distribution of the patient guideline.

~ Presentation of the guideline in Primary and Specialised Care through interactive chats.

~ Dissemination of the guideline in electronic format on the web pages of the health services and of the scientific societies involved in the project.

~ The execution of on-line and/or attended training activities on managing patients with depression.

~ Presentation of the guideline in scientific activities (workshops, conferences, meetings).

~ Publication of the guideline in medical journals.

~ The establishment of good healthcare criteria for patients with depression in contract programme schemes and clinical management contracts.

~ The establishment of support systems for the clinical decision, thereby integrating the guideline and the selected indicators in the computer programme used in primary care.

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10. Recommendations for future research

During the process of preparing these guidelines, multiple gaps in knowledge were detected, for which well-designed studies are required. Proposals from other sources[21, 78, 167] were also taken into account.

Screening

~ Study the cost-effectiveness of screening programmes in risk groups and in the different levels of healthcare.

Suicide

~ Study the possible effects of various pharmacological or psychotherapeutic treatments on suicidal ideas and behaviours.

Drugs

~ Study the role of drugs in the management of mild depression at the primary care level.

~ Do comparative studies with multiple arms that compare a drug versus a drug and placebo, with a long term follow-up and a sufficient statistical strength to detect relevant clinical differences.

~ Foster the research of independent studies avoiding the sponsorship of the pharmaceutical industry.

~ Promote studies on the onset of clinical improvement and the time necessary for reaching the maximum level of improvement using different pharmacological treatments.

~ Study the optimum duration of pharmacological treatment in each risk group, drug and dose.

~ Compare the adverse effects of different drugs through larger and more rigorous observational studies.

Relapses

~ Study the characteristics of patients at a high risk of relapse.

~ Perform studies to more accurately determine the time of duration for treatment in patients with a different risk of recurrence.

Resistant depression

~ Study the most effective therapeutic strategies for resistant depression, both pharmacological and non-pharmacological.

~ Comparative studies would be necessary regarding the different possible options to be adopted after a first treatment failure: dose maintenance, antidepressant switch, combination of the same or augmentation with other drugs. It would be important to differentiate between a partial response and the absence of a response, given that it seems that the right treatment strategy could be different.

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~ Studies of suitable duration that cover antidepressant and augmentation combination strategies are needed. Studies that evaluate the optimum doses of T3, lithium and pindolol are also necessary.

~ It would also be necessary to design research that assesses the possibility of combining pharmacological treatment with psychotherapeutic treatment in the management of resistant depression.

Psychotherapy

~ Use medium- and long-term clinical trials to study the efficacy of the various types of psychotherapy in the different levels of healthcare.

~ Trials for determining the most appropriate duration of psychotherapeutic treatment.

~ Design research that assesses the possibility of combining pharmacological treatment with psychotherapeutic treatment.

ECT

~ Promote additional research to evaluate the long-term effect of the technique and the efficacy of maintenance ECT as treatment for depression.

Self-help

~ Develop adapted material for self-help programmes and test its efficacy through controlled studies.

Support groups

~ Determine the role of social support for isolated or vulnerable people.

Exercise

~ New clinical trials are needed, which, while differentiating the sub-groups of mild, moderate and severe depression, compare the effects of different forms of physical exercise and clarify the dose and appropriate intensity of the same.

Acupuncture

~ Perform additional, randomised controlled trials, with adequate statistical power and a good methodological design, which correctly evaluate the efficacy of acupuncture, thereby comparing this technique with other therapeutic alternatives and evaluating the long-term outcomes and side effects.

General

~ Study the effect of implementing corrective measures in the system, which will allow detecting quality problems and monitoring the evolution of those problems.

~ Study the effect of integrating help tools for the management of depression in electronic medical histories.

~ Study appointment improvement systems and their effect on therapeutic compliance.

~ Study the effectiveness of the various methods of implementing clinical practice guidelines.

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Appendices

Appendix 1. Levels of evidence and degrees of recommendations

Levels of evidence

1++	High quality meta-analyses, systematic reviews of randomized clinical trials or high-quality clinical trials with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews or randomized clinical trials with a low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with a high risk of bias.
2++	High quality systematic reviews of cohort studies or case-control studies or high-quality diagnostic test studies, high-quality cohort studies or case-control studies of diagnostic tests with a very low risk of bias and a high probability that the relationship is causal.
2+	Well conducted cohort studies or case-control studies or diagnostic test studies with a low risk of bias and a moderate probability that the relationship is causal..
2-	Cohort studies or case-control studies with a high risk of bias.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

Strength of the recommendations

A	At least one meta-analysis, systematic review of RCT, rated as 1++, and directly applicable to the target population, or sufficient evidence derived from level 1+ studies that are directly applicable to the target population and that demonstrate overall consistency of results.
B	A body of evidence derived from level 2++ studies that are directly applicable to the target population and that demonstrate overall consistency of results. Extrapolated evidence from level 1++ or 1+ studies.
C	A body of evidence derived from level 2+ studies that are directly applicable to the target population and that demonstrate overall consistency of results. Extrapolated evidence from level 2++ studies.
D	Evidence level 3 o 4 evidence. Extrapolated evidence from level 2+ studies.

The studies classified as 1- and 2- should not be used in the process of preparing recommendations due to their high possibility of skewing.

Good clinical practice

✓[1]	Recommended best practice based on the clinical experience and the consensus of the guideline development group.
Source: Scottish Intercollegiate Guidelines Network. SIGN 50*: A guideline developers' handbook* (Section 7: Forming guideline recommendations), SIGN publication no. 50, 2001.	

1. The development group occasionally notices that there is an important practical aspect that it wants to emphasise but about which there probably is no scientific evidence that supports it. In general, these cases are related to an aspect of the treatment that is considered to be good clinical practice and that nobody would normally question. These aspects are assessed as points of good clinical practice. These messages are not an alternative to the recommendations based on scientific evidence, but rather they must be considered only when there is no other way to highlight that aspect.

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Appendix 2. List of abbreviations

AGREE: Appraisal of Guidelines Research and Evaluation
AHRQ: Agency for Healthcare Research and Quality
BDI: Beck Depression Inventory
BZD: benzodiazepine
CBT: cognitive behavioural therapy
CPG: clinical practice guideline
ECT: electroconvulsive therapy
HAM-D 17: Hamilton depression rating scale
IPT: interpersonal therapy
MADRS: Montgomery-Asberg depression rating scale
MAOI monoamine oxidase inhibitor
MD: major depression
MSC: Ministry of Health and Consumer Affairs
NICE: National Institute for Clinical Excellence
NNT: number-needed-to-treat
NPV: negative predictive value
PPV: positive predictive value
RCT: randomised clinical trial
SADS: Schedule for Affective Disorders and Schizophrenia
SIGN: Scottish Intercollegiate Guidelines Network
SNS: National Health System
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
WHO: World Health Organization

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Appendix 3. Glossary

- ***Beck Depression Inventory* (BDI):** a self-evaluation scale that fundamentally assesses the clinical symptoms of melancholia and intrusive thoughts present in depression.

- **Chronic depression:** major depression in which diagnostic criteria are met for two or more years.

- **Electroconvulsive therapy**: a technique that consists of inducing, for a therapeutic purpose, generalised seizure activity through electrical stimulation of the central nervous system.

- **Full remission:** period of time in which the patient is asymptomatic, thereby taking into account that it does not mean the total absence of symptoms. HAM-D 17 below 7, BDI below 8 and a duration of less than 6 months are used as operational diagnostic criteria.

- **Guided self-help**: it uses self-help materials in conjunction with minimum guidance offered by a professional in order to monitor progress, clarify procedures, respond to general questions or provide general support or stimulus.

- ***Hamilton Rating Scale for Depression* (HAM-D):** an observer-rated scale designed to measure the intensity or severity of depression. It is one of the most-used scales for monitoring the evolution of symptoms in clinical practice and in research.

- **Major depression:** a syndrome or group of symptoms where there is a predominance of affective symptoms (pathological sadness, lassitude, irritability, subjective feeling of distress and impotence in the face of life's demands) although, to a greater or lesser extent, symptoms of a cognitive, volitional or even somatic type are present, wherefore we could also talk about an overall impairment of the psychic life, with special emphasis on the affective sphere.

- ***Mesh*:** also called *Medical Subject Heading*, it is the controlled vocabulary that is used by Medline and other biomedical databases for processing the information that is entered in each database. It consists of over 33,000 terms ordered by hierarchical structures called trees, which are reviewed annually to assure that they constitute a true reflection of current medical practice and terminology.

- ***Mindfulness*:** a variation of cognitive behavioural therapy that prioritises attention to experience. It attempts to get depressed persons to be aware of their negative thoughts but without rejecting them. With this approach, it is hypothesised that a person will feel differently about their negative thoughts without focussing on changing the content of the same.

- ***Montgomery-Asberg Depression Rating Scale* (MADRS):** an observer-rated scale that consists of 10 items that evaluate the symptoms and severity of depression, obtained based on the *Comprehensive Psychopathological Rating Scale*. The scale must be administered by a clinician, and there are self-applied versions.

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- **Mutual support group:** a group specifically created to help its members face a critical life situation, such as chronically mental ill persons, and to inform, guideline and support relatives, thereby offering resources for supporting the anxiety and bearing the prejudices linked to the ignorance of certain illnesses. These groups work autonomously and arise in society when formal healthcare organisations do not satisfy certain needs.

- **Partial remission:** a period in which considerable improvement is observed, but in which the presence of somewhat more than minimum symptoms persist.

- **Recovery:** remission above a certain period of time in which a patient is asymptomatic and only has one or two mild symptoms. The term is usually used to designate recovery of the episode and not of the illness.

- **Recurrence:** the appearance of a new episode in a recovered patient.

- **Relapse:** worsening of an apparently controlled episode, until diagnostic level criteria are reached again, which occurs during remission and before recovery.

- **Resistant depression:** NICE defines it as depression whose symptoms remain after two or more treatment trials with antidepressants, and it considers those patients who do not respond to a single treatment trial to be non-responders in acute treatment[21]. Following more restrictive criteria, other authors define resistant depression as the failure to reach remission after a suitable treatment trial with three different classes of antidepressants in suitable doses and time.

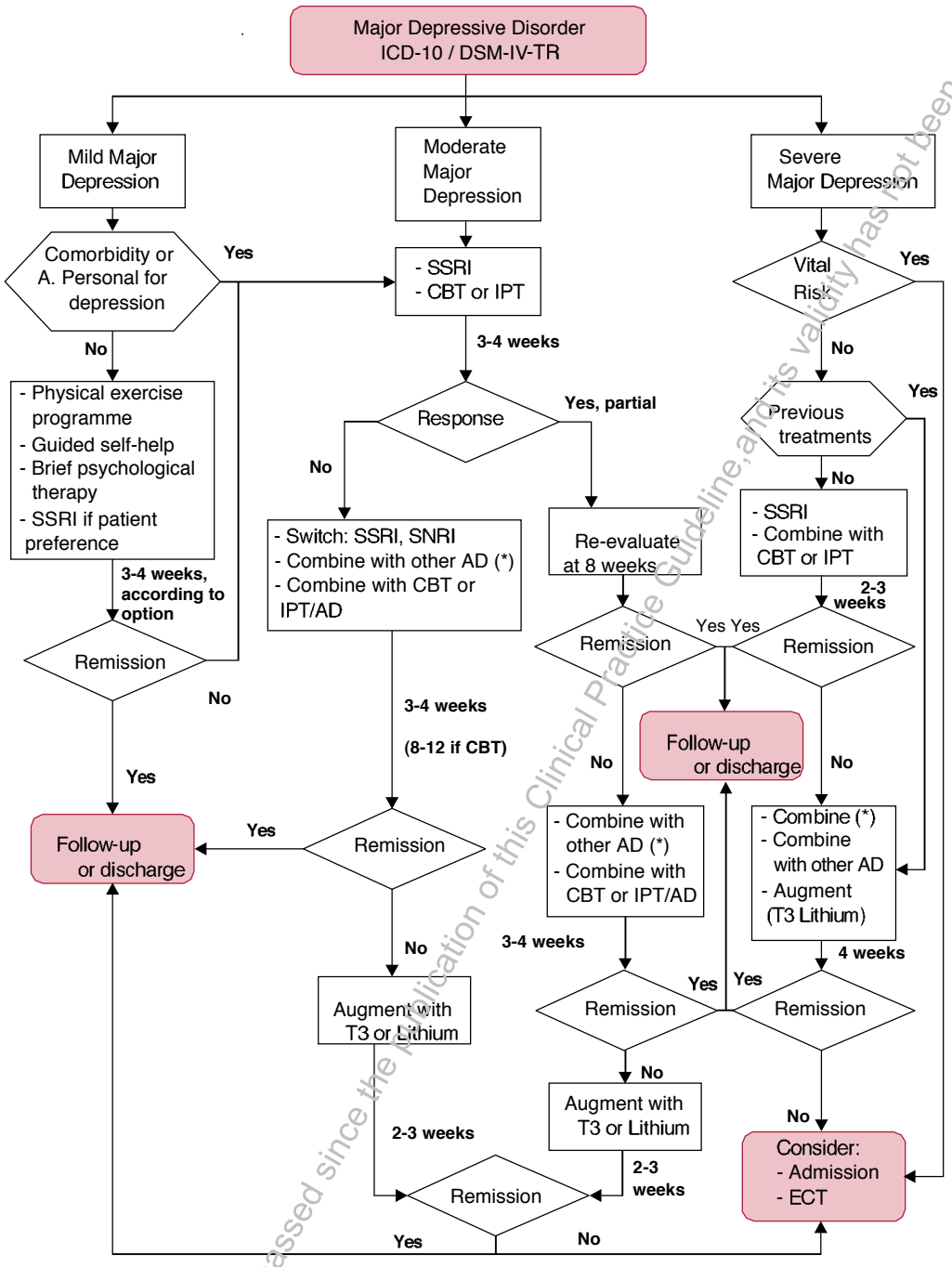
- **Response to treatment:** a decrease of 50% or more in the baseline score of the depression, measured by standardised depression scales. If the reduction is between 25 and 49% of the initial score, this would be a partial response, and if it is less than 25%, no response.

- **Self-help:** training of patients on the pertinent skills for overcoming and managing their health problem. It includes the use of written materials, computer programmes or material recorded in audio/video.

- **Support groups**: they are usually created by a professional and consist of people who share some type of problem that alters or modifies aspects of their normal functioning. Occasionally, these groups can be guided by paraprofessionals who are trained or supervised by professionals who are defined as mental health workers, paid or volunteers, without training regarding psychological treatment for anxiety and depression, and who substitute professionals in treating patients with these disorders.

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Appendix 4. Therapeutic algorithm



(*) Greater evidence with mianserin or mirtazapine
CBT= Cognitive behavioural therapy
IPT = Interpersonal therapy
SSRI = selective serotonin reuptake inhibitor
SNRI = serotonin and norepinephrine reuptake inhibitors

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Appendix 5. Information for patients

Depression

Information for patients, family and interested people.

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CONTENTS

Introduction

What is depression?

What causes depression?

Types of depression

What can I do if I think that I have depression?

What can the health system offer me if I have depression?

How is depression treated?

How can I help someone with depression?

More information

This brochure has been prepared using knowledge based on the scientific information available at the time of publication.

INTRODUCTION

This brochure is designed for people who want to know what depression is and what to do about it.

Depression is one of the most frequent mental disorders. It is estimated that it affects one out of every six Spaniards at some point in their life.

If you think that you or someone you know has depression, take it seriously and seek help.

This brochure provides you with information and useful help. The guideline focuses on depression (major depressive disorder) in adults, and it encompasses mild, moderate and severe depression.

However, this information does not consider specific depressive disorders in certain populations or other mental disorders with depressive symptoms, such as the following:

~ Depression in children.

~ People with major depression that have an additional physical or mental disorder.

~ Dysthymic disorder or dysthymia (a less severe although persistent form of depression that often starts early in life and that can be present simultaneously with a major depressive disorder).

~ Bipolar disorder (an affective disorder that involves extreme changes in mood. The states of high emotion and overwhelming energy are called mania, and the periods of low moods have the same symptoms as major depression).

~ Adaptive disorder with a depressive mood state (a type of pathological reaction to stress that is less severe than the major depressive disorder).

The information that follows does not attempt to explain depression in depth. If you have doubts or would like more information, you can ask your physician or other professional of the health team.

WHAT IS DEPRESSION?

Depression is much more than being down.

Although most of us experience sadness once in a while, for some people these symptoms do not disappear, and they are accompanied by other symptoms that cause distress or difficulties for taking on their daily life. These people may have a disorder called depression.

What are the symptoms of depression?

~ The symptoms of depression can vary from one person to the next. The fundamental symptoms are:

~ Low mood, sadness or feelings of despair, or

~ Loss of interest in the activities that they used to enjoy, or getting scarce pleasure out of doing them most days in recent weeks.

~ Other possible symptoms that are present with certain frequency are the following:

~ Irritability (getting angry easily).

~ Feeling like crying for no apparent reason.

~ Loss of energy or tiredness.

~ Sleep problems.

~ Changes in appetite, which sometimes lead to weight changes.

~ Difficulty at concentrating or memory problems.

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~ Loss of sexual interest.

~ Feelings of uselessness or guilt.

~ Negative thoughts, excessive self-criticism.

~ Desire to die or suicidal ideas.

Often, people with depression also experience constant worrying, which leads to anxiety. This can cause physical symptoms such as pain, heart palpitations or abdominal complaints. In some people, these physical symptoms are their main complaint, and sometimes they eventually feel so bad that they would rather be dead.

Depression can make the smallest task seem like climbing a mountain.

WHAT CAUSES DEPRESSION?

Different events can act like triggers of depression in different people. Sometimes, depression appears with no apparent cause.

Some circumstances that increase the risk of depression are the following:

~ Having suffered a depressive episode in the past.

~ History of depressed persons in the family.

~ Experiences of loss or stress, including the death of loved ones, unemployment, loneliness, changes in lifestyle or problems in interpersonal relationships.

~ Conflictive situations in their environment (for example, at work, at home or in other contexts).

~ Having suffered physical or psychological traumas.

~ Serious physical illness or chronic health problems.

~ Some medicines (this can be consulted with your physician).

~ Alcohol abuse or consuming other drugs can worsen depression.

~ Some women can be more vulnerable to depression after childbirth, especially if any of the aforementioned risk factors are present.

~ Positive experiences such a close relationship with a partner, friend, family or colleagues usually help to prevent depression.

TYPES OF DEPRESSION

Some people have an episode of major depression only once in their life. However, about half of the people who have had one episode of depression have at least one more. The duration of the depressive episode is variable, although most feel better after 4 to 6 months have elapsed. In some cases, the symptoms can persist for a much longer period of time (depression that lasts 2 years or more is called chronic depression).

The severity of depression various enormously.

Some people only have a few symptoms that partially affect their daily life or limit it in some specific aspect. This is called mild depression. Other people can have many more symptoms that eventually cause a impairment or generalised disability; in this case, the depression is qualified as moderate or severe.

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WHAT CAN I DO IF I THINK I HAVE DEPRESSION?

If you think that you may be depressed, ask for help as soon as possible.

There's no reason why you have to face depression alone. You can do any of the following things:

- ~ Talk with someone you trust about your feelings. For example, someone from your family, your partner, a friend or any other person you can think of.
- ~ Talk with your physician or other healthcare professional. You will thus be able to receive a suitable diagnosis, learn about the treatment options and participate in the decision-making in this regard.
- ~ If you have thoughts about hurting yourself, it is a good idea to talk with someone you trust who can be with you until you feel better. You can also call the emergency telephone number (061, 112), seek medical help at the nearest location or request specific telephone support for patients with suicidal ideas (consult the additional information section).
- ~ Contact a support group. Certain NGOs and associations have this support service in some cities.
- ~ Learn more about depression so that you can better understand your symptoms and their meaning.

If you talk with someone and feel that they don't understand you, speak with somebody else.

It may also be beneficial for you to improve your overall health through daily physical exercise and a healthy diet. Some forms of self-help are described on the following pages. It can be very hard to make some of these changes when you are depressed, so turn to friends and family to get their support.

Don't think that it's simply a question of getting tough, and don't resort to alcohol or drugs; these things don't help.

WHAT CAN THE HEALTHCARE SYSTEM OFFER ME IF I HAVE DEPRESSION?

Information and support

If you have depression, healthcare professionals can provide you with information and support. This information refers to the nature, course and possibilities of treatment, as well as information regarding community and self-help resources.

Given the existence of different therapeutic options, it is a good idea to have sufficient information about the illness and the proposed treatment before starting it. It is important for you to feel involved in any decision and for you to perceive that the healthcare professional who takes care of you keeps your preferences in mind.

In general, professionals will use language that you can understand, and they will avoid medical jargon as much as possible. If you don't understand something, it is preferable to ask than to have any doubts.

Confidentiality

Appointments between a patient with depression and healthcare professionals are governed by rules that protect confidentiality.

Your primary care physician (PCP)

Your PCP is probably the first person in the healthcare service who you can contact due to your depression. Most people with depression can be taken care of effectively by their PCP. They will ask you questions about your feelings, thoughts, behaviour, recent changes in your life or physical

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health and about a family history of mental disorders, among other things. It is important that you be as open as possible about the things that you consider important in order to understand what is happening to you. As we have already seen, due to the fact that depression has different causes and different symptoms, every person with depression receives personalised treatment.

Specialised mental health services

Your PCP may think that you need care from a mental health specialist, especially if your depression is severe, it does not respond to treatment or in cases of repeated episodes. Only very occasionally are people with depression hospitalised.

HOW IS DEPRESSION TREATED?

There are several treatments that can help you and that have proven efficacy in depression. They include the following:

~ Self-help techniques.

~ Psychological therapies.

~ Pharmacological therapy.

Mild depression can improve on its own without treatment or with advising on how to face problems. Self-help and psychological therapies are effective. Psychological therapies include counselling and other specific therapies for depression. Antidepressant drugs also help in some cases.

Some people use alternative or complementary procedures, such as acupuncture, yoga, massage or certain food supplements, although there is no solid evidence that allows them to be recommended. St John's Wort is an herbal therapy that could be useful, but it can cause serious interactions with a wide range of medicines that are frequently used, such as oral contraceptives, anticoagulants and anticonvulsants. Consult your physician, given that using it is not harmless.

For moderate depression, psychological therapies and antidepressants work equally well.

For severe depression, the most recommendable treatment is drugs in combination with psychological therapy. In a few cases, electroconvulsive therapy (ECT) or electroshock therapy is recommended, which, despite its bad reputation, is safe, quick and effective treatment that is administered at a hospital under general anaesthesia.

Keep in mind that there are health professionals who are experts and assessing and treating depression and who can help you. The most adequate treatment depends on each specific case and on your preferences. The main thing is to use a treatment that works and to give it the necessary time for that to happen. Keep in touch with your primary care physician, especially if the treatment doesn't seem to help you improve. The first treatment proposed does not always produce the expected results.

Self-help techniques

Day planning

When someone experiences feelings of sadness or depression, it can be truly difficult to get going to do anything. Nevertheless, the more active you are, the greater the likelihood that you will feel better.

The following advice is usually useful:

~ You can make a list of the activities that you propose to do every day (with the help of someone, if necessary).

~ Keep this list handy.

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~ At the beginning, don't be very demanding with yourself.

~ It is important to do some gratifying activity at least once a day.

~ Plan on doing some physical activity every day.

~ If miss some point in your plan, jump to the next activity.

~ If you don't feel like doing anything at all, plan on doing some activity with other people.

~ Observe how your mood changes as you progress, and share this fact with others.

Stress management

~ If problems seem so suffocate your, think about one at a time.

~ Enjoy the small things, and get time for yourself.

~ Learn to recognise when you need to stop, we all have a limit. Don't be too harsh on yourself.

Physical activity

~ Increase your physical activity, and get fresh air and natural light every day.

~ A regular routine of vigorous exercise is ideal, but any physical activity is better than none.

~ It's possible that a group activity may make it easier to meet this objective.

~ If you have doubts about the most appropriate physical exercise for you, check with your doctor.

Sleep problems

~ Keep a routine for your sleep times.

~ Do something relaxing before going to bed.

~ Avoid naps or sleeping during the day; they can aggravate the problem.

~ Avoid or reduce stimulants (coffee, energy drinks or drinks with cola, tobacco or alcohol, especially after nightfall).

~ If you can't sleep, get up and go to another room (you can watch television or read) until you feel sleepy. Don't stay in bed worrying about your sleep difficulties.

~ Don't fall asleep on the sofa.

Abuse of alcohol and other drugs

~ Alcohol abuse or consuming other drugs can make your depression get worse and cause other problems.

~ Ask for help from your friends, family or your doctor for decreasing consumption or reaching abstinence.

~ There are healthcare aids specialised in treating these problems, if you need them.

Psychological therapies

In the healthcare system, treatments that have been specifically designed for people with depression may be proposed, such as cognitive behavioural therapy, interpersonal therapy and couples therapy. Research has demonstrated that these therapies are effective and can help to reduce the appearance of new episodes in the future (recurrence).

Cognitive behavioural therapy focuses on modifying negative thinking styles and behaviour that contribute to triggering and maintaining depression. People with moderate or severe depression normally receive 16 to 20 cognitive behavioural therapy sessions over several months (although it can last longer or shorter, depending on individual circumstances or needs).

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Interpersonal therapy helps people with depression to identify and manage specific problems in relationships with family, friends, colleagues and other people. If your depressive symptoms do not improve with individual psychological therapy, and you have a partner, **couples therapy** might be suggested, in which you both participate.

These therapies are provided by professionals who are trained on these techniques and who are experts at using them, normally clinical psychologists or psychiatrists.

Pharmacological therapy

The main drugs used in treating depression are called antidepressants. These medicines work by increasing the activity and levels of certain substances in the brain, called neurotransmitters, which help to improve your mood. There are several different classes of antidepressants.

If you have sufficient information about antidepressants, your preferences can be taken into account. Your doctor can also assess the outcomes and your experience with any previous treatment.

It is important to know that antidepressants do not cause an addiction or the need to take more medication in order to feel the same effects with the passage of time.

Most treatments need some time before there are any results

Before a person begins taking antidepressants, he must keep in mind that the medication needs a certain amount of time to work (several weeks are normally needed in order to experience any improvement and to determine if a drug is useful). Therefore, you must continue to take the medication as it has been prescribed for you, even if at the beginning you doubt its benefits.

Your physician can inform you about the side effects that can be expected from your medication. Most are tolerable by almost everyone. Even though antidepressants do not cause an addiction, certain symptoms can be experienced when they are withdrawn. These symptoms can consist of dizziness, nausea, anxiety and headaches. They normally have a mild intensity, although the intensity can sometimes be greater, above all if the medication is interrupted abruptly.

The time period during which treatment is received with antidepressants varies from one person to the next. Normally, it is recommended that medication be maintained for a minimum of 6 months at the same dose at which you reached improvement. In some cases, your doctor may advise you to modify the dose or switch the type of antidepressant.

Remember: if an antidepressive drug has been prescribed for you, your doctor can explain:

- **~ About the symptoms that it acts on**
- **~ How long it will take to act**
- **~ How long you will need to take it**
- **~ What are its possible side effects**

HOW CAN I HELP SOMEONE WITH DEPRESSION?

It can be very hard to see that a loved one is depressed. It wouldn't be strange for you to feel very overwhelmed, disoriented or embarrassed about what is happening.

The family, partner and intimate friends of people with depression have found the following strategies to be useful:

- ~ Learn about depression, its treatment and what you can do to help their recovery.
- ~ Consider yourself part of the support and treatment team.
- ~ Don't think that the person with depression does not want to improve, even though at times it may seem so. Try to see the symptoms for what they are: part of a disorder.

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~ Help them to recognise the sources of stress and to find the most suitable way to face it. Your cooperation might be necessary to solve some of the problems that especially worry your family member or friend.

~ Encourage them to be more active, but without overdoing it and without criticising or reprimanding, given that that can make things worse.

~ Help them to lead a healthy life, to do some physical exercise and to have fun.

~ Dedicate part of your time to being with him or her.

~ Praise each one of their advances, especially at the beginning and for however small they may be.

~ Encourage them to maintain the prescribed treatment and to avoid alcohol and other toxic substances.

~ From the outset, take any suicidal though seriously. Don't be afraid about talking with them about this subject openly. If your family member feels insecure about hurting themselves, stay with him or her. You can contact healthcare personnel or use the emergency service telephone number (061, 112).

If you are caring for someone with severe depression, it is essential to find time for yourself without feeling bad or guilty. Living with a family member who has depression can wear you down, and it is therefore important to take care of yourself as best as possible and to stay well psychologically.

MORE INFORMATION

~ Emergency telephone numbers ……. 061 or 112.

~ Confederación Española de Agrupaciones de Familiares y Personas con enfermedad mental (they offer information and support for family members and patients, and they also have some psychosocial resources): www.feafes.com.

~ "Hope" telephone number (they have a 24-hour crisis phone number in the main Spanish cities): www.telefonodelaesperanza. org.

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Appendix 6. Conflict of interests

Coordinator and members of the development group

Arturo Louro González, Mª Consuelo Carballal Balsa, Mª Jesús Purriños Hermida and Victor Torrado Oubiña declared no conflict of interests.

María Alvarez Ariza declared having received financing for meetings, conferences or attending courses (Astra Zéneca, Glaxo, Lilly and Pfizer), financing for educational programmes or courses on behalf of Janssen and financial aid for participating in research (Lilly, Janssen).

Emilio Casariego Vales declared having received financing for meetings, conferences or attending courses (Pfizer, Novartis, Sanofi, Wyeth and Almirall), professional fees as a speaker on behalf of Lilly, financing for educational programmes or Service courses on behalf of Glaxo and financial aid for creating a monographic clinic of the Service on behalf of Novartis, Lacer and Almirall.

Ernesto Ferrer Gómez del Valle declared having received financing for meetings, conferences or attending courses (Astra Zéneca, Esteve, Wyeth and Janssen), professional fees as a speaker on behalf of Lilly, financing for educational programmes or courses on behalf of Pfizer, financial aid for participating in research on behalf of Lilly and having participated as a consultant for a pharmaceutical company (Lilly).

Elena de las Heras Liñero declared having received financing for meetings, conferences or attending courses (Bristol, Lilly, Wyeth and Janssen) and professional fees as a speaker on behalf of Bristol.

Jose Luis Rodríguez-Arias Palomo declared having received professional fees as a speaker on behalf of Merck.

Marta Velasco González declared having received financing for meetings, conferences or attending courses (Altana Farma and Esteve).

External Reviewer Group

José Álvarez Sabín, Mª Jesús Cerecedo Pérez, Rudesindo Couto Nogueira, Alberto Fernández Liria, Montserrat García González, Ana García Laborda, Mª Jesús Gayoso Orol, Antonio Gil Núñez, Fernando Isidro Lago Deibe, Germán López Cortacans, Beatriz Pombo Vide, Alejandro Rodríguez González and Carmelo Vázquez Valverde declared no conflict of interests.

María Fe Bravo Ortiz declared having received financing for meetings, conferences or attending courses (Bristol Mayer, Lilly, Janssen, Almirall and GSK), has performed advising work for Astra Zeneca and Janssen-Cilag, has received financial aid for financing research on behalf of Lumbedk and Janssen and has received financing for educational programmes or courses on behalf of Janssen.

Diego Palao Vidal declared having received financing for meetings, conferences or attending courses (Lilly, Almirall and Pfizer), has received professional fees as a speaker on behalf of Wyeth Farma and GSK and has received financial aid for financing research on behalf of Lilly and Servier.

Finally, Mario Páramo Fernández declared having received financing for meetings, conferences or attending courses (Almirall, Astra-Zéneca, Bristol MS-Otsuka, Boehringer, Esteve, GKS, Janssen, Juste, Lilly, Lundbeck, Pfizer, Sanofi-Aventis and Wyeth) and has received professional fees as a speaker on behalf of AGP, SEP, FEGAS, USC, Almirall, Astra-Zéneca, Bristol MS-Otsuka, Boehringer, GSK, Janssen, Lilly, Lundbeck, Pfizer and Sanofi-Aventis.

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Appendix 7. Diagnostic criteria according to DSM-IV-TR

Major Depressive Disorder Diagnostic Criteria according to DSM-IV-TR

A	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is (1) depressed mood or (2) loss of interest or pleasure. (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. (3) Significant weight loss when not dieting or significant gain, or decrease or increase in appetite nearly every day. (4) Insomnia or hypersomnia nearly every day. (5) Psychomotor agitation or retardation nearly every day. (6) Fatigue or loss of energy nearly every day. (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.
B	The symptoms do not meet the criteria for a mixed episode
C	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
D	The symptoms are not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication), or a general medical condition (for example, hyperthyroidism).
E	The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation.
Source: American Psychiatric Association. DSM-IV-TR. Diagnostic and statistical manual of mental disorders, 4th ed. Barcelona: Masson 2003.	

DSM-IV-TR criteria for severity/psychotic/remission specifiers for current (or most recent) major depressive episode

Note: Coding in the fifth digit. Mild, moderate, severe without psychotic features and severe with psychotic features can be applied only if the major depressive episode criteria are currently met. In partial remission and in complete remission, they can be applied to the most recent major depressive episode of the major depressive disorder and to a major depressive episode of bipolar I or II disorder only if it is the most recent type of mood episode.
Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in only minor impairment of occupational functioning or in the usual social activities or relationships with others.
Moderate: Symptoms or functional impairment between “mild” and “severe”.

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Severe without psychotic features: Several symptoms in excess of those required to make the diagnosis, and symptoms that markedly interfere with occupational functioning or the usual social activities or relationships with others.

Severe with psychotic features: Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent.

a) **Mood-congruent psychotic features**: Delusions or hallucinations whose content is entirely consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism or deserved punishment.

b) **Mood-incongruent psychotic features**: Delusions or hallucinations whose content does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism or deserved punishment. Included are such symptoms as persecutory delusions (not directly related to depressive themes), thought insertion, thought broadcasting and delusions of control.

In partial remission: There are symptoms of a major depressive episode, but the full criteria are not met, or there is a period without any significant symptoms of a major depressive episode lasting less than 2 months following the end of the major depressive episode. (If the major depressive episode was superimposed on dysthymic disorder, the diagnosis of dysthymic disorder alone is given once the full criteria for a major depressive disorder are no longer met.)

In full remission: During the past 2 months, no significant signs or symptoms of the disturbance were present.
Unspecified.

Source: American Psychiatric Association. DSM-IV-TR. Diagnostic and statistical manual of mental disorders, 4th ed. Barcelona: Masson 2003.

DSM-IV-TR diagnostic criteria for major depressive disorder, single episode

A. A single major depressive episode.

B. The major depressive episode is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder or psychotic disorder not otherwise specified.

C. There has never been a manic episode, a mixed episode or a hypomanic episode. Note: This exclusion does not apply if all the manic-like, mixed-like or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

If the full criteria are currently met for a major depressive episode, specify its current clinical status and/or features:

- Mild, moderate, severe without psychotic features/severe with psychotic features.
- Chronic
- With catatonic features
- With melancholic features
- With atypical features
- With postpartum onset

If the full criteria are not currently met for a major depressive episode, specify the current clinical status of the major depressive disorder or features of the most recent episode:

- In partial remission, in full remission
- Chronic
- With catatonic features
- With melancholic features
- With atypical features
- With postpartum onset

Source: American Psychiatric Association. DSM-IV-TR. Diagnostic and statistical manual of mental disorders, 4th ed. Barcelona: Masson 2003.

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DSM-IV-TR diagnostic criteria for major depressive disorder, recurrent

A. Two or more major depressive episodes. Note: to be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a major depressive episode.
B. The major depressive episodes are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder or psychotic disorder not otherwise specified.
C. There has never been a manic episode, a mixed episode or a hypomanic episode. Note: This exclusion does not apply if all the manic-like, mixed-like or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.
If the full criteria are currently met for a major depressive episode, specify its current clinical status and/or features: ~ Mild, moderate, severe without psychotic features/severe with psychotic features. ~ Chronic ~ With catatonic features ~ With melancholic features ~ With atypical features ~ With postpartum onset
If the full criteria are not currently met for a major depressive episode, specify the current clinical status of the major depressive disorder or features of the most recent episode: ~ In partial remission, in full remission ~ Chronic ~ With catatonic features ~ With melancholic features ~ With atypical features ~ With postpartum onset
Specify: ~ Longitudinal course specifiers (with and without interepisode recovery) ~ With seasonal pattern.
Source: American Psychiatric Association. DSM-IV-TR. Diagnostic and statistical manual of mental disorders, 4th ed. Barcelona: Masson 2003.

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Appendix 8. Appraisal of clinical practice guidelines for depression using the AGREE instrument

The AGREE Instrument[20] was developed for the purpose of establishing a common methodology that promoted the rigorous development of CPGs and the appraisal of quality and impact on the practice of guidelines. It consists of 23 items organised in six domains:

- ~ domain 1 (items 1-3): scope and purpose of the guideline
- ~ domain 2 (items 4-7): stakeholder involvement
- ~ domain 3 (items 8-14): rigour of development
- ~ domain 4 (items 15-18): clarity and presentation
- ~ domain 5 (items 19-21): applicability
- ~ domain 6 (items 22-23): editorial independence.

Each item is rated according to a scale that measures the intensity with which a criterion has been met. The instructions for use of the AGREE instrument recommend that the ideal number of appraisers is four in order to increase the reliability of the assessment. The scores of the different domains can be calculated by adding all the points of the individual items of a domain and standardising the total, as a percentage, over the maximum score. The scores of the six domains are independent and must not be aggregated into a single quality score.

A guideline is considered to be "strongly recommended" when it scores high (3 or 4) in most items (over 60%), which indicates that it has high general quality and that it could be considered for use in practice without modifications.

Recommended (with provisos or alterations) is a guideline that scores high (3 or 4) or low (1 or 2) in a similar number of items, and most of the scores of the domains are between 30% and 60%. This indicates that the guideline has moderate overall quality. It is considered that, by introducing some alterations (as long as the information about the development method is well described), the guideline could be considered for use, especially when there are no others available on the same clinical content.

"Would not recommend" is a guideline that scores low (1 or 2) in most of the items, and most of the scores of the domains are below 30%. This translates into a low overall quality of the guideline and involves serious deficiencies, wherefore its use in practice would not be recommended.

METHODOLOGY

1. Bibliographical search

In May 2005, a bibliographic search was carried out on the web pages of the main international bodies that develop/compile clinical practice guidelines, as well as on governmental pages and pages of scientific societies related to the subject. This search was updated in October 2006.

2. Selection criteria

From among the compiled documents, the depression CPGs based on scientific information or on the consensus of experts published between the year 2000 and September 2006 were selected. Those CPGs that only discussed the management of depression in specific groups were not included (for example, postpartum depression, depression in the elderly, etc.), nor adaptations of other, existing guidelines. If updates of previous guidelines were found, the latest versions were selected.

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3. Review

The guidelines obtained in the preceding section were appraised by four technicians of avaliat using the AGREE Instrument. The process was carried out independently.

4. Scoring of the guidelines

The results of the individual appraisals were loaded in a spread sheet for the purpose of obtaining the final scores.

5. Appraisal of the guidelines

It was established by consensus among the appraisers, always following the recommendations of the AGREE Instrument[20].

RESULTS

The bibliographic search yielded 15 clinical practice guidelines. The complete text could not be obtained for one of them[168]. Moreover, one document published in 2005[169] summarised the most important novelties recorded in biomedical literature on treating patients with depression as from the publication of the second edition of the APA guideline[170] in 2000, although it has not been included in this work because it does not contain recommendations and is not an update of the guideline per se.

In June 2005, the *Royal Australian and New Zealand College of Psychiatrists* published an update of the manual for consumers and carers[171] of the guideline published in 2004 and identified in this work as RANZCP[92], although the CPG has not been updated up to now.

The overall assessment of most of the guidelines would be "recommended with alterations", given that the score of most of the domains is between 30% and 60%. According to the AGREE Instrument, after the pertinent modifications these guidelines could be considered for use in practice, as long as there are no other guidelines available on the same condition.

In this case, there is a high quality guideline, the one developed by NICE. Its assessment according to the AGREE Instrument is "strongly recommended", given that in all domains it obtains a score above 60%.

A noteworthy aspect of the NICE guideline is that the authors used the AGREE Instrument as a tool for developing the same. The guideline offers recommendations for identifying, treating and managing depression in people over 18 years of age, in both primary care and specialised care.

CONCLUSIONS

The guideline developed by NICE is a guideline with a high score in most of the criteria of the AGREE Instrument. This indicates that it has a high overall quality, wherefore it could be considered for use in practice without conditions or alterations. However, as the AGREE Instruments recognises, "the clinical content of the recommendations applied in the local context and their impact on the outcomes of patients must be also taken into consideration to reach an overall judgement about the usefulness of the guideline".

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Appendix 9. Instruments for assessing depression

In depressive orders is frequent to use scales as instruments for measuring the severity of the depression and its response to treatment. Their objective is the symptomatic assessment of the patient within a certain time frame, thereby allowing each item to be rated and obtaining a final score. They have no diagnostic aim, which should be done based on the psychopathological information obtained in the clinical interview.

Observer-evaluated scales are those in which an evaluator asks about each one of the items and assesses them. They should be filled out after the clinical interview, and they require high levels of training and experience. The self-assessment scales or questionnaires can be read by the interviewer or by the patient himself, but it is the latter who chooses which of the items best reflects his state.

The scales used the most in research studies are the following:

~ Beck Depression Inventory[172]

~ Hamilton Rating Scale for Depression[173]

~ Montgomery-Asberg Depression Rating Scale[174]

Beck Depression Inventory (BDI)

It is a self-evaluation scale that fundamentally assesses the clinical symptoms of melancholia and the intrusive thoughts present in depression. It is the one that shows the greatest percentage of cognitive symptoms, and the absence of motor symptoms and of anxiety should also be noted. It is usually used to assess the severity of the illness. The original version from 1961 consists of 21 items[172], and two revisions were subsequently published, the BDI-IA[116] in 1979 and the BDI-II in 1996[175]. This scale was adapted and validated in Spanish in 1975[176].

The original version is based on the patient's descriptions about various items: mood, pessimism, feeling of failure, dissatisfaction, guilt, irritability, suicidal ideas, weeping, social isolation, indecision, changes in the physical look, difficulty on the job, insomnia, fatigability, loss of appetite, weight loss, somatic concern and loss of libido. In version II, the assessment of the physical appearance, weight loss, somatic concern and difficulty on the job were replaced by agitation, difficulty at concentrating, loss of energy and feelings of uselessness[175]. In most clinical trials included in the NICE guideline, the first version is used.

Each item is assessed from 0 to 3, and the total score is 63 points. There is no consensus about the cut-off points, wherefore different cut-off points and intervals are used to define levels of severity. The cut-off points recommended by the American Psychiatric Association are the following[177]:

	Absent or minimal	Mild	Moderate	Severe
APA 2000	0-9	10-16	17-29	30-36
13-item version	0-4	5-7	8-15	> 15

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Hamilton Rating Scale for Depression (HAM-D)

The HAM-D or Hamilton Rating Scale for Depression is an observer-rated scale designed to measure the intensity or severity of depression, and it is one of the most-used for monitoring the evolution of the symptoms in both clinical practice and research. The time frame of the assessment corresponds to the time when it is applied, except for some items, such as those pertaining to sleep, which refer to 2 days prior.

The original version is formed by 21 items and was published in 1960[173]. There is a reduced version of 17 items of the same author[178], another version of 24 items[179] and a 6-item version consisting of depressed mood, feelings of guilt, work and activities, inhibition, psychic anxiety and somatic symptoms taken from the 17-item[180] version. The Spanish version of the scale was validated in 1986[181], and a comparative psychometric assessment of the 6-, 17- and 21-item versions[182] was subsequently performed.

The items included depressed mood; feelings of guild; suicide; early, middle and late insomnia; work and activities; inhibition; agitation; psychic anxiety and somatic anxiety; gastrointestinal somatic symptoms; general somatic symptoms; sexual symptoms (sexual dysfunction and alterations of menstruation); hypochondria; weight loss and ability to understand. The additional items in the 21-item version are diurnal variation, depersonalisation and derealization, paranoid symptoms and obsessive-compulsive symptoms.

This scale is difficult to administer to the physically ill due to the excessive weight of the anxiety symptoms and somatic symptoms. It provides an overall severity score of the depressive symptoms and a score in 3 factors or indices: melancholia, anxiety and sleep. The scores in each one of the indices are obtained by totalling the scores of the component items: melancholia (items 1, 2, 7, 8, 10 and 13), anxiety (items 9-11) and sleep (items 4-6). There are no cut-off points defined for the scores in these indices. The overall score is obtained by totalling the scores of each item, with a score range in the 17-item scale that goes from 0 to 54 in the Spanish version. The cut-off points for defining the severity levels of depression recommended by the American Psychiatric Association[177] are the following:

	No depression	Mild/minor	Moderate	Severe	Very severe
APA, 2000	0-7	8-13	14-18	19-22	>23

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Hamilton Rating Scale for Depression (validated by Ramos-Brieva and assoc.[181])

Items	Operational assessment criteria
1. Depressed mood (sadness, hopeless, helpless, worthless)	0. Absent 1. These feeling states are indicated only on questioning. 2. These feeling states spontaneously reported verbally. 3. Communicates feeling states communicated non-verbally, i.e. through facial expression, posture, voice and tendency to weep. 4. Patient reports these feeling states in his/her spontaneous verbal and non-verbal communication.
2. Feelings of guilt	0. Absent 1. Self-reproach, feels he/she has let people down. 2. Ideas of guilt or rumination over past errors or sinful deeds. 3. Present illness is a punishment. Delusions of guilt. 4. Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.
3. Suicide	0. Absent 1. Feels life is not worth living. 2. Wishes he/she were dead or any thoughts of possible death to self. 3. Suicidal ideas or gesture. 4. Attempts at suicide (any serious attempt, rate 4).
4. Insomnia early in the night	0. Absent 1. Complains of occasional difficulty falling asleep, i.e. more than _ hour. 2. Complains of nightly difficulty falling asleep.
5. Insomnia in the middle of the night	0. Absent 1. Patient complains of being restless during the night. 2. Waking during the night – any getting out of bed rates 2 (except for justified purpose: voiding, taking or giving medication, etc.).
6. Insomnia in the early hours of the morning	0. Absent 1. Waking in early hours of the morning but goes back to sleep. 2. Unable to fall asleep again if he/she gets out of bed.
7. Work and activities	0. Absent 1. Thoughts and feelings of incapacity. Fatigue or weakness related to activities, work or hobbies. 2. Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation. 3. Decrease in actual time spent in activities or decrease in productivity. 4. Stopped working because of present illness
8. Retardation (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)	0. Normal speech and thought. 1. Slight retardation during the interview. 2. Obvious retardation during the interview. 3. Interview difficult. 4. Complete stupor.
9. Agitation	0. None 1. Fidgetiness. 2. Playing with hands, biting nails/lips, pulling hair, etc.
10. Psychological anxiety	0. No difficulty. 1. Subjective tension and irritability. 2. Worrying about minor matters. 3. Apprehensive attitude apparent in face or speech. 4. Fears expressed without questioning.

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Items	Operational assessment criteria
11. Somatic anxiety	0. Absent 1. Mild. 2. Moderate. 3. Severe. 4. Incapacitating. Physiological concomitants of anxiety such as: ~ gastro-intestinal: dry mouth, wind, diarrhoea, belching, cramps. ~ Cardiovascular: palpitations, headaches. ~ Respiratory: hyperventilation, sighing. ~ Urinary frequency. ~ Sweating.
12. Gastrointestinal somatic symptoms	0. None. 1. Loss of appetite but eating without encouragement. Heavy feeling in abdomen. 2. Difficulty eating without being encouraged. Requests or requires laxatives or medication for gastrointestinal symptoms.
13. General somatic symptoms	0. None. 1. Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability. 2. Any clear-cut symptom rates 2.
14. Genital symptoms	0. Absent 1. Mild. 2. Severe. 3. Incapacitating. Symptoms such as: ~ Loss of libido. ~ Menstrual disturbances.
15. Hypochondriasis	0. Not present. 1. Self-absorption (bodily). 2. Preoccupation with health. 3. Frequent complaints, requests for help, etc. 4. Hypochondriacal delusions.
16. Loss of weight (Rate either A or B)	A. According to patient statements (first evaluation) 0. No weight loss. 1. Probable weight loss associated with present illness. 2. Definite weight loss (according to patient). B. According to weekly measurements by psychiatrist (subsequent evaluations) 0. Less than 500-g weight loss in one week. 1. Greater than 500-g weight loss in one week. 2. Greater than 1-kg weight loss in one week (on average).
17. Insight (awareness of illness)	0. Acknowledges being depressed and ill. 1. Acknowledges illness but attributes cause to bad food, climate, overwork, virus, etc. 2. Denies being ill at all.

Taken from: Ramos-Brieva J, Cordero Villafafila A. Validación de la versión castellana de la escala Hamilton para la depresión. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1986;14:324-34).

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For assessing the response to a treatment, a decrease of greater than or equal to 50% of the initial score of the scale has been defined as a response; a decrease of between 25 and 49% is a partial response; and a reduction of less than 25% is no response[183]. In clinical trials, the most-used inclusion criteria was a score of 18, and considering remission, a score of 7[184].

Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is an observer-rated scale published in 1979[174] that consists of 10 items that evaluate the symptoms and severity of depression, obtained based on the *Comprehensive Psychopathological Rating Scale*[185]. The scale must be administered by a clinician, and there are self-applied versions.

The items include apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. The score of each item varies between
0 and 6 points, and to assign the score, the clinician can use information from sources other than the patient. It has the advantage over the HAM-D in that it is not contaminated by items that evaluate anxiety, although it continues to maintain several somatic or vegetative items that make it difficult to administer to patients with predominantly physical symptomatology. The time frame of the assessment corresponds to the last week or to the last three days, and the Spanish versions were validated in 2002[186].

The overall score is obtained by totalling the score given to each one of the items, varying between 0 and 60. There are no cut-off points defined, but the recommended ones are the following[184]:

	No depression	Mild/minor	Moderate.	Severe.
Bobes, 2004	0-6	7-19	20-34	35-60

To assess the response to a treatment, as with the HAM-D, a decrease of greater than or equal to 50% of the initial score of the scale has been defined as a response; a decrease of between 25 and 49% is a partial response; and a reduction of less than 25% is no response. Values of 8-12 are considered remission[183].

In conclusion, the scales most-used used in research work on depression are the BDI, the MADRS and the HAM-D. These instruments allow us to do symptomatic monitoring, and they assess the severity of depression and the response to treatment. The HAM-D and the MADRS, by having a greater load of somatic symptoms, are difficult to assess in patients with a medical pathology, versus the BDI scale, which predominantly assesses the cognitive aspects of depression.

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Montgomery Asberg Depression Rating Scale (validated by Lobo and assoc.[186])

1. Apparent sadness The patient expresses despondency, gloom and despair reflected in speech, facial expression and posture. Rate by depth and inability to brighten up. 0. No sadness. 1. 2. Looks dispirited but does brighten up without difficulty. 3. 4. Appears sad and unhappy most of the time. 5. 6. Looks miserable all the time. Extremely despondent.
2. Reported sadness The patient verbally reports depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, despair and feeling of without hope. Rate according to intensity, duration and extent to which the mood is reported to be influenced by events: 0. Occasional sadness in keeping with the circumstances. 1. 2. Sadness but brightens up without difficulty. 3. 4. Pervasive feelings of sadness or gloominess, but the mood is still slightly influenced by external circumstances. 5. 6. Continuous or unvarying sadness, misery or despondency.
3. Inner tension The patient expresses ill-defined feelings of discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency or duration of the reassurance called for: 0. Apparently placid. Only fleeting inner tension. 1. 2. Occasional feelings of edginess or feelings of intermittent panic which the patient can only master with some difficulty. 5. 6. Unrelenting dread or anguish. Overwhelming panic.
4. Reduced sleep The patient expresses reduced duration or depth of sleep compared to the subject's own normal pattern when well. 0. Sleeps as usual. 1. 2. Slight difficulty dropping off to sleep or slightly reduced sleep: light sleep. 3. 4. Sleep reduced or broken by at least two hours. 5. 6. Less than 2 or 3 hours of sleep.
5. Reduced appetite The patient expresses a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat. 0. Normal or increased appetite. 1. 2. Slightly reduced appetite. 3. 4. No appetite. Food is tasteless. 5. 6. Needs persuasion to eat at all.

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6. Concentration difficulties

The patient expresses difficulties in collecting his own thoughts or in concentrating. Rate according to intensity, frequency and degree of incapacity produced.

0. No difficulties in concentrating.
1.
2. Occasional difficulties in collecting one's thoughts.
3,
4. Difficulties in concentrating and sustaining thought, which reduces the ability to read or hold a conversation.
5.
6. Unable to read or converse without great difficulty.

7. Lassitude

The patient expresses or presents difficulty getting started and performing everyday activities:

0. Hardly any difficulties in getting started. No sluggishness.
1.
2. Difficulties in starting activities.
3.
4. Difficulties in starting simple routine activities, which are carried out with effort.
5.
6. Complete lassitude. Unable to do anything without help.

8. Inability to feel.

The patient expresses reduced interest in the surroundings or in activities that normally give pleasure. Reduced ability to react with adequate emotion to circumstances or people.

0. Normal interest in the surroundings and other people.
1.
2. Reduced ability to enjoy usual interests.
3.
4. Loss of interest in the surroundings, even with friends and acquaintances.
5.
6. States the experience of being emotionally paralysed, the inability to feel anger, grief or pleasure, and a complete and/or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

The patient expresses thoughts of guilt, self-reproach, remorse, inferiority, ruin and sinfulness.

0. No pessimistic thoughts
1.
2. Fluctuating ideas of failure, self-reproach or self-deprecation.
3.
4. Persistent self-accusations or indefinite but still rational ideas of guilt or sin. Pessimism.
5.
6. Delusions of ruin, remorse or unredeemable sin. Self-accusations that are absurd and unshakeable.

10. Suicidal thoughts

The patient expresses the idea that life is not worth living, that a natural death would be welcome or states suicidal thoughts or plans.

0. Enjoys life or takes it as it comes.
1.
2. Weary of life. Only fleeting suicidal thoughts.
3.
4. Probably better off dead. Frequent suicidal thoughts. Suicide is considered as a possible solution, but without specific plans or intention.
5.
6. Explicit plans for suicide when there is an opportunity. Active preparation for suicide.

Taken from: Lobo A, Chamorro L, Luque A, Dal-Re R, Badia X, Baro E. Validacion de las versiones en español de la Montgomery-Asberg Depression Rating Scale y la Hamilton Anxiety Rating Scale para la evaluacion de la depresion y de la ansiedad. Med Clin (Barc) 2002;118(13):493-9.

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Appendix 10. Outcome measures in studies on depressive disorders

The absence of consensus and precision, both in the definition and use of outcome measures, makes it difficult to generalise protocols, compare different studies and extrapolate research to clinical practice[187].

The need to use uniform outcome measures in research on depressive pathology in order to compare and interpret the results of different research led the *McArthur Foundation Mental Health Research Network on Depression* to create a working group in 1988, which proposed conceptual definitions and operational criteria for identifying the changes caused by various treatments in the course of depressive disorders.

This effort has not been reflected in subsequent research, and there continues to be disparity in the operational criteria used in clinical trials (different scales, different cut-off points, different required durations to meet criteria, etc.). As a result, and in absence of a quantifiable biological marker, there still is no standard that allows comparing the outcomes of treatments for the major depressive disorder[188].

To measure outcomes, continuous or discontinuous measures can be used, and when we find differences, they can be statistically significant or not, and clinically relevant or not.

Statistical differences and clinical relevance

There is broad inconsistency in defining and using the terms that designate relevant changes in the course of the depressive illness, and this inconsistency generates difficulties for usefully interpreting, comparing and applying the outcomes of different studies. One review by Prien et al.[187] observed that the method used the most in studies for measuring outcomes was the statistical difference, and up to 32% of studies used statistical significance tests as the sole criteria for assessing the effects of a treatment. However, the statistical test by itself does not indicate if a change has clinical relevance, and it does not define a change point in the course of the depressive illness that can be applied in subsequent research or in clinical decisions. From the clinical point of view, statistical significance does not resolve all the questions marks that have to be answered, wherefore we may find associations that are statistically possible but conceptually sterile.

Continuous measures versus discontinuous measures

There are some noteworthy scales among the instruments used to assess mood disorders. They are based on the severity and duration of the symptoms, which in turn help to define the state of the patient and his evolution.

The most-used scales are the Hamilton scale, the Beck scale and the Montgomery-Asberg scale. In some trials, the scales are used as continuous measures of outcome (average scores of the group at the end of the trial), although this has the disadvantage of providing results that are difficult to transfer to clinically solid figures, such as absolute differences and NNTs, or the number of patients needed to treat[189].

In other studies, the measures are frequently dichotomised by establishing a minimum reduction of the symptomatology. Thus, a 50% reduction in the HAM-D 17 or MADRS score is defined as response in various studies[190, 191]. These measures can be arbitrary and have

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uncertain clinical relevance. Thus, a 50% reduction in the symptomatology of mild depression is relevant, while in severe depression, the patient remains at a moderate level of disability despite the response, wherefore it would not be clinically important[190]. Patients who have a lower severity at the start are going to have a faster response than those who start with a higher severity score[192].

Another approach sometimes used in trials on antidepressants is to calculate the proportion of patients with a score below a predefined cut-off value (for example, less than 7 in the Hamilton scale) and to consider these patients to be "recovered"[188]. This approach may be more useful, because it is based on a clinical definition of recovery.

In relation to the application of all these discontinuous measures, a consensus about the cut-off points to be used, their conceptual difference and the operational criteria that would allow elaborating the categories would mean great advances in the design, interpretation and comparison of studies on treatments and on the natural evolution of the illness, in addition to facilitating the development of research and clinical practice guidelines.

Some authors have made their proposals based on the following principles for delimiting them[188]:

~ The definitions are based on observable phenomena such as the severity of the symptoms or the functional state.

~ The change points are independent of whether or not treatment is given and of what treatment is administered.

~ The time to which the concepts refer is independent of the number of episodes that the patient may have had.

Below we will discuss the five necessary concepts for designing the change points in the course of the major depressive illness: recovery, remission, response, relapse and recurrence. These concepts are based fundamentally on operational criteria proposed according to ranges of scores of standardised assessment scales and to the time factor[192, 197].

For a coherent definition of these terms, it is also necessary to define episode, for which it will in turn be necessary to take into account the number, severity and duration of the symptoms. Thus, an episode is a period longer than N days during which the patient has a sufficient number of symptoms so as to meet the illness diagnostic criteria (DSM-IV/CIE-10)[188]. An episode does not end until the patient recovers.

Response and partial remission

The period in which considerable improvement is observed, but in which the presence of somewhat more than minimum symptoms persist, is called a partial remission[188]. A partial remission can be spontaneous or due to a treatment.

Response can be understood as the point of onset of the partial remission as a result of a treatment[188, 193]. It has been defined as a decrease of more than 50% in the base score of a standardised scale[194, 195, 197]. It makes sense to establish this category, because it may lead a professional to not increase the therapeutic dose (if the response is due to a treatment) or to not initiate it (if the partial remission appeared spontaneously).

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Full remission

It is a period of time in which the patient is asymptomatic[192, 194], thereby taking into account that it does not mean the total absence of symptoms. HAM-D 17 below 7, BDI below 8 and duration of less than 6 months are used as operational diagnostic criteria[184]. It has been seen that, using the HAM-D 17, a score of 7 or less establishes the difference between patients with or without depression[193].

Recovery

Recovery is remission above a certain period of time[188] in which a patient is asymptomatic and has only one or two mild symptoms. The term is usually used to designate recovery of the episode and not of the illness. The concept "recovery" denotes a return to normalcy or to the usual state, and it is the primary objective of the treatment for acute depressive episodes[160, 187, 194]. The terms recovery and remission have occasionally been used interchangeably[187].

Relapse

It is a worsening of an apparently controlled episode, to the point where diagnostic level criteria are reached again, and it occurs during remission and before recovery.

Recurrence

It is the appearance of a new episode in a recovered patient[182].

Operational criteria of outcomes in depression.

		HAM-D 17	BDI
Clinical ranges	Asymptomatic	7 points	8 points
	Completely symptomatic	15 points	15 points
Duration	Episode	2 two weeks completely symptomatic	4 two weeks completely symptomatic
	Full remission	2 and <6 months asymptomatic	3 weeks and < 4 months asymptomatic
	Recovery	6 months asymptomatic	4 months asymptomatic
Source: Frank *et al*[188] and Keller *et al*[193].			

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Appendix 11. Psychotherapies

In 1993, F. Guattari stated textually: *"Therapeutic practices and their theoretical formulations are currently in a state of almost total depression. This situation cannot be considered a sign of freedom, a stimulus to invention and to creativity, but rather it is the consequence of the sectarianism that reigns in this area and the consequence of unawareness, which at times reaches irritating extremes, about everything that is happening inside each one of these closed preserves."*

Fifteen years later, this quotation has not only not lost its currentness, but one could say that these words have become prophetic. The quantity of schools and sub-schools, models and meta-models is so broad that the task of putting a little order in the field is as considerable an effort as it is controversial. Such a quantity of names of schools and the variety of their surnames – which refer to nuances, often insignificant – is probably due to interests that are unrelated to scientific rigour or conceptual accuracy[195]. In any event, it represents a difficulty when assessing that outcome that can be expected from psychotherapeutic interventions, with the potential harm that this means for the users.

The purpose of these pages is to be a guideline so that readers can orient themselves and know how to situate themselves in the complexity of proposals that are made by the different schools of psychotherapy. Therefore, the various terms that refer to psychotherapeutic procedures have been classified into four large categories, which in the MeSH Database are included within the category of Psychotherapy. They correspond to the four large, traditional psychotherapeutic approaches. Within each one, the terms included in the MeSH Database are described, thereby sorting them, when possible, into Schools of Psychotherapy and into Techniques. The former are distinguished by offering a more or less structured theoretical framework; the latter are psychotherapeutic procedures whereby it is endeavoured to get psychotherapeutic changes guided by theory. Thus, some schools of psychotherapy share the same techniques, which can be used for similar or different purposes.

The MeSH Database defines psychotherapy as a generic term for the treatment of a mental illness or emotional disturbances, primarily by verbal or non-verbal communication.

In 1993, Feixas and Miró[196] stated that there were over four hundred different schools of psychotherapy. Most of them can probably be framed within one of the four large groups that are described below; or they may be on the fence between two of them; or they may use techniques coming from any of them; or they may lean towards the premises and goals of one or another according to the cases and circumstances in which they have to be applied.

1. The Psychodynamic Approach

Its basic thinking is that the behaviour of people is influenced by unconscious conflicts – to which the patients themselves don't have access without the assistance of the psychotherapist – which must be resolved as a form of release from the tyranny of the symptoms. These are nothing more than the tip of the iceberg, and therefore it is not necessary to pay them any more attention than what is necessary.

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1.1. Psychoanalysis.

Definition: Psychotherapy procedures based on Freudian principles that seek to decrease the undesirable effects of unconscious conflicts by making them more conscious, identifying their origin, recognising the inappropriate expression of emotions and understanding the meaning of current behaviour.

From the perspective of some theoreticians, it is the reference point for any other school of psychotherapy[197]. When one talks about Psychoanalysis on its own, it is usually in reference to orthodox Freudian Psychoanalysis, which includes different schools –almost one school per psychoanalyst master – but Psychoanalysis frequently needs some surname in order to identify the school to which it refers. In all of them there is a common theoretical and epistemological background, and they usually differ in the central focus that they give to a concept as the almost universal "explainer" of the behaviour of persons.

Among the most well-known schools of Psychoanalysis, in addition to Orthodox Freudian, the following classical ones could be cited: Individual or Adlerian Psychoanalysis, Jungian Psychoanalysis – the first two and most important dissents from orthodox Freudian – and Lacanian Psychoanalysis, which is perhaps currently the most widespread in Spain, France and other European countries.

The most common psychotherapeutic techniques and procedures are the following:

- ~ Free Association: Spontaneous verbalisation of the first thing that comes to mind, which is what is considered important. It can be considered the central technique of the psychoanalytical school. Through it, and precisely due to the freedom and lack of conscious critique of the procedure of associating, the patient reveals unconscious content and experiences to his psychoanalyst.
- ~ Transference Psychology: It refers to unconsciously attributing feelings and attitudes to the psychotherapist, which were originally associated in childhood to important family figures.
- ~ Countertransference Psychology: Emotional reaction – conscious or unconscious – of the psychotherapist towards the patient, which can interfere with the psychotherapeutic treatment. It is the complementary concept of "Transference", although, as it is deduced from the definition itself, with a few nuances: "Countertransference" can be conscious, "Transference" cannot. Both fit the bidirectionality of relationships, and from this perspective, they can be considered the equivalent of the "Therapeutic Relationship", which is a factor that is common to all schools of psychotherapy.

Healing from the point of view of psychoanalysis consists of an abreaction that occurs when the patient is able to verbalise an unconscious and repressed conflict – Catharsis.

Some forms of psychotherapy, such as Play Therapy or Music Therapy, use the different psychoanalytical theories as the interpretation framework of the patients' behaviour.

1.2. Brief Psychotherapy

Brief Psychotherapy merits special mention, and it is an effort to bring psychoanalytical intervention to the limited times and resources of the users and of the Public Health Services.

This designation groups together a series of schools that propose to produce psychotherapeutic change within a minimal amount of time, generally no more than 20 sessions. They are considered a substitute for Psychoanalysis per se, which from this perspective would be the appropriate and

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ideal treatment. These psychotherapies are applied 1) when the patient does not have sufficient resources – time or financial – to continue long-term treatment and 2) when a "focal point" affected by the disturbance can be defined and it is limited.

Among the Brief Psychotherapies with a psychoanalytical orientation, we could cite Balint's Focal Psychotherapy, Mann's Time-Limited Psychotherapy, Davanloo's Short-term Dynamic Psychotherapy and Sifneos's Brief Dynamic Therapy, as the most traditional.

2. The Behavioural Approach[1].

It is based on the idea that what has to be changed is behaviour, and it is therefore based on the Psychology of Learning. Only what can be observed is of interest, thereby understanding that cognition and emotions are also expressed through behaviour, and they therefore can also be the object of treatment.

2.1. Behaviour Therapy

Definition: The application of Learning and Conditioning Theories to the modification of behaviour. It is a school of psychotherapy with a long tradition. It sustains that mental illness or psychological problems are derived from erroneous learning experiences, and the psychotherapeutic treatment is designed to correct them by replacing them with other, more suitable or adaptive learning experiences. Moreover, it considers that the only thing observable, and therefore the only thing treatable, is behaviour.

The following are some of the most extensively applied psychotherapeutic techniques and procedures:

- ~ Psychological Desensitization, which consists of associating muscular relaxation with anxiety-producing stimuli in order to inhibit the anxiety that they cause in a person. This technique is applied in anxiety disorders and is valuable help for exposure to the feared stimuli in phobic disorders.
- ~ Implosive Therapy, which is a procedure for extinguishing anxiety by saturation exposure to the feared stimulus situation or its substitute. This technique is an alternative to systematic desensitization for treating the same type of cases, generally phobias.
- ~ Aversion Therapy, which is applied to suppress an undesirable behaviour by exposing the subject to unpleasant consequences.
- ~ Biofeedback, which consists of using biofeedback information to gain voluntary control over processes and functions that are under autonomic control.

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1 Feixes and Miró differentiate, following Mahoney, between behavioural and cognitive models. Agreeing that they are two different schools of psychotherapy, they can be considered and included in the same "group of schools" because they coincide in theoretical premises and because of their commitment to the empirical foundation.

2.2. Cognitive or Cognitive Behavioural Therapy

Definition: It is based on the interpretation of situations (cognitive structure of experiences) that influence the feelings and behaviours of people. It assumes the premise that the process of acquiring knowledge and forming beliefs is a primary determinant of mood and behaviour.

The development that this procedure has acquired has resulted in it being considered a school of psychotherapy that is independent of Behaviour Therapy, although it is related to it and the latter can be considered a derivation or a subsequent development of the former. It is often referred to by the name of Cognitive Behavioural Therapy.

Cognitive Therapies propose the goal of updating and modifying the cognitive schema that are contributing to causing distortions in the way of perceiving others and the environment in which one lives. They are brief therapies of approximately twenty sessions at a weekly frequency.

Some of the most well-known within this school include Beck's Cognitive Therapy, which was initially designed to handle depressed patients, and Ellis's Rational-Emotive Psychotherapy. It attempts to replace irrational ideas with other, more realist ones as a result of direct confrontation by the therapist.

3. The Systemic Approach.

It is characterised by applying General Systems Theory[198] – mental health problems are the result of the disturbance of a system and therapeutic strategies are applied and designed to re-establish the balance of the system – and Human Communications Theory[199] – which identifies behaviour with communication: all behaviour has a message value and every message is a behaviour that can be modified.

3.1 Family Therapy

It is a form of group psychotherapy. It involves having more than one family member in the psychotherapy session at the same time.

Like Systemic Therapy, it considers that the problems of people depend on the nature of the relationships in which a person conducts himself, and since the family is the human group in which the most intense relations usually occur, Family Therapy is, by definition, a Systemic Therapy[2].

However, the field of Family Therapy is particularly confusing due to the multiplicity of schools that have been developed under this name.

Some consider that Family Therapy simply alludes to a psychotherapeutic intervention format that involves attendance in a session by two or more members of the same family. This is the concept that seems to be drawn from the MeSH Database definition. From this point of view, the family format is used by almost all psychotherapy approaches, and we could talk about following types of Family Therapy: psychodynamic, behavioural, systemic, etc.

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2 This is why Family Therapies are included in the Systemic Therapies section. However, not all Family Therapies are systemic, and not all Systemic Therapies are family therapies.

On the other hand, others think that Family Therapy is a different approach, which is characterised by centring the focus of the intervention on the family relationships and considering the pathology to be so much personal, but rather interpersonal or, in the worst case, the personal pathology affects and is affected by the quality of the interpersonal relationships. Thus, the focus, interest and intervention of the person and the intrapsychic is expanded to the relational focus.

Two dissimilar formats fall within this second sense: from the joint family format – all members of the family go – to individual formats – just one person goes, and through that person, changes are provoked in the entire family – and passing through formats in which family members go without the identified patient – this is how, in some Family Therapy approaches, the member of the family who identifies with the "sick person" becomes known – in order to achieve certain goals referring to that person.

The following could be cited among the schools of Family Therapy that have had the most influence among psychotherapists: the so-called Palo Alto School, Minuchin Structural Family Therapy, Haley's Strategic Family Therapy, Selvini's Milan School, Andolfi's Rome School and S. de Shazer's Solution-Focused Therapy. They all coincide in applying the systemic approach to Family Therapy. They are brief psychotherapies with about ten sessions, maximum.

These schools of psychotherapy are designed to be brief, because that's how the treatment has to be; they consider that they focus on and resolve the entire problem presented; and they develop appropriate strategies to reach this objective. They also don't believe that brief psychotherapy is of lesser importance for addressing more minor or focal problems (such as with Brief Dynamic Psychotherapy); quite the contrary, they think that if they achieve the same thing as other psychotherapeutic procedures in less time, then this gives them a certain advantage with respect to efficiency.

Analytic Family Therapies have been developed from psychoanalytical approaches that have originated from particularly innovative psychoanalysts such as Bowen, Whitaker or Ackerman – this latter psychoanalyst became the first family therapist – and in Europe, they have experienced their greatest development in France. We could likewise talk about Behavioural Family Therapies, whose most well-known example is Liberman.

3.2. Marital Therapy and Couples Therapy

It is a form of psychotherapy that involves the husband and wife, and its objective is to improve the couple's relationship. Some consider Couples Therapy to be a particular case of Family Therapy: when there is intervention preferably on the relationship between the parents.

It seems that the only difference between "Marital Therapy" and "Couples Therapy" is that the couple is linked by the marriage bond or not. The psychological processes of a couple are not, in principle, differentiated either by legal statute or by the sex of the members. Apart from ideological considerations, it is proposed that both terms be unified.

Moreover, as with family therapies, there are multiple couples therapies with different orientations: from psychodynamic orientation couples therapy to behavioural orientation couples therapy, passing through systemic orientation therapies.

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4. The Humanistic Approach.

It is characterised by promoting personal growth. All the schools that are grouped under this heading sustain the concept of an "ideal existence" towards which all people should strive. They do not attempt to cure pathologies so much as develop abilities.

4.1. Gestalt Therapy

This school of psychotherapy emphasises interplay between the organism and the environment. As the basic goal, it proposes personal development and the development of knowledge, maturity and self-confidence more than resolving conflict or correcting deficit.

4.2. Non-directive Therapy

It is a procedure in which the psychotherapist reflects back to the client what the latter has said as a procedure to refrain from directing the "client". It is a school of psychotherapy that has considerable influence on the premises of other schools of psychotherapy, which assume positions that are close to non-directiveness, thereby giving clients the leading role over the role played by the psychotherapists. Thus, For example, the Narrative or Collaborative Therapies of Anderson and Golishian, which could be better framed within the systemic family models, propose that the psychotherapist assume submissive positions in order to give a greater leading role to the clients.

Talking about "client" instead of "patient" is a change derived from the influence of Non-directive Therapy in order to signify that the client is not considered to be someone who is ill and who "suffers" from distress, but rather a competent person in charge of his own life who is making a request.

4.3. Counselling[3]

These types of treatments have a pedagogical and support objective, wherefore they offer information and the exchange of experiences. It is debatable and debated whether or not Counselling is a psychotherapeutic intervention. Those who think that it is not underscore that its ultimate purpose is not to "heal", but rather to guideline, support and inform, and they argue that the times and format are far different from psychotherapies, ruled by long duration in which a therapist (who knows) heals or helps to heal a sick patient (who therefore does not know how to heal himself). At the opposite end are those who find no differences between the forms and purposes of the "Counselling" and those of some schools of brief psychotherapy – between the latter and Counselling there are no time differences – and non-directive schools, which consider those who request psychological help not to be sick people who need curing, but rather people with problems and the sufficient resources to resolve the problems by themselves. The psychotherapist only facilitates the change, like a catalyst in chemistry.

As with Family Therapy and with Psychoanalysis, there also is a distinction between different forms of Counselling: from the Gordon method, which is non-directive and is inspired in Rogers's Client-Centered Therapy, or Jackins's Co-counselling, which is a form of therapy without a therapist, to directive methods of counselling, in which the client is told exactly what they have to do to resolve the problems that are being consulted. There is also Marriage Counselling, which in Spain is usually applied at Family Guidance Centres (often linked to denominational institutions)

3 Most Counselling or Guidance is based and founded on the teachings and assumptions of Carl Rogers's Non-directive Therapy. This is why it is included among the humanistic approaches and right after Non-directive Therapies.

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and which proposes to provide guidance so that a couple can improve their relationship, and Sexual Counselling, which is a particular case of the former.

4.4. Transactional Analysis

Psychoanalytical Treatment wherein each social transaction is analysed to determine what state of the ego is involved (parent-like, child-like or adult-like) as the basis for understanding behaviour.

Even though the definition offered by MeSH Database includes it as a psychoanalytical treatment, and even though the parallelism between the theories of Freud and of Berne is obvious, it can be better framed within a Humanistic Approach of Psychotherapy rather than a sub-school within psychoanalysis. The procedures and techniques that are used in Transactional Analysis propose the personal growth of the patients by becoming aware of their experiences and life positions, which are considered to be unconscious to a large extent.

4.5. Psychodrama

It is a technique of Group Psychotherapy that basically consists of dramatising or acting out a patient's personal and emotional problems. Although it initially starts from Freudian theoretical positions, psychodrama sufficiently distances itself from psychoanalysis to be considered an independent school of psychotherapy. It is almost always applied in group, but there are also individual approaches, wherefore it cannot always be considered a form of group psychotherapy. Role Playing is one of the fundamental techniques of psychodrama, a technique that has been exported to other schools of psychotherapy and to other contexts, such as teaching. It consists of adopting or playing the role of another significant person in order to increase understanding of that person's behaviour, and it works not only towards comprehension, but also towards training certain skills and behaviours.

5. Final comments.

There are two terms included in the MeSH Database that have not been described up to now, because they are characterised by using a special format and application mode and are therefore not characterised by belonging to a school. They are Group Psychotherapy and Bibliotherapy.

- ~ Group [4] Psychotherapy is a form of psychotherapy in which two or more patients participate under the guidance of one or more psychotherapists for the purpose of treating emotional disturbances, social maladjustments or psychotic states.
- ~ Group Psychotherapy is a format which can encompass the entire spectrum of Psychotherapy Schools – from analytical to conceptual, passing through the humanistic – which use the group as experience for promoting personal growth.
- ~ In addition to the classical schools, which can offer their services in a group formatby intervention on the groups themselves and on each of members using the same techniques and the same theoretical premises as for the individual format, there are other schools that are only applicable to the group format (T Groups, Encounter Groups, etc.).

4 The MeSH Database includes Family Therapy, Marital Therapy, Couples Therapy and Psychodrama within group therapies. They are all psychotherapeutic approaches or formats that give rise multiple schools, just like Group Psychotherapy, wherefore it is proposed that the concept of Group Therapy be reserved for those groups that come together only because they share the same pathology or the same therapeutic purposes and that are not joined by any family link or link related to living together.

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~ Sensitivity Training Groups are groups of people who meet in an unstructured setting to learn about themselves, their interpersonal relationships and group processes and about larger social systems.

~ Bibliotherapy. It is a form of psychotherapy in which the patient is given carefully selected material to read in order to treat their emotional and behavioural problems. Bibliotherapy can be oriented from any psychotherapeutic approach. Intervention by the professional is considered to be minimal, and reading the texts gives rise to a process of self-help through the patient's own reflection. These reflections are only occasionally discussed with the professional.

Moreover, there is a psychological treatment that the NICE Guideline studies and that has yet to be defined: Interpersonal Therapy.

It is a treatment format of particular interest to this guideline, because it is perhaps the psychological treatment that obtains the best outcomes with depressed patients[200, 201], and it arose specifically as maintenance therapy for major depression. It covers four aspects: grief, interpersonal conflicts, the failure to adapt to role transitions and deficits in interpersonal relationships. It prioritises the interpersonal aspect of behaviour, but it is not Family Therapy; it focuses on the problems that can justify depression, but it is not Problem-Solving Therapy. It is an approach that takes ideas and techniques from other schools and organises them in an original way. It can therefore be considered an independent school.

The preceding list of psychotherapeutic schools and techniques has been prepared based on the terms that are used in the MeSH Database. Therefore, there are some absences that are worth mentioning:

~ Existential Therapies: The central theme of Binswanger's Existential Analysis is a person's free will and ability to decide, their unity and integration in the whole and the future project as a human being. Frankl's Logotherapy proposes the will to meaning or the search for the meaning of one's own existence as the core of psychotherapeutic intervention.

~ Bioenergetics: It is a psychotherapeutic approach developed by Lowen based on the theories of Reich. Lowen himself defines this type of psychotherapy as corporal mediation psychoanalysis.

~ Neurolinguistic Programming: its authors, Bandoleer and Grinder, propose this psychotherapeutic procedure as a meta-model. What they do is focus on certain linguistic expressions of patients that denote altered visions of the world, which are related to a problematic existence. The therapy consists of "reprogramming" the language of patients to increase the available alternatives in their vision of the world.

~ Acceptance and Commitment Therapy: It is a psychotherapeutic proposal by Hayes that offers itself as a development of Cognitive Behavioural Therapy, thereby incorporating aspects proper to some humanistic approaches, such as Frank's or Roger's.

~ There are certainly are other approaches that are worth mentioning and that have been omitted from this list. This document can be considered open to including other schools and to explain, reclassify or redefine any other for the sake of greater clarity in the bibliographical review in order to assess its scientific status, which in the end is what it's about.

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